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AN EVALUATION OF

EXPERIMENTAL STRATEGIES AND ESTIMATORS

FOR THE QUANTAL RESPONSE PROBLEM

by
Richard Allen Beldin

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ABSTRACT

AN EVALUATION OF EXPERIMENTAL STRATEGIES AND ESTIMATORS FOR THE QUANTAL RESPONSE PROBLEM

by
Richard Allen Beldin

Several types of experimental designs and corresponding estimators of the mean and standard deviation of a Gaussian tolerance distribution from quantal response observations are compared for various errors in the experimenter's prior estimates of these parameters. The concept of an experimental strategy as a design with certain parameters unspecified is introduced. In fixed strategies, in which all stimulus levels are defined a priori in terms of prior estimates of the parameters, probit and Spearman-Karber estimation are compared by computation of exact sampling distributions. In stochastic strategies, where observations are used to determine subsequent stimulus levels, Dixon-Mood and Spearman-Karber estimators are compared using Monte Carlo methods. In mixed strategies using a combination of stochastic and fixed strategies, the estimators appropriate to the final stage are compared for various choices of first stage estimators by combining results previously developed separately.

Fixed strategies are seen to be most appropriate when the experimenter's prior information is nearly exact and confirmation is required. Stochastic strategies are found to be nearly independent of the error in the prior estimate of the mean. Mixed strategies are shown to provide the greatest protection against degenerate outcomes for a wide range of prior estimates.

Differences between estimators of the mean are slight compared to differences between estimators of the standard deviation. The Spearman-

Karber estimators appear to be less severely affected by improbable outcomes than the alternative estimators. In general the Spearman-Karber estimator of the standard deviation is heavily biased but has little variability. The bias is such as to allow correction by a linear function of the estimator and the prior estimate, independent of other design characteristics. For mixed and stochastic strategies approximate corrections are suggested.

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CHAPTER I

INTRODUCTION TO THE QUANTAL RESPONSE PROBLEM

#1.1 The Basic Quantal Response Model

1.1.1 Subjects, stimuli, and responses. These three basic elements of every quantal response model are related to each other in the same way as the elements of the well known "black box" model. The subject, whose nature frequently remains unspecified, acts as a sealed mechanism within which a certain input (the stimulus) causes a corresponding output (the response). Although there is a causal relation between stimulus and response, this factor is rarely featured in formal descriptions of the model.

The features which distinguish quantal response data from other stimulus response situations are characteristics of the subject, stimulus, and response which are closely related to the nature of the physical objects and processes modeled and their interrelations.

The subject is frequently such that the application of a given stimulus changes the nature of the subject irreversibly regardless of the response elicited. Thus in quantal response problems one rarely encounters repeated trials on the same subject.

The class of stimuli appropriate to the quantal response model is the class of continuous measurable stimuli which can be controlled to a greater or lesser degree by the experimenter. Although the stimulation

process may occur over a period of physical time, this characteristic is usually not featured in the model.

The most distinctive characteristic of the quantal response model is reflected in its name. The response is quantal, i.e. dichotomous and therefore logically equivalent to a "yes or no" answer to a question. The positive response is observable but its complement may be noted only by the absence of the positive response. Since the real situation exists in physical time, some time limit for observation must be set in order to terminate the experiment and record all observations in a finite (and practical) period of time. Many applications of the quantal response model incorporate this time limit only in the definition of the positive response. Although in some situations the elapsed time between the application of the stimulus and the positive response can be informative, the more usual formulations of the model ignore this aspect.

1.1.2 Populations, tolerances, and tolerance distributions. Since the stimulus-response action may cause an irreversible change in the subject, the interest of the experimenter is focused on inferences from a sample of subjects to a population of a more or less homogeneous nature. The subject is usually assumed to be a random selection from such a population.

The actual mechanism assumed is that a subject will respond to a stimulus if and only if its intensity exceeds a certain level peculiar to the subject. This level, which presumably varies from subject to subject within a population, is termed the tolerance of that subject. It is assumed to be a continuous but unobservable attribute. Hence, indirect measurement via the stimulus-response relationship is required.

By assigning probabilities to sets of tolerance values, a "tolerance distribution" is constructed. The assignment is usually made by defining a cumulative distribution function on the set of possible tolerances or more frequently (but with less mathematical generality), by choosing a probability density.

Thus we may summarize the description of the model in the following manner. A quantal response datum consists of the observation of either a positive or negative response of a subject, sampled from the population of interest, to which a known quantitative stimulus has been administered. The occurrence of a positive response is taken as evidence that the level of the stimulus exceeded the unknown tolerance of the subject whereas the negative response is assumed to indicate the opposite.

Inferences from quantal response data are usually formulated in terms of certain characteristics of the tolerance distribution, most especially, a location and a scale parameter. The most common choices are the median (i.e. the ED50 or LD50 and in some models, the mean) as a measure of central tendency and the standard deviation as a measure of variability. Particularly in biological assay an alternative set of parameters termed the "intercept" and "slope" has been used frequently. The origin of these terms is probably due to the use of a particular formulation of the estimation problem known as "probit analysis".

1.1.3 Selected applications. As can be seen from the above, the model is not limited to any particular field of application although much of the methodology has been developed due to work in the biological sciences. We shall briefly discuss some of the numerous examples of such

applications along with an indication of the types of inferences frequently encountered.

The field of bioassay, broadly defined as the use of organic reactions (in vivo or in vitro) as a means of determining quantitative estimates of amounts of biologically active substances in various preparations, encompasses numerous examples. Some are aimed at comparing the activity of a test preparation with a well known standard. These usually involve the estimation of the difference (or ratio) of corresponding location and/or scale parameters from different tolerance distributions. [18],[54],[56]

The quantal response model lends itself to toxicological problems in a very natural way. A predetermined quantity of some toxic substance is administered to a laboratory animal and its death or survival are observed. One of the interesting statistical problems in this situation involves the attempt to estimate extreme percentiles of the tolerance distribution. In Chapter 2 we shall discuss briefly the difficulties involved. [4]

In the study of diagnosis and treatment of disease, the quantal response model has been used to predict whether or not a certain therapeutic procedure would be effective when applied to patients with various symptomatic complexes. The model is frequently used in a discriminatory analysis context under such situations.

The quantal response model has been used to develop understanding of the role of various (presumably) causative factors in disease processes. This type of application may involve the study of the interactions of several types of stimulus simultaneously.

Psychologists have used the model in the study of various problems. A possible application would be the attempt to measure the intensity of external stimulus required to make a neuron "fire". Other applications can be visualized in studies on perception and learning.

In industrial testing, the use of destructive tests for quality control provides examples of the use of this model. Interest here may be in describing a batch of products or in testing whether a manufacturing process in under control. [45],[64]

1.1.4 Formal statement of the model. We proceed to define the model in more formal mathematical terms. We represent the subject (s) as an element of a set (S) which represents the population. The tolerance X is defined as a continuous attribute of s. The stimulus assigned to subject s is denoted by u and is measured on the same scale as X. We define the response of subject s to stimulus u by

$$(1.1) \qquad Y(u) = \begin{cases} 0 & X \geq u \\ 1 & X < u \end{cases}$$

We assume that a probability density f may be defined on the set of values of X corresponding to members of S and define

$$(1.2) \qquad F(x) = \int_{-\infty}^{x} f(t; \mu, \sigma)\, dt$$

where μ and σ are the mean and standard deviation of the distribution of X defined by

$$(1.3) \qquad \mu = \int_{-\infty}^{+\infty} t\, f(t; \mu, \sigma)\, dt$$

$$(1.4)\quad \sigma^2 = \int_{-\infty}^{+\infty} (t-\mu)^2 f(t;\mu,\sigma)\, dt$$

The parameterization chosen is not the only possible one. Much of the biological assay literature refers to the alternative parameterization

$$(1.5)\quad \alpha = -\mu/\sigma \qquad \beta = 1/\sigma$$

Because the parameter pair (μ,σ) is more generally used and understood we have decided to use it as the basic formulation although the pairs (α, β) and (μ, β) will occasionally be used to simplify certain arguments.

There has been much discussion as to what form to assume for $f(X;\mu,\sigma)$. The most popular choices have been the Gaussian probability density

$$(1.6)\quad f(x;\mu,\sigma) = \frac{1}{\sigma}\phi\left(\frac{x-\mu}{\sigma}\right)$$

where

$$(1.7)\quad \phi(t) = \frac{1}{\sqrt{2\pi}}\, e^{-t^2/2} \qquad \Phi(z) = \int_{-\infty}^{z} \phi(t)\, dt$$

and the logistic density

$$(1.8)\quad f(x;\mu,\sigma) = \frac{1}{\sigma}\psi\left(\frac{x-\mu}{\sigma}\right)$$

where

$$(1.9)\quad \psi(t) = \frac{e^{-\gamma t}}{\gamma(1+e^{-\gamma t})^2} \qquad \gamma = \frac{\sqrt{3}}{\pi} \qquad \Psi(t) = \frac{1}{1+e^{-\gamma t}}$$

We will not involve ourselves in a discussion of the pros and cons of either choice but will choose the Gaussian distribution. Due to the simi-

larities between these distributions we feel that few of our conclusions would be modified if the logistic distribution were assumed. Figures 1 and 2 compare the Gaussian and logistic densities and cumulative distributions.

Frequently one encounters a population whose tolerance distribution departs rather severely from anything approximating a Gaussian distribution. The most popular solution to this problem is to transform the stimulus (and tolerance) scale so as to make the transformed distribution more nearly Gaussian. This technique is sufficiently well known so as to make further discussion unnecessary. An alternative approach is to use a method of estimation which is "robust" to such differences. Some aspects of this solution will be discussed in section 1.5.5.

#1.2 Information in the Quantal Response Model

One of the interesting (and troublesome) characteristics of quantal response experimentation is that the stimulus levels employed determine the precision of the estimators. The inaccuracies of the prior estimates of the tolerance distribution parameters may lead to greater variability of the estimators than the experimenter desired or anticipated. The choice of stimulus levels implies a choice of corresponding values of the probability of a positive response. Since the probability of any combination of positive and negative responses depends on the probabilities of positive responses, the distributions of estimators are affected.

From consideration of the concepts of "information" or "intrinsic accuracy" developed by Fisher [57],[58],[79]* one can determine a minimum value for the variance of any estimator of a parameter. However, in or-

*See Kendall and Stuart for a thorough discussion.

FIGURE 1

Gaussian Φ and Logistic Ψ Densities

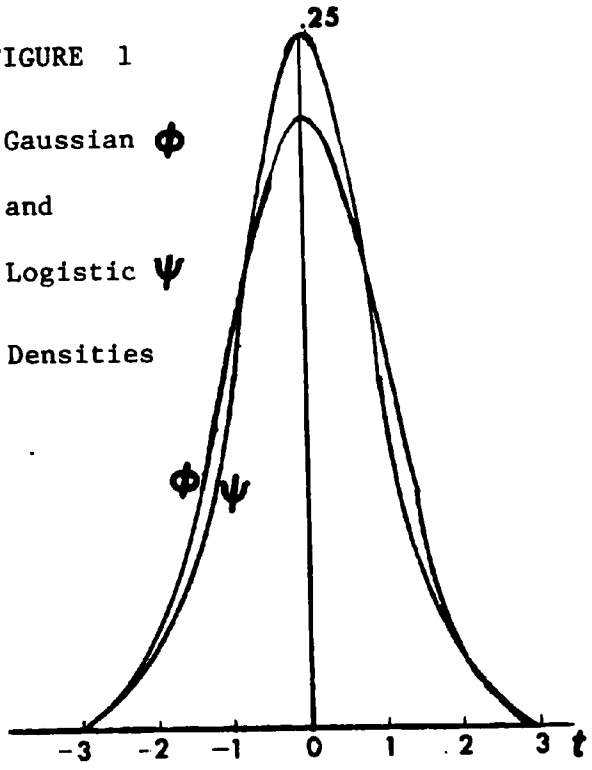


FIGURE 2

Gaussian Φ and Logistic Ψ Distributions

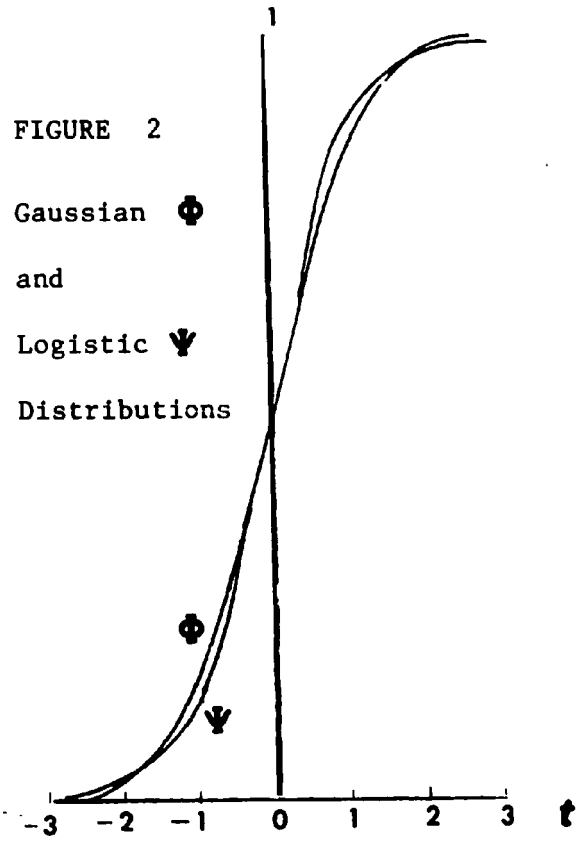
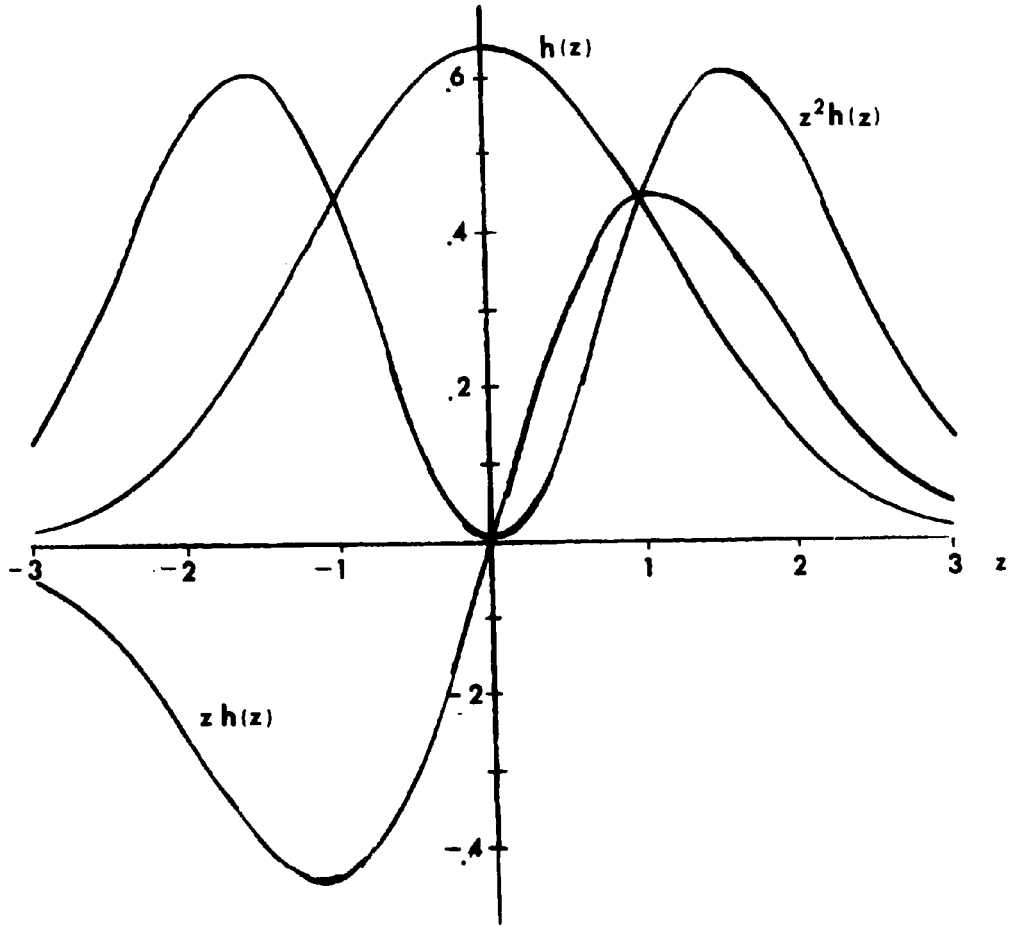


FIGURE 3 Information as a Function of Stimulus Level



der to select those stimulus levels which would reduce that minimum variance bound as much as possible for a fixed number of subjects, one must know the parameters in advance of the experiment.

Let $H[\theta; u]$ denote the information available for the parameter θ from an observation on the random variable $Y(u)$ as defined in (1.1). Then we find that if we assume a Gaussian tolerance distribution

$$(1.10) \quad H[\mu; u] = \frac{\phi(z)^2}{\sigma^2 \Phi(z) [1 - \Phi(z)]} = \frac{h(z)}{\sigma^2}$$

where $z = (u - \mu)/\sigma$ and

$$(1.11) \quad H[\sigma; u] = \frac{z^2 h(z)}{\sigma^2}$$

Figure 3 shows a graph of $h(z)$, $z^2 h(z)$ and a third quantity $zh(z)$ as functions of z. The function $zh(z)$ is involved in the "joint information",

$$(1.12) \quad H[\mu,\sigma; u] = \frac{zh(z)}{\sigma^2} .$$

These quantities enter the "information matrix" H_u as follows

$$(1.13) \quad H_u = \begin{bmatrix} H[\mu; u] & H[\mu,\sigma; u] \\ H[\mu,\sigma; u] & H[\sigma; u] \end{bmatrix} = \frac{h(z)}{\sigma^2} \begin{bmatrix} 1 & z \\ z & z^2 \end{bmatrix}$$

It is obvious that the determinant of H_u is zero so that the information matrix is singular. This is a reflection of the fact that the parameters μ and σ are inextricably interrelated with the stimulus level u when a single stimulus level is used. Even if one knew the values of $\Phi(\frac{u-\mu}{\sigma})$ and u, he could not ascertain a unique solution for μ and σ. For this reason one must use more than one stimulus level and thus must sample from different distributions.

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From the additivity of information [79] it can be shown that for a complete experiment utilizing k stimulus levels $u_1, u_2, \ldots, u_k$ and n_i subjects at the i'th level (i = 1, 2,...,k) the information matrix would be

$$(1.14)\quad H^* = \sum_{i=1}^{k} n_i H_{u_i} = \frac{1}{\sigma^2} \sum_{i=1}^{k} n_i h\left(\frac{u_i-\mu}{\sigma}\right) \begin{bmatrix} 1 & \frac{u_i-\mu}{\sigma} \\ \frac{u_i-\mu}{\sigma} & \left(\frac{u_i-\mu}{\sigma}\right)^2 \end{bmatrix}$$

One point of interest is that one cannot specify a set of levels to use that will make the information for μ a maximum since $h(\frac{u-\mu}{\sigma})$ has but one maximum and two or more distinct stimulus levels are required to eliminate the singularity. By using two stimulus levels symmetrically placed about (i.e., $u_2-\mu = \mu-u_1$) and an equal number of subjects, $\frac{n}{2}$, at each level, the joint information term becomes zero and H* is then diagonal of the form

$$(1.15)\quad H^* = \frac{n}{\sigma^2} \begin{bmatrix} 1 & 0 \\ 0 & \left(\frac{u_2-\mu}{\sigma}\right)^2 \end{bmatrix} h\left(\frac{u_2-\mu}{\sigma}\right)$$

Compare this with the information matrix for random sampling of n observations from a Gaussian distribution.

$$(1.16)\quad H = \frac{n}{\sigma^2} \begin{bmatrix} 1 & 0 \\ 0 & 2 \end{bmatrix}.$$

We see that $h(\frac{u_2-\mu}{\sigma})$ indicates the information for μ of this quantal response experiment relative to that of the direct observations on the Gaussian distribution. In a similar fashion $\frac{1}{2}(\frac{u_2-\mu}{\sigma})^2 h(\frac{u_2-\mu}{\sigma})$ gives

the corresponding quantity for estimation of σ. If σ were the parameter of major interest, the experimenter with perfect prior information could choose $u_2 = \mu + 1.6\sigma$ in order to maximize this "relative information" for σ since as can be seen from Figure 3, $z^2h(z)$ is near its maximum (approximately .62) at $z = 1.6$. This implies that a quantal response experiment of this type has less than one third the information for σ than does ordinary random sampling from the Gaussian distribution.

In some situations the experimenter may wish to maximize $z^2h(z)^2$, the determinant of H*. Clearly, $z^2h(z)^2$ has its maximum when $|zh(z)|$ is maximum and thus from Figure 3 we obtain approximate values of $z = 1.2$, $h(z) = .4$, and $z^2h(z) = .5$ and thus the relative information for μ is approximately $\frac{2}{5}$ and for σ, $\frac{1}{4}$.

The point is clear that if experimentally feasible, the quantal form of observation should be rejected in favor of random sampling of the tolerance distribution. Note that the figures given above require that the experimenter have perfect prior information and that as a consequence, a two level experiment is satisfactory. The former condition, if satisfied, obviates the necessity of experimentation.

Some quantitative expression of the experimenter's prior knowledge of the parameter values is clearly necessary, since the precision of the estimators depends upon his choice of stimulus levels. A subjective probability distribution for the values of μ and σ would provide a natural model for such prior information, but we feel that few practical experimenter's are both able and willing to expend the time and effort required to assess realistically their prior opinions by such methods as those proposed by Savage [97],[98]. We will assume only that the experimenter can obtain prior point estimates of μ and σ. These we will denote by

μ_o and σ_o. Although we will not formally use subjective probability distributions in our study, we will not hesitate to invoke the properties of hypothetical prior distributions as an aid to exposition.

The values of μ_o and σ_o are measured on the same scale as the stimulus levels and the tolerances. Any transformation of these latter quantities induces the same transformation on μ_o and σ_o. In particular, the linear transform

$$(1.17) \quad u' = \frac{u - \mu}{\sigma}$$

which transforms the stimulus level and tolerance scale, will transform μ_o and σ_o as follows:

$$(1.18) \quad \mu_o' = \frac{\mu_o - \mu}{\sigma}$$

$$(1.19) \quad \sigma_o' = \frac{\sigma_o}{\sigma}$$

where the primes denote the quantities on the new scale. All of the estimators which we will study share this property so that the dependence of the distributions of estimators on the prior information can be studied under the assumption that $\mu = 0$ and $\sigma = 1$ with the proviso that the appropriate inverse location and scale transforms are made in considering such quantities as moments. The primes will not be carried through further discussion and unless otherwise specified, we assume that the standardized Gaussian distribution describes the population of tolerances.

#1.3 Observations on the Suitability of the Model

It seems advisable that we discuss some of the characteristics of the model with regard to realism and the implications of its simplicity and generality. Several modifications of the model for specific situations will be suggested by these considerations.

1.3.1 The simplicity of the model. Conceptually the model is quite simple. As noted earlier, in section 1.1, it can be described as a particular kind of black box model in which only input and output are observed. In the translation from a conceptual description to a mathematical formulation the logical and temporal distinctions between input and output are lost. The model is completely static. This static nature makes it inappropriate for situations in which circadian rhythm or waiting time from stimulus to response are important aspects of the experimental configuration.

The incorporation of time into the model would be a natural first step towards greater realism. By specializing the model in this way we gain realism at the cost of time and effort devoted to problem definition. It seems that many experimenters might not want to pay the necessary price for more sophisticated models. Another factor which must be considered is the availability of necessary background information.

1.3.2 Generality of the model. The generality of the model flows in part from its simplicity. However, there is another aspect which frequently remains unrecognized. The quantal response model, as we have presented it, implicitly assumes that the stimulus enhances the probability of a positive response. In the mathematical formulation this is reflected by defining the probability of a positive response as the cumulative dis-

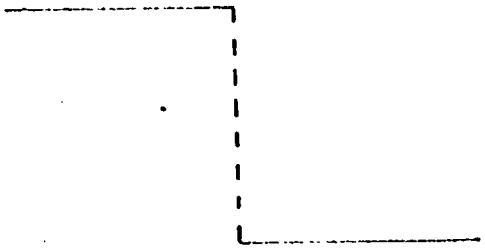
tribution function of a tolerance distribution. If this function is considered as a stimulus-response relationship apart from any interpretation in relation to a distribution, then the scale parameter loses its interpretation as a statistical entity restricted to nonnegative values (as in equation 1.5) and becomes a formal mathematical parameter with no restriction as to sign. In this modified interpretation the formal parameter β can take on negative values without violating the nature of the model. For the remainder of this discussion, we will consider the probability of a positive response as a monotonic function, not necessarily a distribution function. We will continue to refer to the parameters μ and β but they will not necessarily be parameters of a tolerance distribution.

Let us consider the implications of various values of the formal parameter β as illustrated in Figure 4. If β is negative we have a decreasing probability of the positive response with increasing "stimulus" intensity. Our "stimulus" is now an inhibitory factor with respect to the "positive" response. If we wish to insist that a population of "tolerances" exists such that the positive response is suppressed if and only if the tolerance is exceeded by the stimulus level, then we have reversed our definition of a tolerance. A strategem frequently encountered is to redefine suppression as the positive response. Provided one does this and is as sure of the inhibitory effect as he would usually be of a stimulation effect, no problem is encountered. The experimenter has defined his terms in such a way as to make our original statement of the model adequate. He has a distribution of tolerances with statistically interpretable parameters.

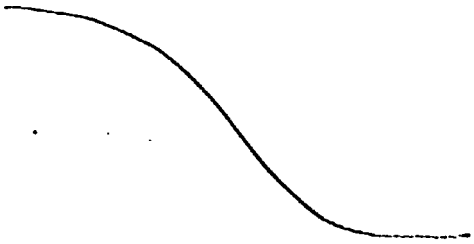
Suppose, however, that our experimenter is dealing with a radically new compound and is not at all sure the substance is active and if it is

Figure 4-

Types of Stimulus Response Relationships

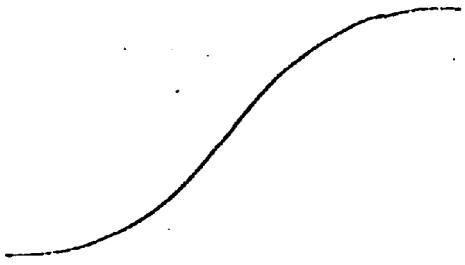


Inhibitory Threshold $\beta = -\infty$

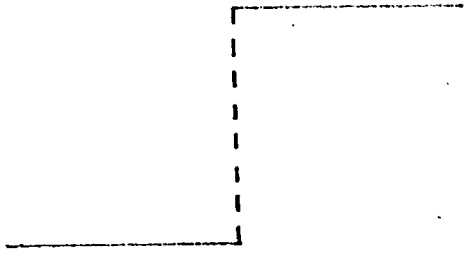


Inhibitory Distribution $-\infty < \beta < 0$

Independence $\beta = 0$



Excitory Distribution $0 < \beta < \infty$



Excitory Threshold $\beta = \infty$

active, he is still unsure as to whether the compound will stimulate or inhibit a particular response which he has defined. In addition, the experimenter may be quite ignorant of the scale on which a quantity of compound should be measured. By restating the model in such a form as to indicate that the probability of the response designated as "positive" is a monotonic function of the stimulus level which involves the formal parameters μ and β devoid of any statistical interpretation, the five situations indicated in Figure 4 can be modeled.

This generality of the mathematical formulation indicates clearly that the only mathematical difference between a tolerance distribution formulation and one based on a stimulus-response relationship is the restriction of the scale parameter to nonnegative values in the former. This topic will be discussed in more detail in sections 3.2.1 and 4.1

#1.4 Types of Designs

Since the set of stimulus levels used in an experiment will typically be dependent on the experimenter's prior estimates of the parameters, we will define a "strategy" as the specification of an experimental design up to the values of the prior estimates. By this we mean that the stimulus levels are determined as functions of the prior estimates but not numerically known until such estimates are specified.

We can classify strategies as to the manner in which the stimulus levels used are selected. The "fixed" strategy uses levels which are determined solely by the prior information of the experimenter and certain strategy parameters. In a "stochastic" strategy the subjects are

used sequentially and levels are chosen on the basis of prior information and previous results. A "mixed" strategy is a two (or more) stage experiment which uses a preliminary stochastic strategy to assist in the planning of a fixed experiment. (See Cochran and Davis [33],[34] for a discussion of a variation which begins with a fixed strategy experiment and ends with a stochastic experiment.)

The specifications of the particular strategies studied will be discussed in section 2.2.2.

1.4.1 Fixed strategies. A fixed strategy is defined as the specification of an experiment in which all stimulus levels to be used are defined a priori as functions of the prior estimates of the parameters of the tolerance distribution. We will denote the number of stimulus levels by k, the number of subjects at the i'th stimulus level by n_i and the value of the i'th level by u_i. The simplest type of fixed strategy uses an equal number of subjects at each of the k equally spaced levels. This is the type of strategy recommended by most authors when the prior information is minimal. The number of subjects per level for this fixed strategy will be denoted by n. The values of the levels can be expressed as follows:

$$(1.20) \quad u_i = \mu_0 + \frac{2z}{k-1} \sigma_0 \left(i - \frac{k+1}{2}\right)$$

where z is chosen so that the levels extend from $\mu_0 - z\sigma_0$ to $\mu_0 + z\sigma_0$ Thus we can characterize this fixed strategy by the strategy parameters k, n, and z which the experimenter selects so as to minimize cost and maximize the precision with which the tolerance distribution parameters are estimated.

The sample space for the general fixed strategy experiment consists of a k-dimensional rectangular lattice with n_i points in the i'th dimension. Thus a sample point consists of a k-tuple $r_1 \ldots r_k$ where $0 \leq r_i \leq n_i$. The probability of the sample point $r_1 \ldots r_k$ is the product of k binomial probabilities,

$$(1.21) \quad \Pr[r_1 \ldots r_k] = \prod_{i=1}^{k} \binom{n_i}{r_i} F(u_i;\mu,\sigma)^{r_i} \; [1-F(u_i;\mu,\sigma)]^{n_i - r_i}$$

1.4.2 Stochastic strategies. A stochastic strategy is defined as a design in which a first set of stimulus levels is selected on the basis of prior information alone and subsequent levels are determined partially by the observations obtained previously. One example would be the "up and down" type of experiment in which the experimenter chooses an initial stimulus level u_0, a step size h_0, and a stopping rule. [43],[44],[45], [86] Subsequent levels are determined by the relation

$$(1.22) \quad u_{n+1} = u_n + (1-2y_n)h_o$$

and experimentation ceases when the stopping rule is satisfied. Other stochastic strategies modify the step size in various ways dependent on the number of trials already made and the responses obtained. A good example of these is the Robbins-Monro stochastic approximation process [95],[96] which uses the following rule to generate a stochastic process which converges in probability to the median of the tolerance distribution.

$$(1.23) \quad u_{n+1} = u_n + (1-2y_n)\frac{h_o}{n+1}$$

There are several drawbacks to stochastic strategies in general. First and most important are the effects of prolonging the time during which experimentation is carried out. The cost to the experimenter in time may be considerable and drastic changes in the stimulus and subject may occur over the extended time period. The choice of a stopping rule may well be critical but no clear answers are yet available. (See Wetherill [106] for some comparisons of stopping rules.) Stochastic approximation processes in particular have another characteristic which may cause problems. There is no natural estimator of the scale parameter in the specification of the general process and no internal estimator of the variances of the estimators provided.

The sample space for a stochastic experiment depends on the rule for modification of the step size (if any) and on the stopping rule. It is not as easily described as that of the fixed experiment. One characteristic that can be noted is that the stochastic experiment executes a modified random walk. If one examines the possible outcomes of an experiment, it can be seen that the lengths of "runs" are statistics which are common to stochastic experiments. To observe a run of length k starting with a positive response at stimulus level u_0 the following k-1 observations must be positive responses and the k'th following observation must be a negative response. Thus the probability of a run of successes of length k can be expressed as

$$(1.24)\quad \Pr[k] = [1 - F(u_0 - \sum_{i=0}^{k-1} h_i)] \prod_{i=1}^{k-1} F(u_o - \sum_{j=0}^{i-1} h_j)$$

1.4.3 Mixed strategies. One of the major reasons for selecting a stochastic rather than a fixed strategy is that there is less dependence of the former on the prior information available concerning the mean of the tolerance distribution. There are situations in which the fact that trials must be executed sequentially introduces a serious cost due to the length of time which must be expended to execute a complete experiment.

For this reason interest has been drawn to "mixed" strategies utilizing small stochastic strategies for the first stage. It is hoped that the stochastic experiment will correct for gross errors in the prior estimate of the median with a minimal number of trials and that the fixed experiment would provide more precise estimation given a reasonably placed set of stimulus levels.

Mixed strategies have been used informally by many experimenters with only intuitive justification but the only reported study seems to be that of Cochran and Davis mentioned above. For our purposes a mixed strategy will consist of the specification of a stochastic strategy, a fixed strategy, and a rule for using the results of the former in selecting the stimulus levels for the latter.

The sample space for a mixed experiment will be the cartesian product of the sample spaces for the component experiments. Unless the stochastic experiment is void of information, the probability of a sample point in the fixed portion will depend on the results of the stochastic experiment.

#1.5 Multiplicity of Estimation Procedures

One of the aspects of estimation from quantal response data is the many sets of estimators available. Some of these are based on general principles of statistical inference while others are specifically oriented to the quantal response model. The latter will be referred to as "opportunistic" methods as an indication that their validity depends on characteristics of the strategy used and the quantal response model as well as on distribution assumptions.

A number of studies which compare various estimation procedures for fixed strategies have been reported in the literature. [21],[23],[35], [36],[37],[39],[48],[91],[104]

Wetherill [106] and Brownlee et al [28] appear to be the only investigators who have considered comparisons among estimators for stochastic strategies.

1.5.1 Maximum likelihood. As a general principle of estimation, this well known method was first proposed by Fisher [57],[58]. It may be defined as follows: the maximum likelihood estimators are those functions of the observations which maximize the probability of the observed sample as a function of the parameters. The properties which give this method its value are of two kinds: large sample or "asymptotic" properties and small sample properties.

The large sample properties are (under general conditions) nearly always true given the legitimacy of the model. Maximum likelihood estimators are consistent, asymptotically normally distributed and asymptotically efficient. This means that if the sample size increases without bound the maximum likelihood estimators will have a multivariate Gaussian

distribution with expectation equal to the parameters estimated and the individual variances less than or equal to those of any alternative estimators. [38],[57],[58],[79]

When a set of minimal sufficient statistics exists, the maximum likelihood estimators will be functions of them and the desirable properties of the former are inherited by the estimators [57],[58],[79]. Such a set of minimal sufficient statistics has not been exhibited for the quantal response model with a Gaussian tolerance distribution (and we doubt, but cannot disprove, its existence). Failing the existence of such a set, the advantages and disadvantages of maximum likelihood estimators must be studied separately for each type of problem. Many investigators take the position that in the absence of proven superiority of an alternative method, the method of maximum likelihood is preferable to other methods due to the large sample properties. There seems to be little to criticize in this view as long as its extra-statistical basis is realized and attempts are made to evaluate competing estimators.

In many applications of maximum likelihood estimation (including the quantal response problem) the estimating functions can be given only implicitly by the formal equation of the partial derivatives of the likelihood function to zero. In such cases the numerical values of the estimates must be obtained by iterative procedures such as the Newton-Raphson technique [15],[35],[54],[62] for solving such nonlinear equations.

Let the system of equations to be solved be given by

$$(1.24) \quad g_i(\underline{t}) = 0 \qquad i = 1, 2, \ldots, p$$

where p is the number of components of the vectors $\underline{t}$ and $\underline{x}$, $\underline{t} = (t_1, t_2, \ldots, t_p)$ $\underline{x} = (x_1, x_2, \ldots, x_p)$.

We approximate $g_i(\underline{t})$ by

$$(1.25) \quad g_i^*(\underline{t}) = g_i(\underline{x}) + \sum_{j=1}^{p} \frac{\partial}{\partial t_j} g_i(\underline{t}) \Big|_{\underline{x}} (t_k - x_j)$$

and solve the linear system obtained by substituting the right side of (1.25) into (1.24). This presupposes that one has an initial guess at the solution given by the vector $\underline{x}$ and that the solution $\underline{t}$ is then resubstituted for $\underline{x}$ and the process continued until (1.24) is satisfied to the accuracy desired. The convergence of this system is not guaranteed in general but experience has shown that the Newton-Raphson technique most often leads to a convergent system of equations.

In statistical applications the functions g_i usually involve the observations as random variables. It is frequently computationally convenient to substitute the expected values of the derivatives of (1.25) for the observed values. This additional approximation must be considered on its merits for each type of problem. [35]

In our application we have (denoting $f(u; \mu, 1/\beta)$ by $f(u)$]

$$(1.26) \quad g_1(\mu,\beta) = -\beta \sum_{i=1}^{k} \frac{f(u_i)}{F(u_i)[1 - F(u_1)]} [r_i - nF(u_i)]$$

and $$g_2(\mu,\beta) = \sum_{i=1}^{k} \frac{f(u_i)(u_i - \mu)}{F(u_i)[1 - F(u_i)]} [r_i - nF(u_i)]$$

so that the maximum likelihood estimator of (μ, β) is the solution to

$$(1.27) \quad \sum_{i=1}^{k} \frac{f(u_i)}{F(u_i)[1 - F(u_i)]} [r_i - nF(u_i)] \begin{bmatrix} -\beta \\ \\ u_i - \mu \end{bmatrix} = \begin{bmatrix} 0 \\ \\ 0 \end{bmatrix}$$

The matrix of partial derivatives is given by

$$(1.28) \quad [a(\mu, \beta)] = -\sum_{i=1}^{k} \frac{f(u_i)[nf(u_i) + T_i]}{F(u_i)[1 - F(u_i)]} \begin{bmatrix} \beta^2 & -\beta u_i \\ -\beta u_i & u_i^2 \end{bmatrix}$$

where the T_i's are terms with expectation zero, specifically

$$(1.29) \quad T_i = \frac{[r_i - nF(u_i)]}{F(u_i)[1-F(u_i)]} \left\{ f(u_i)^2 \left[\frac{1}{F(u_i)} - \frac{1}{1-F(u_i)} \right] - \frac{\partial}{\partial \beta (u_i - \mu)} f(u_i) \right\}$$

By utilizing the Gaussian tolerance distribution assumptions, the system of equations which must be solved iteratively is obtained.

An alternative formulation called "probit analysis" utilizes the inverse Gaussian probability transform or probit of the observed and expected response rates thus yielding an equivalent system of equations comparable to that for a linear regression with unknown weights. The probit differs from the inverse probability transform only by the addition of the constant 5 so as to reduce the frequency of negative values in the computation. Strictly speaking, probit estimation refers to the use of this additive constant, but we shall use the term to include the use of the unmodified inverse probability transform, sometimes referred to as the "normal equivalent deviate" transform when a Gaussian model is involved.

1.5.2 Minimum chi square. An alternative method of estimation chooses as estimators the functions of the observations which minimize the chi square "goodness of fit" statistic. The rationale is that if the statistic is minimized then the estimates fit the data best in the sense of the adopted criterion. This method is restricted to problems in which the data are frequencies or can be reduced to such (frequently with some loss in information). In the quantal response problem, the chi square statistic which is to be minimized is

$$(1.30) \qquad \chi^2 = \sum_{i=1}^{k} \frac{[r_i - nF(u_i)]^2}{nF(u_i)[1 - F(u_i)]}$$

In order to find the estimators one usually equates to zero the partial derivatives of (1.30) with respect to the parameters. The resulting system of equations is similar in form to (1.27) but is usually reduced to

$$(1.31) \qquad \sum_{i=1}^{k} \frac{f(u_i)}{r_i(n - r_i)} [r_i - nF(u_i)] \begin{bmatrix} \beta \\ \\ u_i - \mu \end{bmatrix} = \begin{bmatrix} 0 \\ \\ 0 \end{bmatrix}$$

by making the assumption that

$$(1.32) \qquad r_i(n - r_i) \doteq n^2 F(u_i)[1 - F(u_i)]$$

The incorporation of this approximation leads to the "modified minimum chi square" estimation procedure.

This system can be solved without iteration if the probit transformation is made. Berkson [12] gives a detailed discussion of this method of estimation under the name "normit" chi square estimation.

Neyman [88] has shown that maximum likelihood, minimum chi square, and modified minimum chi square are asymptotically equivalent methods of estimation under conditions which are satisfied by the quantal response model. Although in real life experimentation, asymptotic properties are rarely achieved due to the small samples with which we deal, this fact does lend support to the use of minimum chi square vis a vis maximum likelihood as a general principle of estimation.

Several writers have carried out numerical comparisons of maximum likelihood and modified minimum chi square estimation [2],[7],[36],[37], [194] without finding either method to be consistently superior for all choices of stimulus levels (i.e. prior information). For this reason we felt it reasonable to select one of the two methods as "representative" of asymptotically efficient methods of estimation. Since the method of maximum likelihood is regarded so highly even when the small sample properties are not assured, we decided to use it although it is more complicated computationally.

1.5.3 Opportunistic methods. In many situations the experimenter is more knowledgeable about the standard deviation than about the mean. One example of this type of situation would be the case of a comparison of a test preparation to a standard as in the estimation of relative po-

tency. The experimenter may be sufficiently familiar with the population and the stimulating agent to be confident that the standard deviation does not vary from preparation to preparation. Because of this feature, a number of estimation procedures have been proposed which provide no estimate of the scale parameter. On general principles we consider the use of such techniques as unwise because there is no ability to check one's prior estimates. We will not attempt to evaluate such procedures.

Apart from considerations of efficiency etc., the major defect is this aspect of the opportunistic estimation procedures. Another criticism is often suggested that no estimate of the precision of the estimate of the location parameter can be obtained from the sample. In the case of the Reed-Muench method such an estimate is available [92] and in any case, if an estimator has sufficient merit to justify investigation its variability can be assessed by numerical methods. We will not consider such methods as the Reed-Muench, Dragstedt-Behrens or moving average methods further. (See Finney [56] for a discussion of these methods.)

1.5.4 Graphical techniques. A number of graphical methods of estimation have been proposed. [40],[63],[66],[81],[84] Since the use of nomograms and other graphical techniques is subject to variability due to the user as well as that inherent in the underlying numerical method, the study of graphical methods of estimation is not amenable to numerical methods but would rather require sampling of a population of investigators. This task, while of interest, is not within the scope of this dissertation.

1.5.5 Spearman-Karber estimation. Of the opportunistic methods of estimation this has the most substantial theoretical justification. Cornfield and Mantel [35] showed that the Spearman-Karber estimators are

maximum likelihood for a certain logistic model and they are functions of a set of minimal sufficient statistics for that model. Hence if that model is correct, all of the advantageous small sample properties of minimal sufficient statistics acrue to the Spearman-Karber estimators. The major differences between the model we have adopted and the logistic model described by Cornfield and Mantel (aside from the distribution assumption) are differences in the parameter definitions. The parameters μ^* and σ^{2*} are defined by

$$(1.33) \qquad \mu^* = \sum_{i=-\infty}^{\infty} \left(\frac{u_i + u_{i+1}}{2} \right) [F(u_{i+1}) - F(u_i)]$$

$$(1.34) \qquad \sigma^{2*} = \sum_{i=-\infty}^{\infty} \left(\frac{u_i + u_{i+1}}{2} - \mu^* \right)^2 [F(u_{i+1}) - F(u_i)]$$

rather than by integrals as is usually done. The parameters estimated by the Spearman-Karber method thus vary from the usually used set by what can be considered as errors of approximation of the order of magnitude encountered when integrals are approximated by sums or when continuous data are grouped. As Cornfield and Mantel point out, the justification for grouping data into classes is neither stronger nor weaker in quantal response problems than in situations where direct observations are made.

The spirit of the Spearman-Karber estimation procedure is akin to that of the method of moments, due to Pearson [38],[79]. The sample esti-

mates of the response rates are substituted into equations (1.33) and (1.34) to obtain

$$(1.35) \qquad \hat{\mu}_{SK} = \sum_{i=1}^{k-1} \left(\frac{u_i + u_{i+1}}{2}\right)\left[\frac{r_{i+1}}{n_{i+1}} - \frac{r_i}{n_i}\right]$$

$$(1.36) \qquad \hat{\sigma}^2_{SK} = \sum_{i=1}^{k-1} \left(\frac{u_i + u_{i+1}}{2} - \hat{\mu}_{SK}\right)^2 \left[\frac{r_{i+1}}{n_{i+1}} - \frac{r_i}{n_i}\right]$$

as the estimators of μ^* and σ^{2*}. We note that in addition to substituting empirical for theoretical response rates, we have limited ourselves to a finite range of summation. To the extent that this implicit truncation of the tolerance distribution includes a large probability, we may have distorted the distribution of our estimators so that their expectations are quite different from μ^* and σ^{2*}. For this reason an assumption that $p_1 = 0$ and $p_k = 1$ is frequently listed as crucial to the method. However, one can always take the position that the truncated tolerance distribution is of sufficient interest by itself that this effect on the estimators is unimportant. Another alternative is to assume that at stimulus levels u_o and u_{k+1} (suitably defined but not used) the true response rates would be zero and one respectively. This introduces a modification of the range of summation in (1.35) and (1.36) to extend from i=0 to i=k.

Very frequently, the stimulus levels are equally spaced. Utilizing this fact we can develop simpler computing forms for the estimates where h denotes the step size between levels, $p_i = \frac{r_i}{n_i} = 1-q_i$ is the observed

response rate at the i'th stimulus level.

$$(1.35') \quad \hat{\mu}_{SK} = u_k + \frac{h}{2} - h \sum_{1}^{k} p_i = u_1 - \frac{h}{2} + h \sum_{1}^{k} q_i$$

$$(1.36') \quad \hat{\sigma}^2_{SK} = h^2[(2k+1 - \sum_{j=1}^{k} p_j) \sum_{i=1}^{k} p_i - 2 \sum_{i=1}^{k} i\, p_i]$$

From (1.35') we can easily derive the variance of the simplified estimator of μ^*. Epstein and Churchman [32],[48] derived formulas for the moments of the sampling distributions of $\hat{\mu}_{SK}$ and $\hat{\sigma}^2_{SK}$. Cornfield and Mantel [35], showed that $\hat{\sigma}^2_{SK}$ is biased and gave the correction term. Because of the inherent grouping, a Sheppard's correction is often recommended when the parameter of interest is σ^2 rather than σ^{2*}.

Although the Spearman-Karber estimation procedure was not "in vogue" for several decades, several investigators have advocated its use as a possible alternative to more sophisticated methods such as probit analysis or modified minimum chi square estimation [23],[24],[25],[26], [27],[32],[35],[48]. Since these estimators are based on moments they are appropriate whenever the tolerance distribution possesses first and second moments.

Perhaps the most encouraging work apart from the discussion of Cornfield and Mantel is that of Bross. [23] On comparing what he calls the "worth" of an estimator (i.e. the probability that the estimator departs from the parameter by more than a fixed amount) for Spearman-Karber, Reed-Muench, and probit estimation, Bross finds that for the situations studied the worth of the Spearman-Karber estimators is comparable to that of probit analysis and that both are decidedly superior to estimation by the Reed-Muench method.

We therefore feel that the Spearman-Karber approach is a natural competitor with probit estimation and the comparison of these methods will be a major part of the discussion of fixed strategies.

Although we have found no reference to the use of Spearman-Karber estimation in data collected from an up and down experiment, it seems natural that the method be applicable. The fact that an up and down experiment insures that there will be no responses at the lowest stimulus level and no failures at the highest level makes the Spearman-Karber estimation procedure quite natural since the assumption that this is the case is part of the basis for the estimation procedure.

1.5.6 Dixon-Mood estimation. Dixon and Mood [45] proposed an estimation procedure for the up and down stochastic experiment described above in section 1.4.2. They showed that the information yielded by the observations of nonresponse and that yielded by responses were approximately equal. Using that fact, they developed maximum likelihood estimation equations conditional on the difference between the number of responses and the number of nonresponses observed. They found functions which provided close approximations to the solutions for a broad range

of sample results. Their results were based on the assumption of a normal tolerance distribution.

The estimators which they proposed can be defined in the following manner:

Let I(y) be defined by

$$(1.37)\quad I(y) = \begin{cases} 1 \text{ if } y \text{ is the less frequent type of event} \\ 0 \text{ is } y \text{ is the more frequent type of event} \end{cases}$$

Let u_i be the ith stimulus level and let y_i denote the response. Then we define

$$(1.38)\quad K_j = \sum_{i=1}^{N} u_i^j \, I(y_i)$$

Then the estimators $\hat{\mu}_{DM}$ and $\hat{\sigma}_{DM}$ are given by

$$(1.39)\quad \hat{\mu}_{DM} = \frac{K_1}{K_o} + \frac{h_o}{2}(-1)^{I(1)}$$

$$(1.40)\quad \hat{\sigma}_{DM} = 1.620 \left[\frac{K_o K_2 - K_1^2}{K_o^2}\right] + .029\, h_o$$

Note that $\hat{\sigma}_{DM}$ is an estimate of σ where in the Spearman-Karber approach $\hat{\sigma}^2_{SK}$ is an estimate of σ^2.

Dixon and Mood give estimators of the precision of $\hat{\mu}_{DM}$ and $\hat{\sigma}_{DM}$ which can be obtained from the experimental data. They show that the approximations to the solutions of the conditional maximum likelihood equa-

tions are valid when the step size h_0 is less than twice σ . When this is not so the solutions must be obtained iteratively from the equations

$$(1.41)\quad \sum_{i=1}^{N} \left[\frac{\Phi\left(\frac{u_{i-1}-\mu}{\sigma}\right)}{1-\Phi\left(\frac{u_{i-1}-\mu}{\sigma}\right)} - \frac{\Phi\left(\frac{u_i-\mu}{\sigma}\right)}{\Phi\left(\frac{u_i-\mu}{\sigma}\right)} \right] I(y_i) = 0$$

$$(1.42)\quad \sum_{i=1}^{N} \left[\frac{\frac{u_{i-1}-\mu}{\sigma}\,\Phi\left(\frac{u_{i-1}-\mu}{\sigma}\right)}{1-\Phi\left(\frac{u_{i-1}-\mu}{\sigma}\right)} - \frac{\frac{u_i-\mu}{\sigma}\,\Phi\left(\frac{u_i-\mu}{\sigma}\right)}{\Phi\left(\frac{u_i-\mu}{\sigma}\right)} \right] I(y_i) = 0$$

1.5.7 Stochastic approximation. Although we will not attempt to study general stochastic approximation strategies, some comments on the problem of estimation from such experiments are appropriate. The method of maximum likelihood is available for any configuration of stimulus levels. However, if there is any information in the sequence in which the trials occur, estimation by maximum likelihood will formally ignore it. Since the process converges in probability, one might think that the later trials should be weighted more heavily than the earlier ones. The method of maximum likelihood effectively weights each observation according to the propinquity of the stimulus level to the estimate of μ . This fact suggests that the information in the sequence of trials is effectively used by the method of maximum likelihood. Since stochastic approximation taken as a method of estimation ignores the problem of estimation of the scale parameter, it is hoped that further study of the process might suggest a means of estimating the scale parameter of the distribution.

CHAPTER 2

SCOPE OF THE DISSERTATION

#2.1 Problems of Interest

2.1.1 Need for prior information. One of the criteria for choosing one type of strategy over another is the dependence of the efficiency with which parameters can be estimated on the prior information available. Other things being equal the experimenter would prefer that strategy which is least dependent on the prior information. Of course "other things" are rarely equal and therefore this attribute will be weighted against cost and convenience considerations.

It is intuitively clear that a stochastic strategy is less dependent on the prior information than a fixed strategy. It remains to quantify this so that an experimenter can make the comparisons required to choose a design with greater security.

To what extent a mixed strategy improves the dependence on prior information compared to a fixed strategy is a question which must be answered. Hopefully with this kind of information the experimenter can make a choice from among the three competing types of strategies.

A related problem is the choice of an estimator from those available for a particular type of strategy. Presumably that estimator which makes best use of the information in the data would be least affected by

variation in prior estimates of the parameters. However, some estimators may be more dependent on prior information about μ than σ or vice versa. If we can compare estimators with respect to this type of differential dependence on prior information, we may be able to assist the experimenter in his choice of an estimator.

2.1.2 Small sample behavior of estimators. Since for the Gaussian model a set of minimal sufficient statistics is not available, the small sample behavior of the estimators must be studied. In our study of the fixed strategy we will attempt to compare the Spearman-Karber and maximum likelihood estimators for a variety of combinations of strategy parameters and levels of prior information. Similarly the Dixon-Mood and Spearman-Karber approaches will be studied for various stochastic strategies and varying accuracy of prior estimates. Finally in the mixed strategy we will attempt to compare the fixed stage estimators for various choices of stochastic stage estimators.

2.1.3 Choice of a strategy. The choice of estimator does not hold the promise of augmented efficiency that may be available by choosing alternative experiments. The choice of a strategy is a choice among (perhaps) radically different approaches to the problem. A priori we expect that the differences between strategies is likely to be of much greater significance than the difference between estimators for a given strategy.

Since the choice of a strategy is the decision which impinges most on the cost of the experiment, our analysis should cover such economic decisions. However, the range of variations in experimental material is so great as to make any general economic analysis intractable. We will therefore restrict ourselves to a study of those components of the cost

which vary according to some probability distribution, while holding fixed those components which are usually selected by the experimenter.

2.1.4 Discovering promising mixed strategies. We hope that as a by product of this study we will be able to give some general direction to the search for "good" mixed strategies. We will not be able to follow up such problems in this dissertation, but perhaps some "blind alleys" may be revealed.

2.1.5 Interpretation of boundary value estimates. The interpretation and treatment of estimates which are numerically inconsistent with the model should be studied and discussed more thoroughly than in the present literature. We will attempt to carry out this program.

#2.2 Limitations on the Breadth of the Study

2.2.1 Range of prior information included. Once we have decided to use prior point estimates of the parameters μ and σ as indications of the prior information available to the experimenter, the remaining problem is to decide how many and which different values of the prior estimates should be considered. The number of distinct combinations of value for μ_0 and σ_0 will of course be dependent on computational cost considerations. The specific values to be used should reflect the more frequent sizes of errors implicit in the experimenter's prior estimates.

Through conversations with several persons with experience in the field of toxicological applications we arrived at the range of values

$$-3 \leq \frac{\mu_0 - \mu}{\sigma} \leq 3$$

$$0 < \frac{\sigma_0}{\sigma} \leq 3$$

as being fairly reasonable.

Since the underlying tolerance distribution assumed is symmetric we can restrict $\frac{\mu_0-\mu}{\sigma}$ to positive values. The probability of the sample point $r_1 \ldots r_k$ is antisymmetric in μ_0 for any fixed strategy with equally spaced levels centered on μ_0 and with any symmetric allocation of subjects to levels (i.e. $n_i = n_{k+1-i}$) since

$$1 - \Phi\left(-\mu_0 + \frac{2z}{k-1}\sigma_0\left(i - \frac{k+1}{2}\right)\right) = \Phi\left(\mu_0 - \frac{2z}{k-1}\sigma_0\left(i - \frac{k+1}{2}\right)\right)$$

Using this fact it is easily seen that a change of sign of μ_0 changes only the sign of $\hat{\mu}$. For stochastic strategies with equally spaced stimulus levels a similar consideration holds. Thus we are freed from having to consider explicitly negative values of μ_0.

2.2.2 The strategies considered. A fixed strategy with equal size groups and equally spaced levels can be specified by three parameters n, k, and z as we have seen in section 1.4.1. We note that the product of z and σ_0 is all that is involved in the final experimental design so that if we vary σ_0 over a range, changes in z can be reflected by imputing corresponding values to σ_0.

Basically we are left with the decision as to how many and which fixed strategies should be studied. From mathematical studies [54],[56] we know that for the probit analysis estimators an increase in the number of levels holding the total number of subjects fixed improves the precision of the scale parameter estimator at the expense of estimation of the location parameter. For Spearman-Karber estimation the converse holds. [24],[25],[26]

In order to hold the computing cost of the dissertation to a minimum we decided to study the following strategies as representative of much of fixed strategy experimentation as currently practiced.

To compare strategies which are nearly equal in cost we chose to hold $k \cdot n$, the total number of subjects, constant at $nk = 24$. Table 1 shows the possible strategies with this restriction. The number of sample points, $(n + 1)^k$, is seen to increase exponentially with k so that the exploration of all of these strategies would be excessive in terms of computing time.

Table 1

Fixed Strategies with 24 Subjects

n	k	$(n + 1)^k$
24	1	25
12	2	169
8	3	729
6	4	2401
4	6	15625
3	8	65536
2	12	531441
1	24	16777216

It is rare that an experimenter would be sufficiently sure of his preliminary estimates of the parameters that he would be satisfied with a design with as few as three levels. However, we feel that by exploring the strategy with $n = 8$, $k = 3$ with a fine lattice of prior estimate values, and gradually increasing the coarseness of the lattice with increasing values of k, that the trends and relationships would be sufficiently well revealed to serve our purposes. Thus we have restricted the fixed strategies to those with 3, 4, or 6 levels of the stimulus.

With regard to the stochastic strategies used, there is apparently sufficient interest in the simple up and down strategy as a competitor with fixed strategies that it should be studied thoroughly. Among the questions which need most illumination is that of the choice of a stopping rule. We therefore will concentrate on comparisons of stopping rules.

We have chosen three types of stopping rules for our study. The first rule to which we refer as Rule 1(k) stops the experiment after the completion of the k'th run of stimulus levels in either direction (or equivalently after the k'th change of response type). The second rule (Rule 2(n)) terminates the experiment after the n'th subject has been observed. The third rule is based upon an observation by Grubbs and Golub [64] that if the observed proportions responding follow a pattern (0, 0,...,0, 1, 1,...,1) the maximum likelihood estimate of the parameter β is infinite. It is easy to see that if the maximum level at which a nonresponse is observed exceeds the minimum level at which a response occurs, this pattern of response rates does not occur. Thus the third stopping rule (Rule 3) uses the satisfaction of the inequality given above as the criterion for stopping the experiment. We should note that Rule 2(n) gives absolute control over the size of the experiment, Rule 1(k) gives a moderate amount of control, while Rule 3 leaves the size of the experiment completely to chance but insures a finite estimate of β (or a nonzero estimate of σ). We used Rule 1(k) with k=5, and 10; Rule 2(n) with n=10, and 20; and Rule 3 in our simulation study. A second study concentrated on Rule 1(k) alone with k=5, 10, 20.

Only exploratory study of other stochastic strategies was attempted.

2.2.3 The estimators studied. As indicated above we restricted our consideration of estimation procedures to the probit and Spearman-Karber for the fixed strategy and the Dixon-Mood and Spearman-Karber estimators for the stochastic strategies.

#2.3 Limitations on the Depth of the Study

2.3.1 Restriction to conditional distributions. Since the interpretation of estimates which fall outside or on the boundary of the restricted parameter space is qualitatively different from that of estimates which satisfy the constraints, it is appropriate to separate the study of strategies and estimators into two parts. The first is the study of the conditions under which estimates fall outside or on the boundary of the parameter space and the probability that such events occur. The second portion of the study concerns the comparison of strategies and estimators conditional on sample results yielding estimates inside the restricted parameter space.

Another reason for segmenting our study in this way is that infinite or indeterminate values of the estimators imply that the sampling distributions do not have moments. By considering conditional distributions we can use the usual techniques as applied to distributions possessing at least first and second moments.

The Spearman-Karber estimators as they are usually used do not give the same indications of infinite scale parameter estimates as do the probit method of estimation and the Dixon-Mood method. This can be attributed to a rather arbitrary convention employed with the Spearman-Karber method in that if the largest (smallest) stimulus level does not provide an estimated response proportion of one (zero), the next level above (below) is assumed to do so. Thus this convention tacitly assumes a finite range for the tolerance distribution and thus effectively eliminates infinite estimates of the moments of the tolerance distribution. If a probit type procedure were developed for such a truncated tolerance distribution model, it would demonstrate the same characteristic. This is, perhaps, a solu-

tion to the problem of the infinite estimates of the scale parameter but not necessarily a desirable one. This approach should be investigated further.

Due to this feature of the Spearman-Karber estimation procedure, we will define the set of "degenerate" sample points as that set for which either the location parameter estimate is infinite or indeterminate and/or the scale parameter estimate is not positive and finite when estimation is carried out by the probit method. We will compute (or estimate) the probability of this set of sample points and the joint first and second moments of the estimators conditional on the complementary set of sample points.

2.3.2 Use of first and second moments. While in principle one would like to base his decisions concerning the choice of designs and estimators on the entire sampling distributions of competing estimators, the number of different sampling distributions to be investigated is so large as to make such an approach impractical. Since considerations of bias and variability are the most frequently encountered criteria for choice of estimators and designs, we will limit our investigation to first and second moments of the joint distributions of the estimators under study conditional on the set of sample points described above.

2.3.3 Economic considerations. A complete analysis of the costs of experimentation would be very dependent on the nature of the stimulus, response, and subjects used and therefore would require handling each problem as a special case. The best that can be done on a general level would be to consider the cost of subjects as the overriding cost factor and equalize that cost when making comparisons. For that reason all of

the fixed strategies studied involve the same number of subjects, specifically twenty four. Comparisons between fixed and stochastic strategies will prove more cumbersome in that the stopping rule used may cause the number of subjects to be a random variable.

#2.4 Omitted Topics

A number of important related topics have been omitted. The basic reason underlying each omission is that in our judgement, specific problems in these areas require concentration on details of a particular experimental configuration and thus become of less general interest than the majority of the topics which we will study.

2.4.1 Hypothesis testing. Some quantal response experimentation (eg. quality control or life testing) may be oriented toward tests of hypotheses concerning the parameters of the tolerance distribution. We will not be directly involved in such problems. Certain of our results may have bearing on the treatment of such problems.

2.4.2 The choice of a tolerance distribution. The study of more than one tolerance distribution model was considered to be prohibitive in terms of computing time.

2.4.3 Stochastic approximation. For reasons discussed in section 1.5.7 above we will not attempt to consider stochastic approximation as an estimation procedure.

2.4.4 Multivariate stimuli. The variety of interactions possible makes it appear that the most fruitful study of multivariate stimuli would

be in the context of a specific problem, rather than in any general discussion or numerical study.

2.4.5 Estimation of extreme percentiles. The estimation of the ED_{90} or ED_{95} of a tolerance distribution is of no small practical importance. The choice of a tolerance distribution model is of crucial importance here and therefore detailed consideration would be beyond the scope of this dissertation. Since the parameter of interest in such problems is dependent on the "tails" of the tolerance distribution model, the degree of approximation accepted in the choice of a model will be reflected in the behavior of the estimator used. In any case, small sample estimators are rather inadequate for such problems. See Wetherill [106] for futher discussion of this problem.

CHAPTER 3

METHODOLOGY USED IN THE INVESTIGATION

#3.1 Types of Methods Used

3.1.1 Fixed strategies: exact sampling distributions. For the fixed strategies we computed numerically the first and second moments of the joint distributions of the Spearman-Karber and probit estimators of the parameters by applying the definitions of moments in conditional distributions directly. The probability of observing nondegenerate sample points was computed simultaneously. Thus for each strategy and set of prior estimates of the parameters we obtained a probability, a mean vector, and a covariance matrix. Figure 1 of the Appendix shows a flow chart of the computer program used.

3.1.2 Stochastic strategies: Monte Carlo simulation. Since the calculation of the moments of the estimators from the exact sampling distributions for stochastic strategies was impractical, we decided to estimate these moments by calculating sample moments of the estimates obtained from simulations of the stochastic strategy experiments obtained by using pseudo random sequences generated by the computer. Figure 2 of the Appendix shows a flow chart of the simulation program.

Our first simulation used the Knut Vik Graeco Latin square of order five given in Table 2.

Table 2

Graeco-Latin Square Design

Step Size	Initial Stimulus Level				
	0	1	2	3	4
1/8	A α	B β	C γ	D δ	E ϵ
1/4	C δ	D ϵ	E α	A β	B γ
1/2	E β	A γ	B δ	C ϵ	D α
1	B ϵ	C α	D β	E γ	A δ
2	D γ	E δ	A ϵ	B α	C β

The justification for using a predetermined design rather than a randomly selected one is based on the judgement that the sources of variation are completely specified by the following factors and levels:

Table 3

Design Specifications

Rows	Error in prior estimate of σ	$\frac{\sigma_0}{\sigma} = (\frac{1}{8}, \frac{1}{4}, \frac{1}{2}, 1, 2)$
Columns	Error in prior estimate of μ	$\frac{\mu_0 - \mu}{\sigma} = (0, 1, 2, 3, 4)$
Roman letters	Stopping rule	
	A maximum number of subjects = 20	
	B maximum number of runs = 5	
	C maximum number of runs = 10	
	D maximum number of subjects = 10	
	E $\min [X_i \blacktriangleright Y_i = 1] < \max [X_i \blacktriangleright Y_j = 0]$	
Greek letters	Random starts* (Octal representation)	
	α 261026554774	000346544645
	β 003664506716	272573063167
	γ 343174511640	114103652511
	δ 046643165562	131265313033
	ϵ 320334712504	321304224355

*These random starts were used to initialize the random normal deviate generator used. They are octal integers selected at random from the interval from 1 to 377777777777.

For each cell in the design one hundred simulated experiments which did not result in degenerate sample points were obtained by negative binomial sampling.* The numbers of experiments yielding degenerate sample points were recorded for use in estimating the probabilities of such events.

One of the results which should have been anticipated was in the cell (1, 4) of the design. Here we took step size $\frac{1}{8}$, starting at stimulus level 3 with a maximum of 10 subjects to be used. Clearly at least 24 subjects would be needed to reach stimulus level 0, the mean of the tolerance distribution. Thus all estimators for this experiment were very biased and the probability of a nondegenerate sample point was exceedingly small. This suggests that stopping rules based on a total number of subjects should only be used when very good information is available a priori.

The Graeco-Latin square design suggested that the stopping rule based on the number of runs was promising. We therefore ran a three cubed factorial design with one hundred replicates (again sampling in a negative binomial fashion). The design is described in Table 4. These results will be reported at a later date since they show little more than the original design.

Table 4

Factorial Design

Factor				Levels
1	Error in prior estimate of μ	$\frac{\mu_0 - \mu}{\sigma}$	=	(0, 2, 4)
2	Error in prior estimate of σ	σ_0/σ	=	($\frac{1}{4}$, $\frac{1}{2}$, 1)
3	Maximum number of runs	k	=	(5, 10, 20)

*That is, sampling until 100 nondegenerate sample points were obtained.

3.1.3 Mixed strategies: combination of results. Since a mixed strategy consists of two separate experiments, it is natural to estimate the moments of the estimators of the tolerance distribution parameters by using the relationships

$$(3.1)\quad E(X) = E\,(E\,(X \mid Y))$$

$$(3.2)\quad V(X) = V\,(E\,(X \mid Y)) + E\,(V\,(X \mid Y))$$

In our application the stochastic strategy estimators play the role of the "Y" and the moments of the fixed strategy estimators given the prior information "Y" play the role of $E(X|Y)$ and $V(X|Y)$. The "X" represents the estimator from the final stage of the mixed strategy.

Since we do not have the exact distributions of the stochastic strategy estimators, the sample results were used in the following manner. For each type of stochastic strategy in the Graeco-Latin square design, the values of the estimators for each simulated experiment were used as prior estimates for the fixed strategy under consideration. The tables of the moments of the fixed strategy estimators were considered as functions of the prior estimates and the second stage expectations were obtained by interpolation. These interpolated moments were averaged to obtain estimates of $E(E(X|Y))$ and $E(V(X|Y))$ and the covariance matrix of $E(X|Y)$ was estimated to use the relationships given above to produce estimates of the moments of the estimators from mixed strategy experiments.

#3.2 Computational Techniques

3.2.1 Detection of degenerate sample points. From the work of Cramer [36],[37] we find that sample points which we have described as "degenerate" fall into three classes, those with infinite, negative, and

zero estimates of β .

Referring back to Figure 4 we see that infinite values of β correspond to threshold relationships between the stimulus and the response. In order to be consistent with such a model the data would have to follow a pattern such as

$$(3.3) \quad r_i = \begin{cases} 0 & i \leq j \\ n & i > j \end{cases}$$

for some j or the complementary pattern obtained by interchanging 0 and n in (3.3). In addition, if j is neither 0 nor n, the probit estimate of β is infinite although the data are inconsistent with a threshold model.

Cramer states that sample points which satisfy

$$(3.4) \quad \sum_{i=1}^{k} (x_i - \mu_0)\, r_i = 0$$

for equally spaced stimulus levels and an equal number of subjects at each level yield zero estimates for β . Most members of the set of sample points which yield a zero estimate of β are symmetric in the r_i's, that is

$$(3.5) \quad r_i = r_{k-i+1} \qquad i=1, 2, \ldots, k$$

However, there are some nonsymmetric sample points which also yield zero estimates of β such as (for k=5)

$$(3.6) \quad \underline{r} = (1, 4, 3, 2, 2).$$

For each sample point $\underline{r}$ which yields a positive estimate of β, say

(3.7) $\underline{r} = (r_1, r_2, \ldots, r_k)$

there exists a sample point $\underline{r}'$ which yields a negative estimate of with the same magnitude. The correspondence is easily defined as complementary pairs of sample points in which

(3.8) $r_i' = n - r_i$

An example of such a complementary pair is illustrated in Figures 5 and 6. Here we see the contour map* of the likelihood functions in the (μ, σ) space for a situation in which

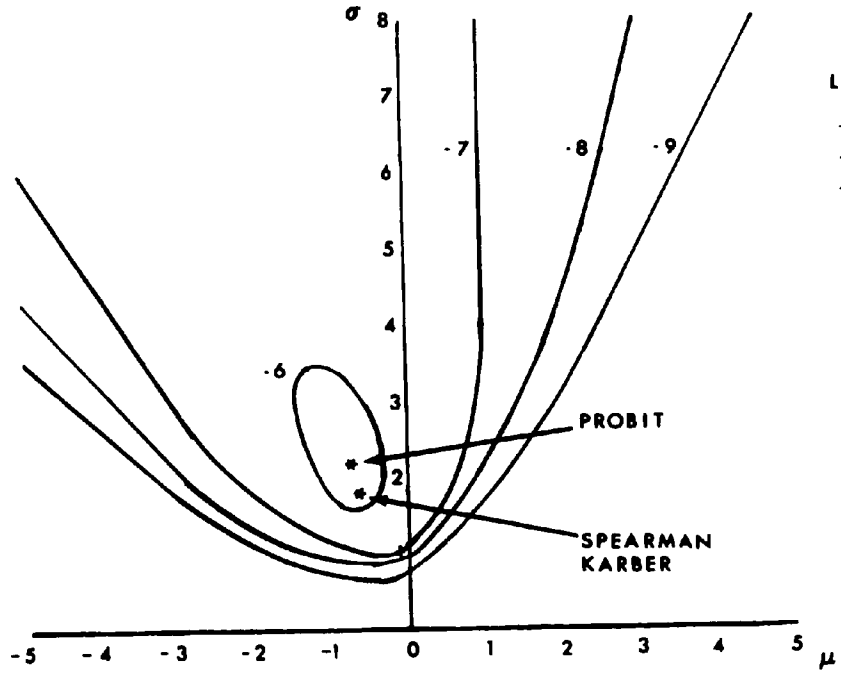
(3.9) $\underline{r} = (1, 2, 3, 2, 3, 4)$ and $\underline{r}' = (3, 2, 1, 2, 1, 0)$

3.2.2 Spearman-Karber estimates. The Spearman-Karber estimates were computed (and adjusted for bias) according to Cornfield and Mantel's recommendations. Since the parameter of interest was σ rather than its square, the estimate of σ was taken to be the positive square root of $\hat{\sigma}^2_{SK}$

3.2.3 Calculation of probit estimates. The probit estimates were calculated to a level of accuracy such that the sum of the squares of the derivatives of the likelihood function was less than .02. No interpolation was used in the 5 place normal probability tables** since prior investigation indicated an increase of less than one per cent in accuracy and at least seven per cent in time when linear interpolation was used. Subsequent checks of results using values for the normal distribution accurate to seven significant digits substantiated this result. In any

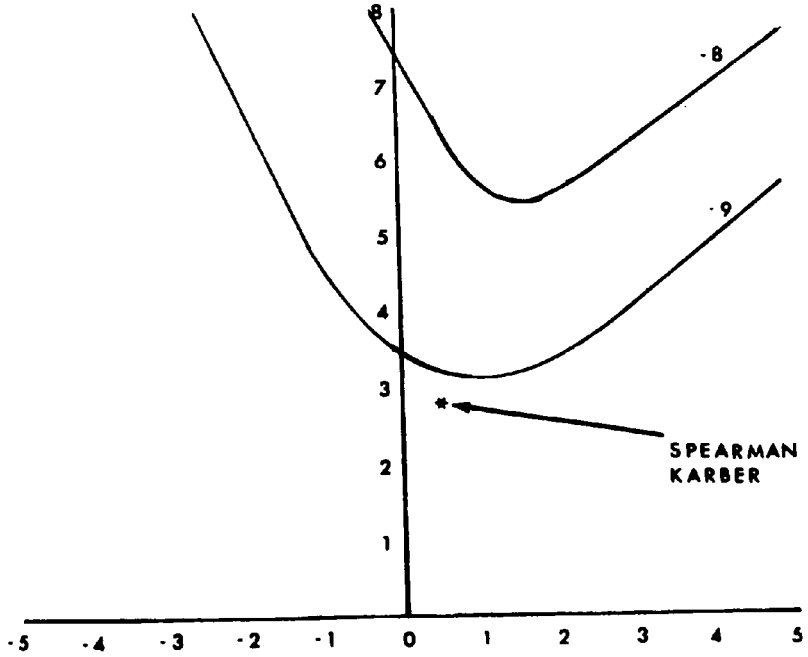
*See below, section 3.3.1 for a discussion of contour maps.
**That is, areas accurate to five places were stored in tables internal to the computer.

FIGURE 5 $\log_{10} \ell(\mu,\sigma \mid \underline{r}, \underline{x})$



Level	Responses
-2.0	1
-1.2	2
-0.4	3
0.4	2
1.2	3
2.0	4

FIGURE 6 $\log_{10} \ell(\mu,\sigma \mid \underline{r}', \underline{x})$



Level	Responses
-2.0	3
-1.2	2
-0.4	1
0.4	2
1.2	1
2.0	0

case the accuracy of the probit estimates is at least as good as that usually obtained by desk-top calculator methods. Since we are attempting to mimic the behavior of an experimenter with real data who may or may not have access to a modern electronic computer, this level of accuracy was felt to be sufficient for our purposes. No more than five iterations were required for those sample points which did not yield degenerate estimates. All such sample points yielded convergent systems of equations to be solved.

3.2.4 Calculation of Dixon-Mood estimates. The formulae given by Dixon and Mood were used directly. When the screening process for degenerate sample points accepted a sample point, the criterion for satisfactory approximation given by Dixon and Mood was usually satisfied. Hence the iterative solution they proposed was not utilized although it was build into an early version of the stochastic experiment simulator.

#3.3 Graphical Presentation Techniques

One of the basic problems when discussing many topics is that brevity frequently suffers and with it the patience and interest of the reader. In order to make it possible to condense this dissertation to reasonable proportions, we have made extensive use of graphical techniques to describe our findings. In addition to well known graphical representations of data and functional relationships such as histograms, scatter plots, graphs of curves and the like, several other graphical presentations have been used which require some description.

3.3.1 Contour maps. The idea of contour mapping of mathematical relationships is equivalent to the topological contour maps prepared by cartographers. Mathematically, a contour map of a function f can be

defined as the graph of a set of curves which satisfy

(3.10) $f(x, y) = z$

where a curve is generated by each distinct value of z. A contour map shows the separate and the joint roles of the two variables in the determination of the value of the function. Figure 7 gives an example of a contour map.

3.3.2 Traces. We use the term trace as denoting a curve generated by a pair of equations given in parametric form as follows.

$$\begin{aligned} x &= f(t) \\ y &= g(t) \end{aligned} \tag{3.11}$$

Thus with a trace we can see how each of two quantities changes in response to changes in a third quantity. Figure 8 is an example of a trace.

3.3.3 The ellipse of concentration. When comparing several bivariate distributions one would like to have displayed differences in means, variances, and the correlation among the distributions. The plotting of ellipses of concentration provides as nearly satisfactory a solution to this problem as we have been able to encounter. The ellipse of concentration is defined (Cramer [38]) as follows.

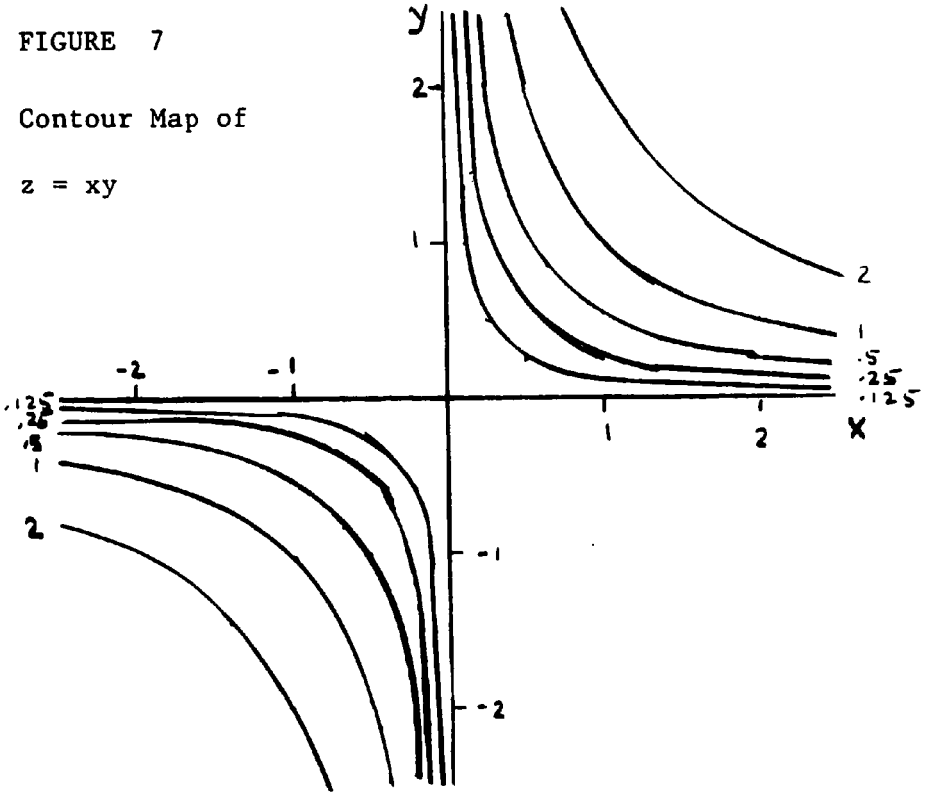
The ellipse of concentration of a bivariate distribution is defined mathematically as the region bounded by

$$(x - \mu_x,\ y - \mu_y) \begin{bmatrix} \sigma_{xx} & \sigma_{xy} \\ \sigma_{xy} & \sigma_{yy} \end{bmatrix}^{-1} \begin{pmatrix} X - \mu_x \\ Y - \mu_y \end{pmatrix} = 4 \tag{3.12}$$

FIGURE 7

Contour Map of

$z = xy$



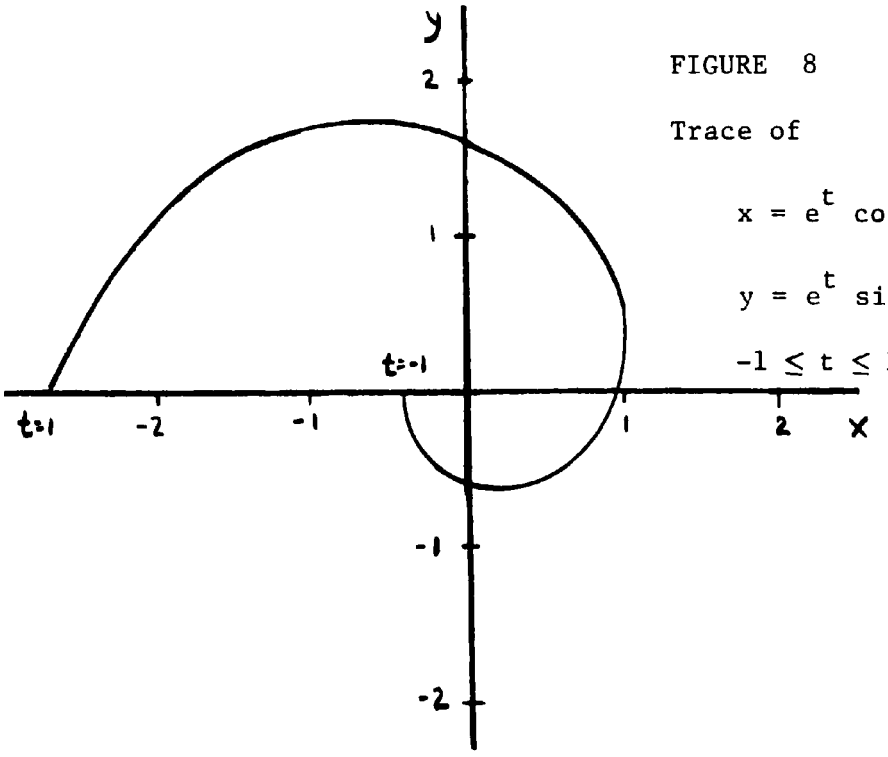


FIGURE 8

Trace of

$x = e^t \cos \pi t$

$y = e^t \sin \pi t$

$-1 \leq t \leq 1$

It can be used to represent a bivariate distribution by virtue of the fact that the first and second moments of a hypothetical distribution having a uniform density over the region given in (3.12) are identical to those of the bivariate distribution under consideration regardless of the density of the latter. By referring to Figure 9 which illustrates the ellipse of concentration for a certain bivariate distribution we see that the center of the ellipse is the point corresponding to the two means. The vertical and horizontal dimensions of the ellipse are proportional to σ_y and σ_x respectively. The standard deviations of the deviations from the regression lines are proportional to the distances from the center to the boundary in the directions parallel to the axes. The correlation coefficient is represented as the ratio of the lengths of two readily identified lines, i.e. from the points where the slopes of the boundary are zero and infinity perpendicular to one of the axes.

By performing the orthogonal transformation which rotates the ellipse counter clockwise through the angle θ, one obtains the principle components of the distribution whose standard deviations are proportional to the major and minor diameters of the ellipse of concentration. This transformation of the variables is frequently used to obtain uncorrelated (or if the distribution is bivariate normal, independent) variates.

Since many of the most important characteristics of a distribution can be discerned from the ellipse of concentration, it would appear to be a very useful entity for graphical presentation of information concerning bivariate distributions.

A computer program to assist in the preparation of such plots was prepared. The program (GRAFIX) prepares plots of contour maps, traces, and families of curves from functions defined by the user and scatter plots, strata plots, histograms, and ogives of sample data from user specified data files. The program is described briefly in the Appendix.

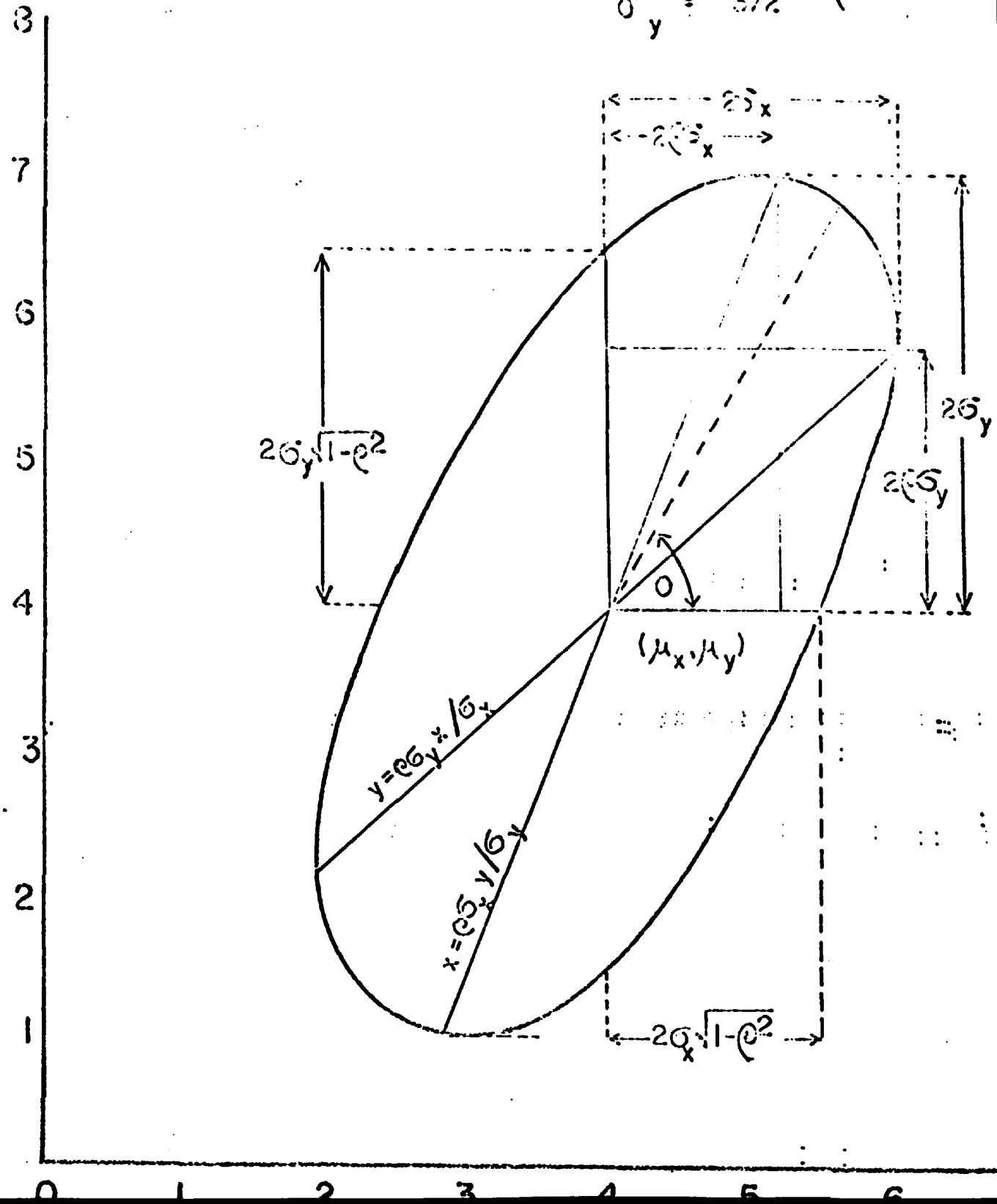
Figure 9

Ellipse of Concentration $\mu_x = 4$

$\mu_y = 4$

$\sigma_x = 1$

$\sigma_y = 3/2$ $\rho = .6$



CHAPTER 4

CONCLUSIONS

#4.1 Degenerate Estimates

4.1.1 Probability of nondegenerate estimates. Figures 10 through 12 show contour maps of the probability of observing nondegenerate values of the probit estimators as a function of μ_0 and σ_0 for the three fixed strategies studied.* There is a clear difference between the strategy with three stimulus levels and the other two, the former having an appreciably smaller probability of nondegenerate estimates for fixed μ_0 and σ_0. The difference between four and six level strategies is less pronounced. The former is favored by smaller values of σ_0 as we might expect, but for large values of σ_0 the latter is preferred while for values of μ_0 close to μ, the four level strategy appears slightly preferable.

Figures 13 through 16 and Tables 5 through 8 show the estimated probability in stochastic experiments and mixed experiments as functions of the stochastic strategy characteristics. Figure 17 compares the relationships of this probability to prior information for the fixed, stochastic and mixed strategies. To make the fixed strategy curves comparable to those of the other strategies we constructed synthetic curves which averaged the function over the same set of prior information parameters as used in the stochastic strategy.

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*(k = 3, n = 8; k = 4, n = 6; k = 6, n = 4)

FIG. 10

PROBABILITY OF NON-DEGENERATE ESTIMATES FROM A FIXED EXPERIMENT DESIGNED WITH 8 SUBJECTS AT EACH OF 3 STIMULUS LEVELS

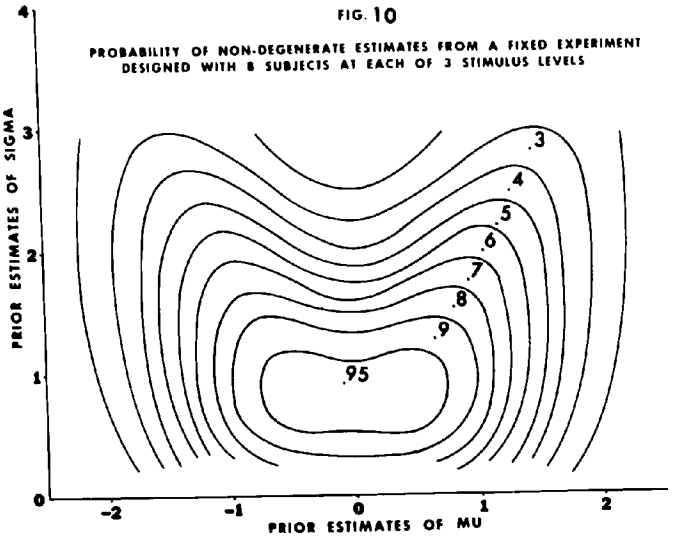


FIG. 11

PROBABILITY OF NON-DEGENERATE ESTIMATES FROM A FIXED EXPERIMENT DESIGNED WITH 6 SUBJECTS AT EACH OF 4 STIMULUS LEVELS

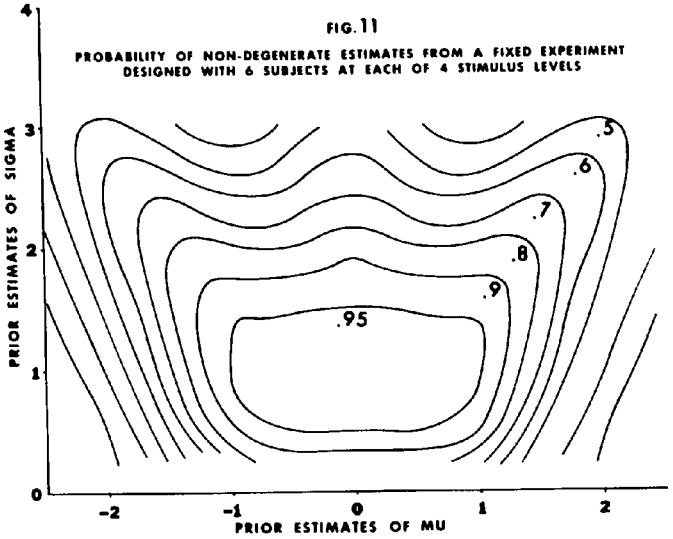


FIG. 12

PROBABILITY OF NON-DEGENERATE ESTIMATES FROM A FIXED EXPERIMENT DESIGNED WITH 4 SUBJECTS AT EACH OF 6 STIMULUS LEVELS

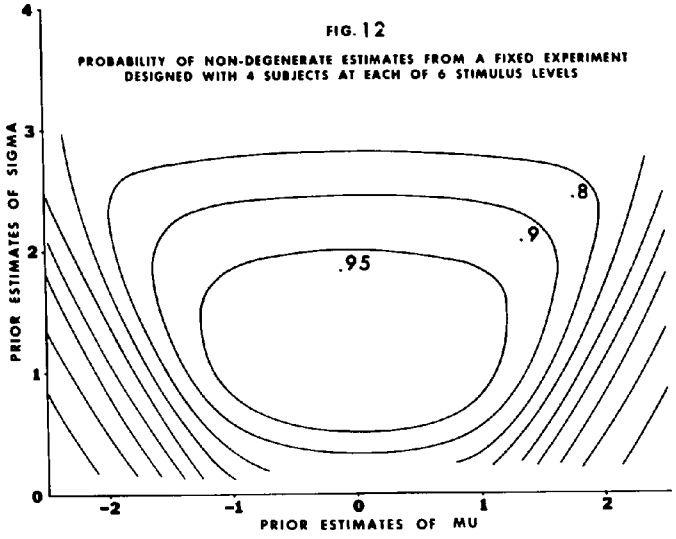


Table 5

Estimated Probability of Non-Degenerate Estimates in Stochastic Experiments

Cell Means

			Initial Stimulus				
			0	1	2	3	4
S	S	1/8	.990	.812	.990	.052	1.000
T	I	1/4	.916	.761	1.000	.925	.846
E	Z	1/2	1.000	.970	.635	.916	.248
P	E	1	.330	.674	.482	1.000	.825
		2	.102	1.000	.201	.140	.154

Mean Estimated Probability by Strategy Characteristic

Factor	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.668	.843	.662	.607	.615
Step size	.769	.890	.754	.662	.319
Stopping rule	.782	.553	.730	.329	1.000
Random start	.610	.675	.782	.686	.642
Grand mean	.679				

FIGURE 13

ESTIMATED PROBABILITY OF NON-DEGENERATE ESTIMATES UP AND DOWN EXPERIMENTS.

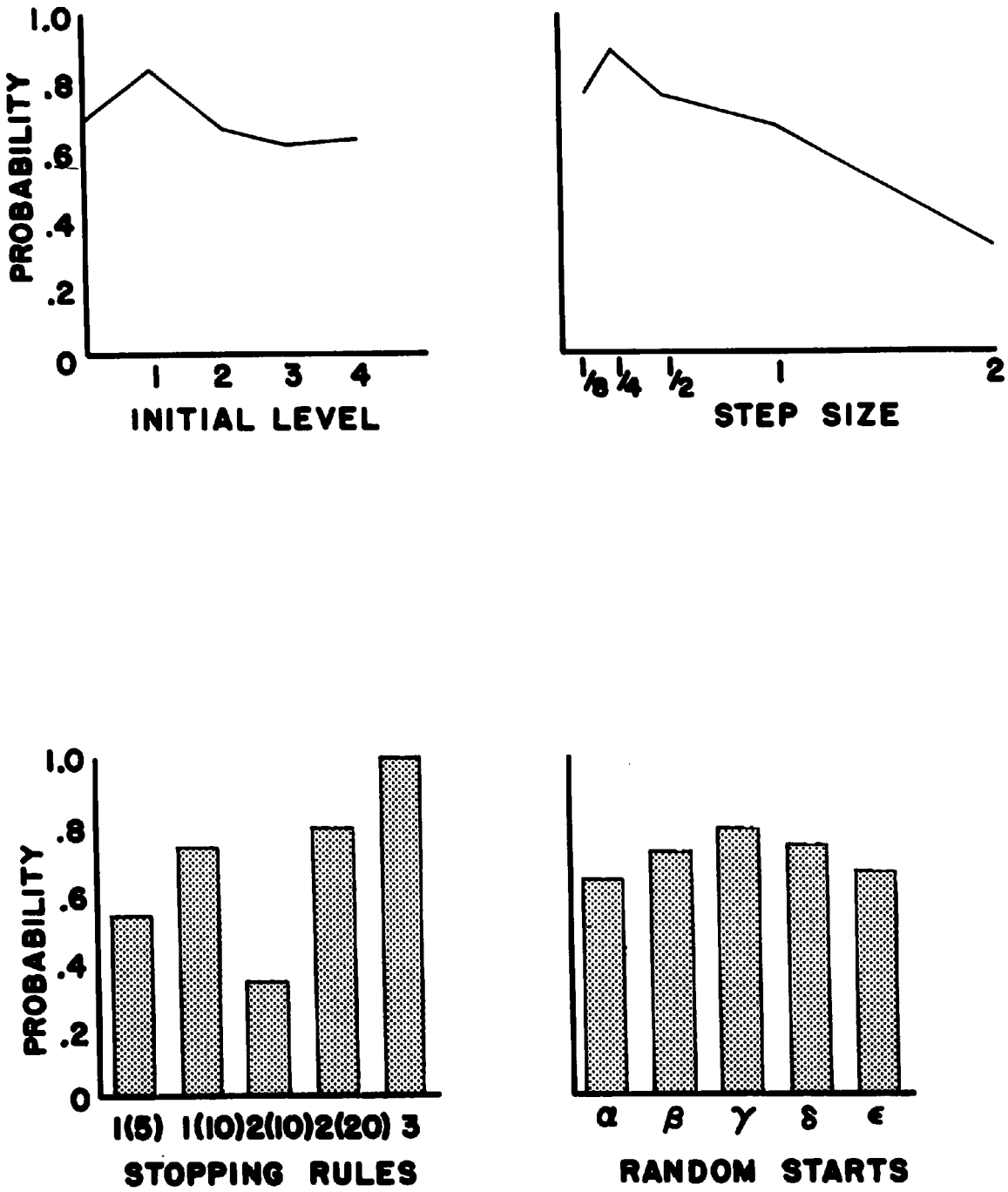


Table 6

Estimated Probability of Non-Degenerate Second Stage Estimates in Mixed Experiments, Conditional on Non-Degenerate First Stage Estimates

Second Stage - Eight subjects, three levels

First Stage - Spearman Karber Estimation

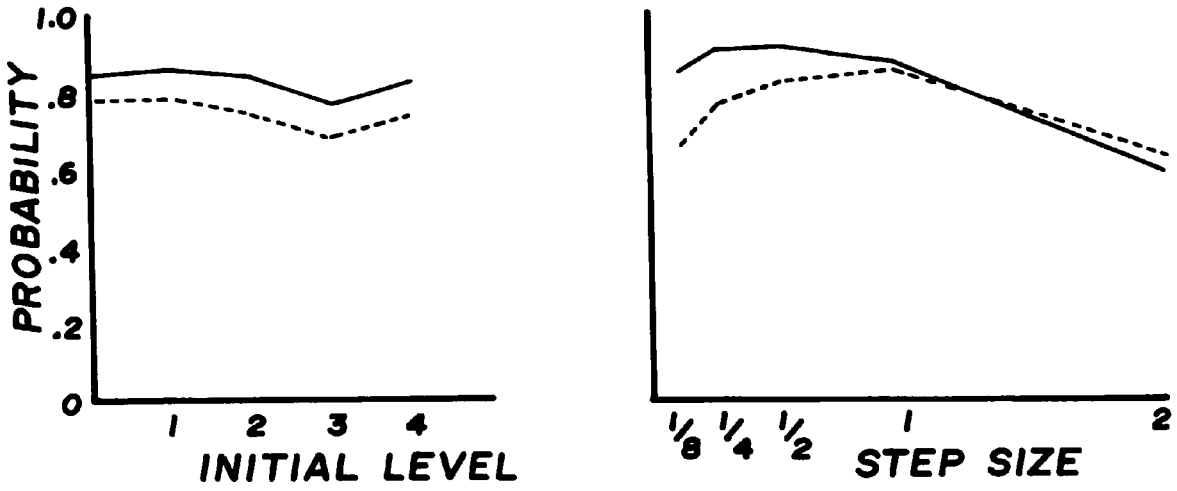
Factor	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.829	.875	.734	.619	.725
Step size	.627	.790	.857	.872	.632
Stopping rule	.838	.780	.839	.645	.681
Random start	.737	.806	.773	.678	.789
Grand mean	.757				

First Stage - Dixon-Mood Estimation

Factor	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.810	.751	.714	.559	.745
Step size	.579	.713	.822	.849	.609
Stopping rule	.793	.717	.793	.610	.662
Random start	.723	.760	.612	.587	.792
Grand mean	.715				

FIGURE 14

ESTIMATED PROBABILITY OF NON-DEGENERATE ESTIMATES MIXED EXPERIMENTS THREE LEVELS IN FIXED STAGE



UP AND DOWN STAGE ESTIMATORS

SPEARMAN-KARBER ——— ■

DIXON-MOOD ····· □

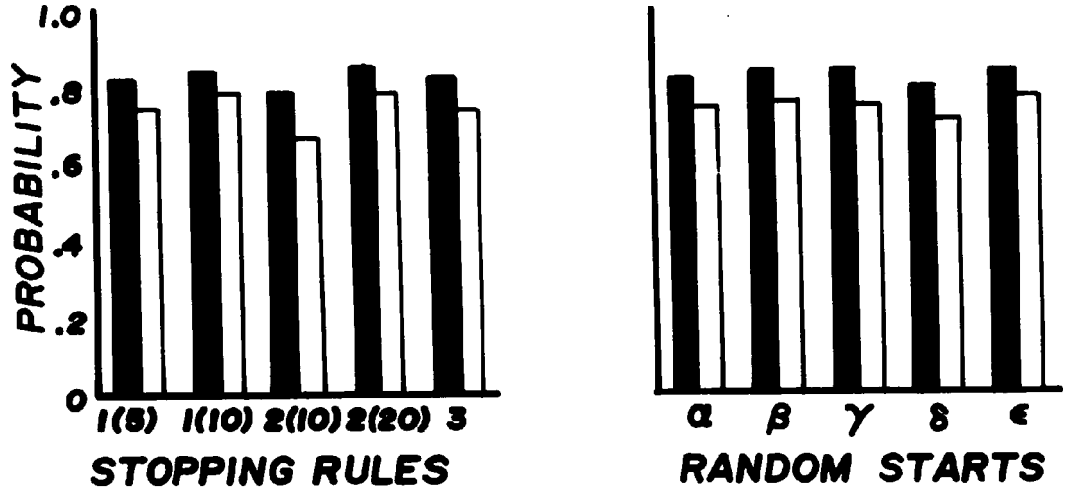


Table 7

Estimated Probability of Non-Degenerate Second Stage Estimates in Mixed Experiment, Conditional on Non-Degenerate First Stage Estimates

Second Stage - Six subjects, four levels

First Stage - Spearman-Karber Estimation

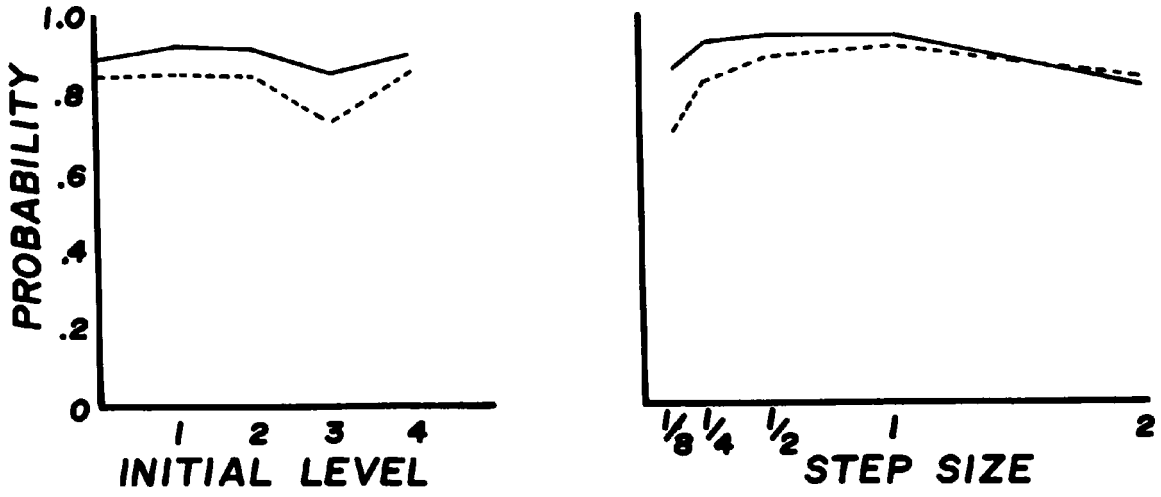
Factor	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.894	.939	.869	.728	.861
Step size	.731	.885	.920	.950	.804
Stopping rule	.903	.888	.908	.728	.863
Random start	.877	.891	.865	.754	.901
Grand mean	.858				

First Stage - Dixon-Mood Estimation

Factor	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.867	.857	.809	.705	.835
Step size	.668	.791	.886	.925	.805
Stopping rule	.852	.813	.858	.727	.826
Random start	.806	.839	.827	.732	.870
Grand mean	.815				

FIGURE 15

ESTIMATED PROBABILITY OF NON-DEGENERATE ESTIMATES MIXED EXPERIMENTS 4 LEVELS IN FIXED STAGE



UP AND DOWN STAGE ESTIMATORS

SPEARMAN-KARBER ——— ■

DIXON-MOOD - - - - - - - □

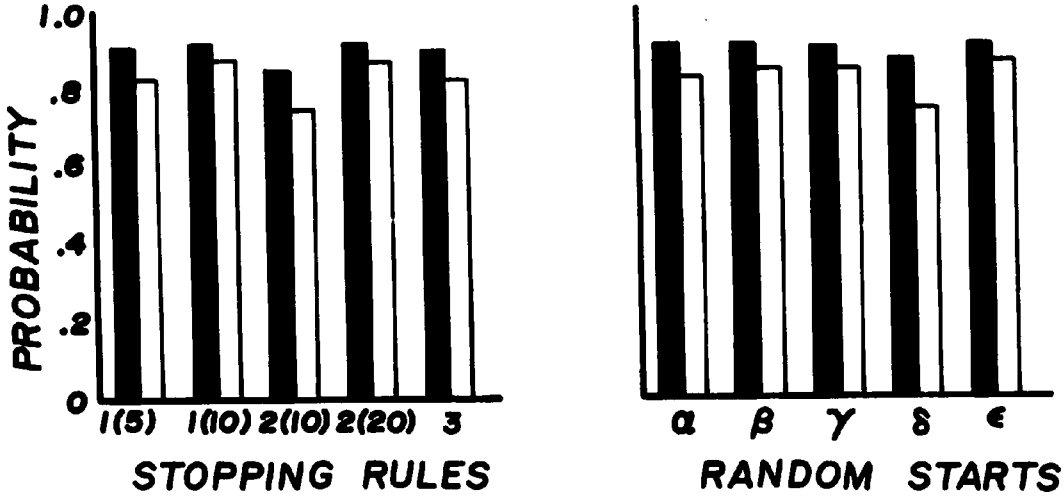


Table 8

Estimated Probability of Non-Degenerate Second Stage Estimates in Mixed Experiments, Conditional on Non-Degenerate First Stage Estimates

Second Stage - Four subjects, six levels

First Stage - Spearman-Karber Estimation

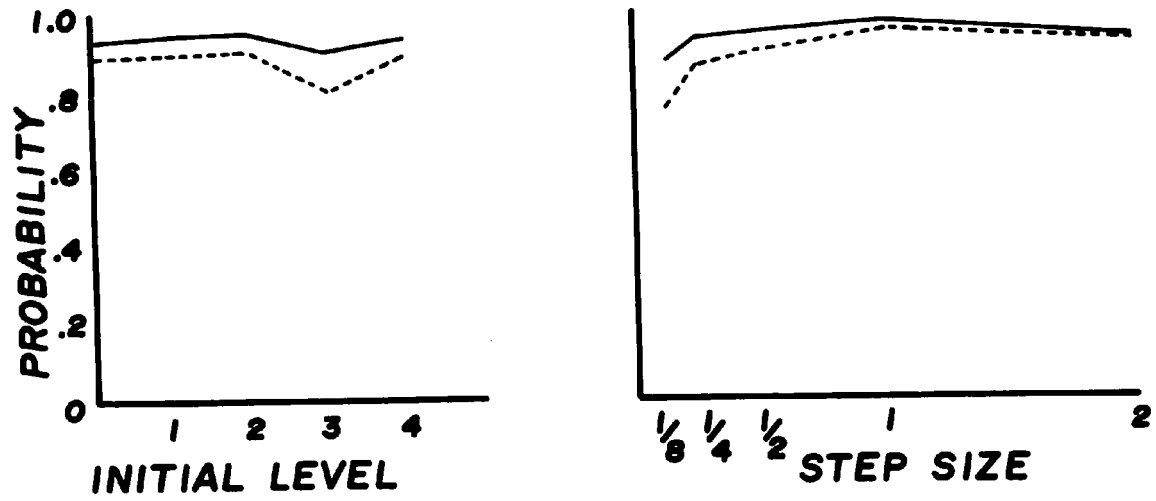
Factor	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.926	.949	.948	.902	.936
Step size	.872	.933	.957	.973	.926
Stopping rule	.944	.947	.926	.901	.941
Random start	.936	.944	.941	.905	.934
Grand mean	.932				

First Stage - Dixon-Mood Estimation

Factor	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.884	.902	.897	.795	.901
Step size	.741	.851	.914	.959	.915
Stopping rule	.897	.885	.909	.813	.876
Random start	.874	.895	.899	.806	.907
Grand mean	.876				

FIGURE 16

ESTIMATED PROBABILITY OF NON-DEGENERATE ESTIMATES MIXED EXPERIMENTS 6 LEVELS IN FIXED STAGE



UP AND DOWN STAGE ESTIMATORS

SPEARMAN-KARBER ——— ■

DIXON-MOOD ------- □

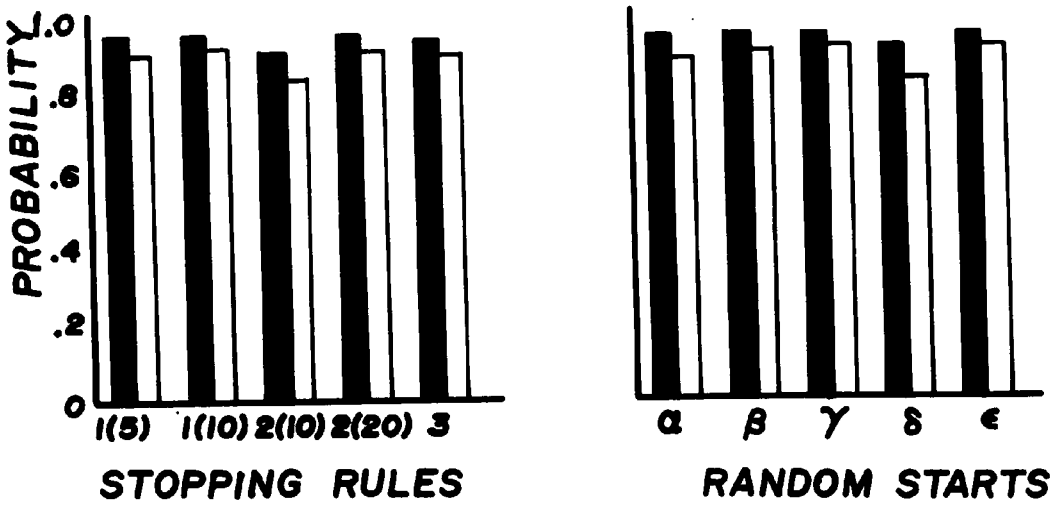
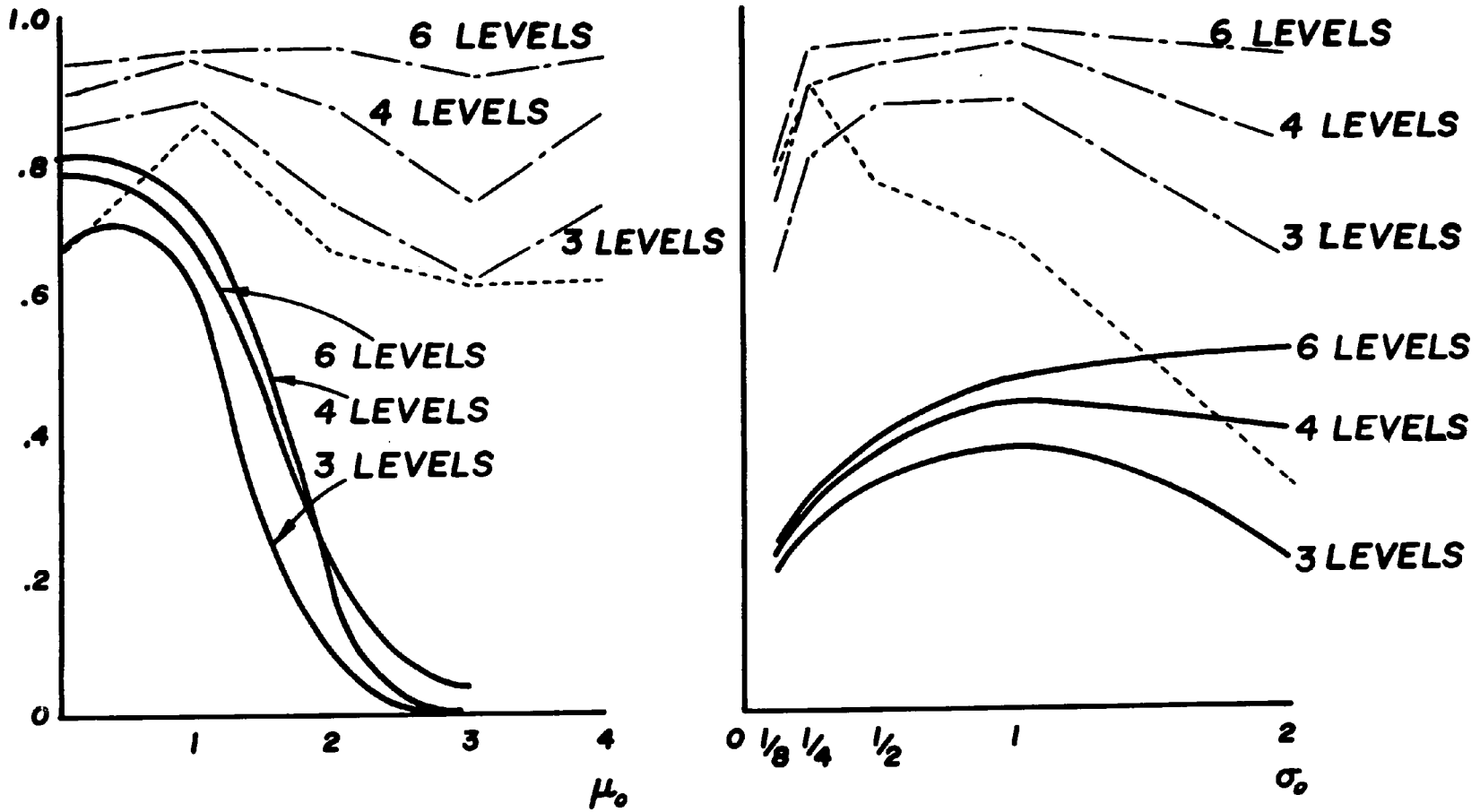


FIGURE 17

DEPENDENCE OF PROBABILITY OF NON-DEGENERATE ESTIMATES ON PRIOR ESTIMATES FOR SEVERAL STRATEGIES

FIXED —— (AVERAGED OVER PRIOR ESTIMATES OF μ OR σ)
STOCHASTIC ·····
MIXED —·— (SPEARMAN-KARBER ESTIMATION AT FIRST STAGE)



While the difference between the plots for stochastic and mixed strategies may be partially due to a larger number of subjects observed in the latter, the difference between the stochastic and fixed strategies is not so affected since the mean number of subjects in the stochastic experiments was of the same size or smaller than that for the fixed strategies. See Tables 30 and 31 on page 114 for the actual results.

The fixed experiment is clearly more strongly affected by the value of μ_0 while the stochastic experiment is the more strongly affected by σ_0. In all strategies a serious underestimate of σ can lead to increased probability of degenerate estimates, but the overall picture indicates that the mixed strategy with a second stage employing six stimulus levels provides a strategy where the probability of nondegenerate estimates is very nearly independent of prior information. Whether, for a fixed cost, this strategy actually guarantees a higher probability of nondegenerate estimates is still an open question since the costs of the strategies are not controlled sufficiently to make this comparison. In any case, it seems that in the absence of fairly substantial knowledge the mixed strategy is preferable to either of the others since the probability of nondegenerate estimates is less strongly dependent on μ_0 and σ_0. Although it is possible that the mixed experiments appear less affected by errors in the prior estimates simply because they had larger sample sizes, a bit of reflection indicates that the first few trials in an up and down experiment account for most of the effect on probability of nondegenerate estimates. Reference to Figures 10 through 12 show that the probability of nondegenerate estimates is less than .1 for any of the three fixed strategies. By using five subjects in an up and down trial and taking $\mu_0=x_4$ we are likely to attain a probability of nondegenerate estimate of approximately .8, at least an 8-fold increase. Clearly, subsequent up and down experimentation can do little but improve the precision and accuracy of the estimators.

4.1.2 Interpretation of degenerate estimates. From a relative frequency view of probability, the occurrence of degenerate estimates causes a disjuncture in the estimation procedure. The experimenter is faced with data which seem to contradict the model which he assumed. To obtain estimates consistent with his model he must resort to boundary solutions* to the likelihood equations. The most frequent reaction of experimenters seems to be that the experiment is valueless for precise estimation and

*i.e., solutions where one estimate lies on a boundary of the parameter space.

that a new experiment must be executed using whatever qualitative information can be salvaged.

The experimenter who holds a subjective probability view has the advantage of a formal mechanism for modifying his quantitative opinions concerning the parameters of the tolerance distribution. As long as he has not assigned zero probability to any set of positive measure of the unrestricted parameter space, he can merely use Bayes theorem to obtain a posterior probability distribution for μ and σ. Of course his assessment of his subjective probability distribution a priori usually is a rather formidable task and therefore should perhaps be considered as a cost of experimentation in this problem.

4.1.3 Recommendations. In line with the view that foresight is preferable to hindsight, the first recommendation we would make is obvious. The experimenter should select a strategy which is going to give him a reasonably small probability of degenerate estimates for a wide range of errors in prior information. The surer he is of the value of σ, the more reasonable a purely stochastic strategy becomes. If on the other hand, he is reasonably sure of μ he might decide to use a fixed strategy with a moderately large number of stimulus levels and a wide range of levels to protect himself against a serious underestimate of σ.

If a stochastic strategy is chosen, the stopping rule should <u>not</u> be based solely on the number of subjects used since a sufficiently large error in μ and an underestimate of σ will make it almost certain that he will obtain degenerate estimates. We feel that stopping rule 3 is to be recommended since it insures that nondegenerate estimates will be obtained. The total cost of the experiment then becomes a function of the

accuracy of the prior information. This is, perhaps, the manner in which one would prefer to pay for his lack of knowledge.

#4.2 Fixed Strategies: Probit Estimation Versus Spearman-Karber Estimation

Figures 18 through 21 show ellipses of concentration for the joint distribution of the probit and Spearman-Karber estimators of μ in the fixed strategy with eight subjects at each of three levels and equally spaced levels centered at μ_o and extending σ_o units in either direction for selected values of μ_o and σ_o. Several conclusions can be drawn from these graphs.

First note that the dashed lines are the traces of the means of the two estimators. Since they lie completely above the 45 degree line we see that the probit estimator is less biased than the Spearman-Karber for those values of μ_o and σ_o studied.

Since the major diameters of the ellipses become more nearly parallel to the axis corresponding to the probit estimator as σ_o decreases, we see that for fixed μ_o, the Spearman-Karber estimator becomes less variable than the probit estimator when σ_o is small.

Figures 22 through 27 bear on the choice of the fixed strategy parameters. From Figure 23 we see that a large number of levels favors the Spearman-Karber estimator by decreasing the variance. This is in accord with Brown's findings [24],[25],[26],[27] that the minimum variance of the Spearman-Karber estimator occurs when the number of levels equals the number of subjects and each subject is thus tested at a different level. Conversely, the probit estimator has its smallest variance when all the subjects are tested at the mean of the tolerance distribution, a rather

Figure 18

ELLIPSES OF CONCENTRATION

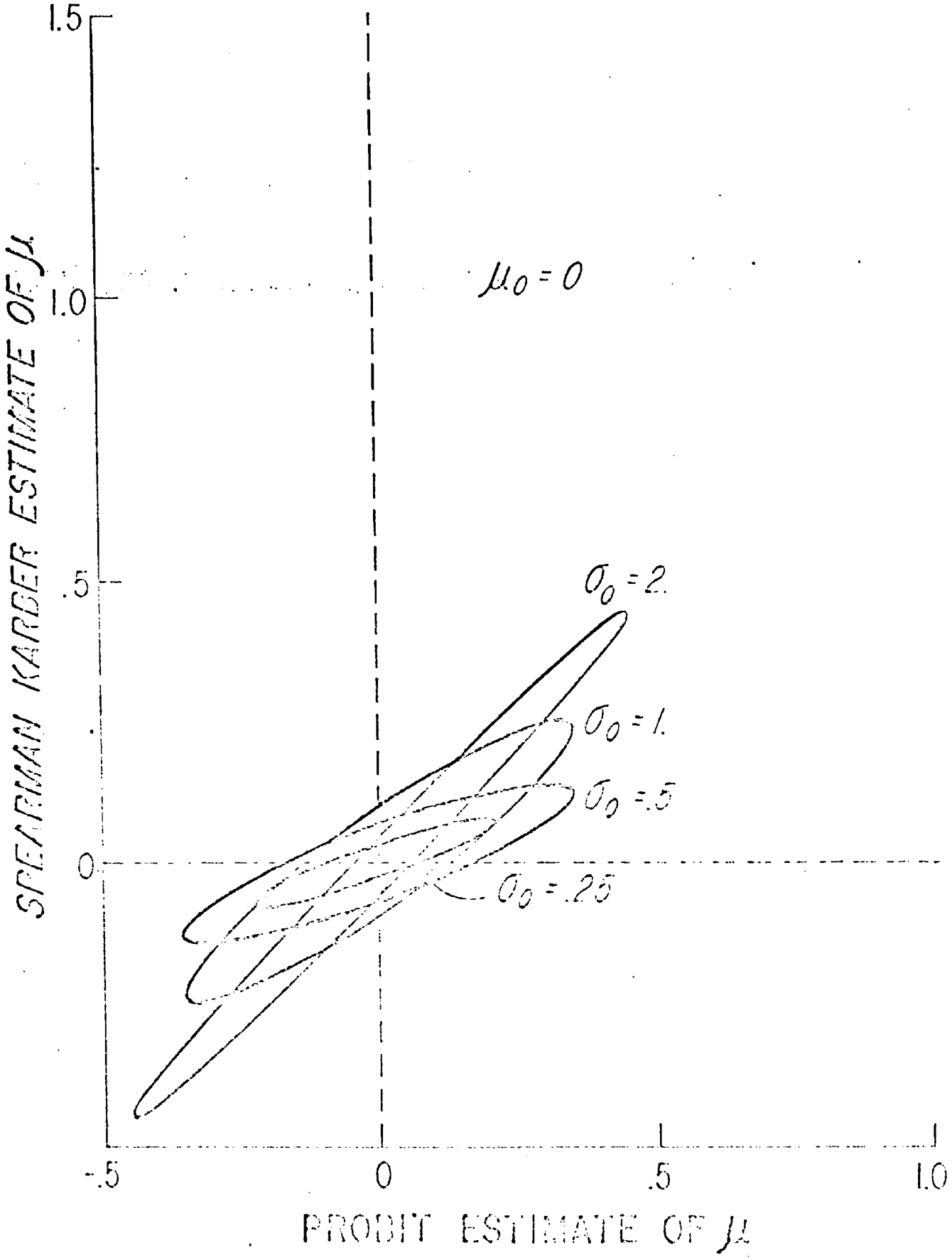


Figure 19
ELLIPSES OF CONCENTRATION

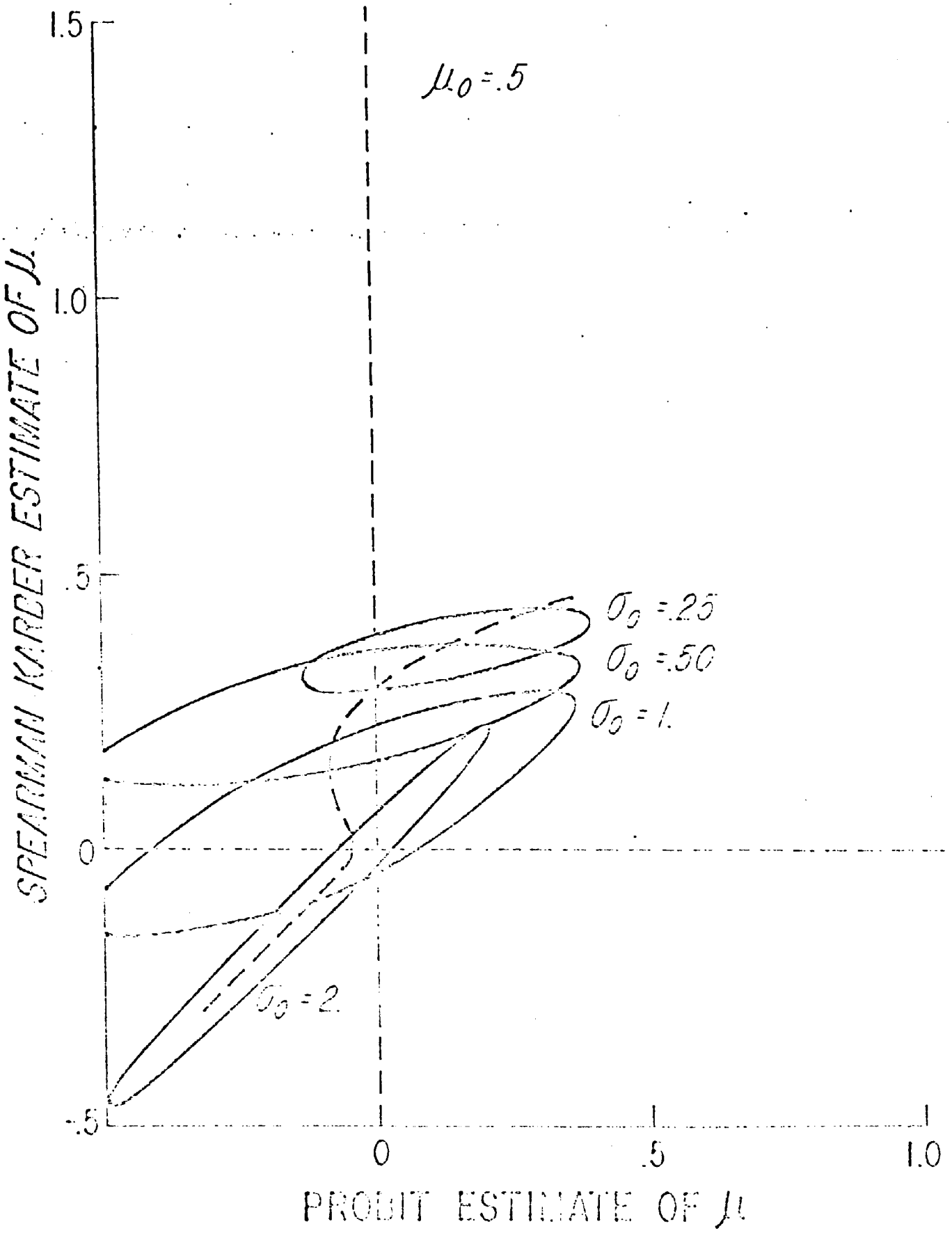


Figure 20

ELLIPSES OF CONCENTRATION

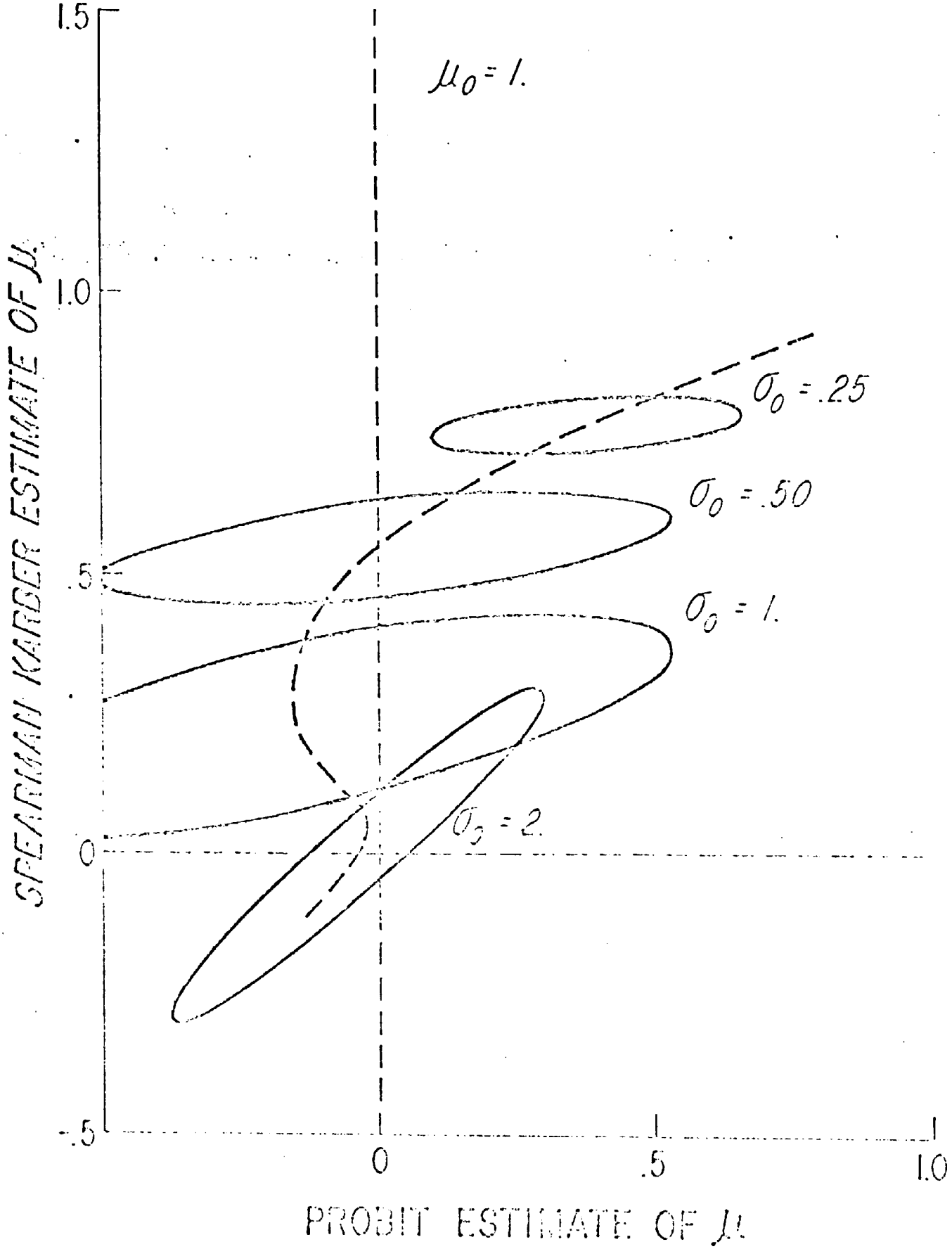


Figure 21

ELLIPSES OF CONCENTRATION

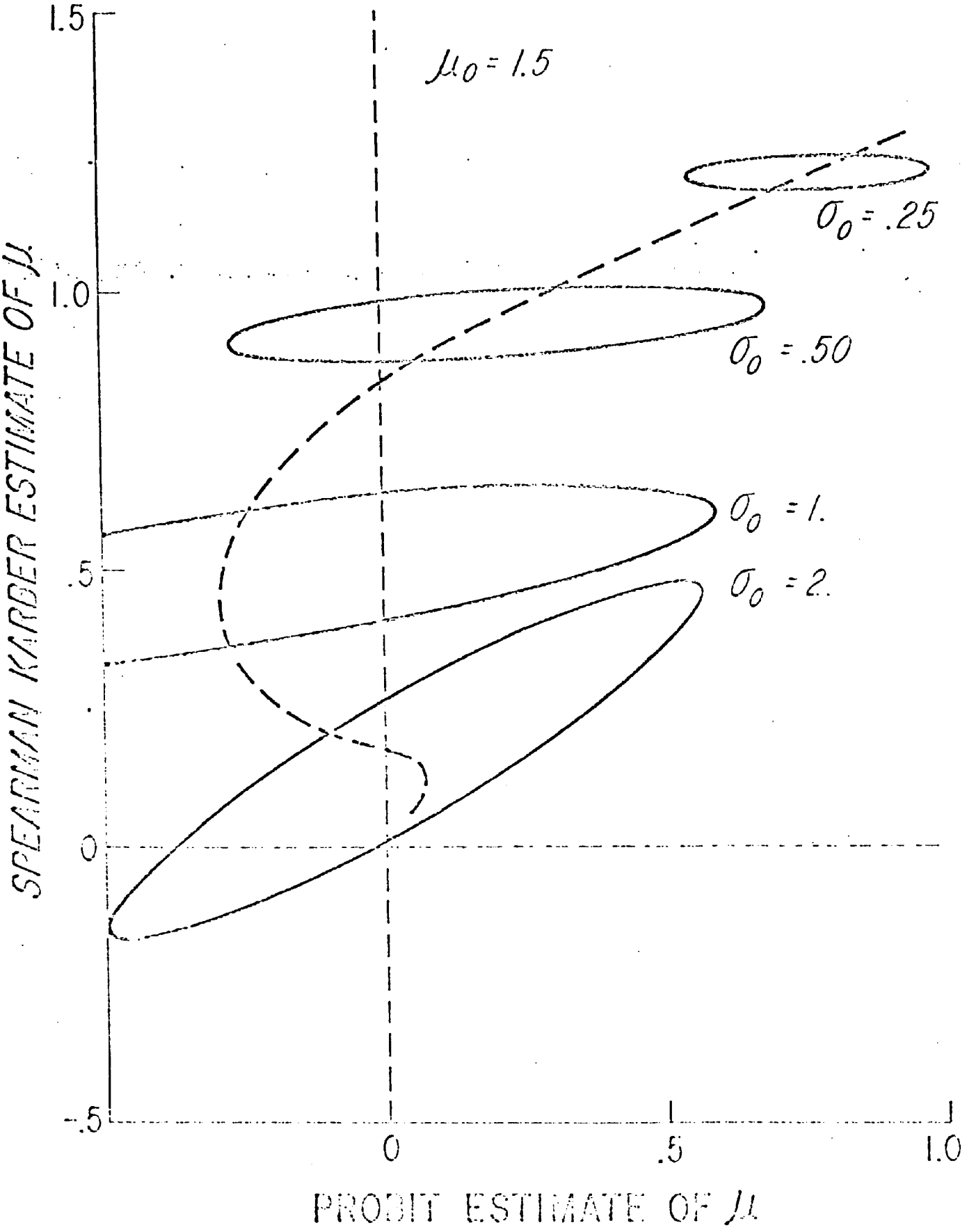
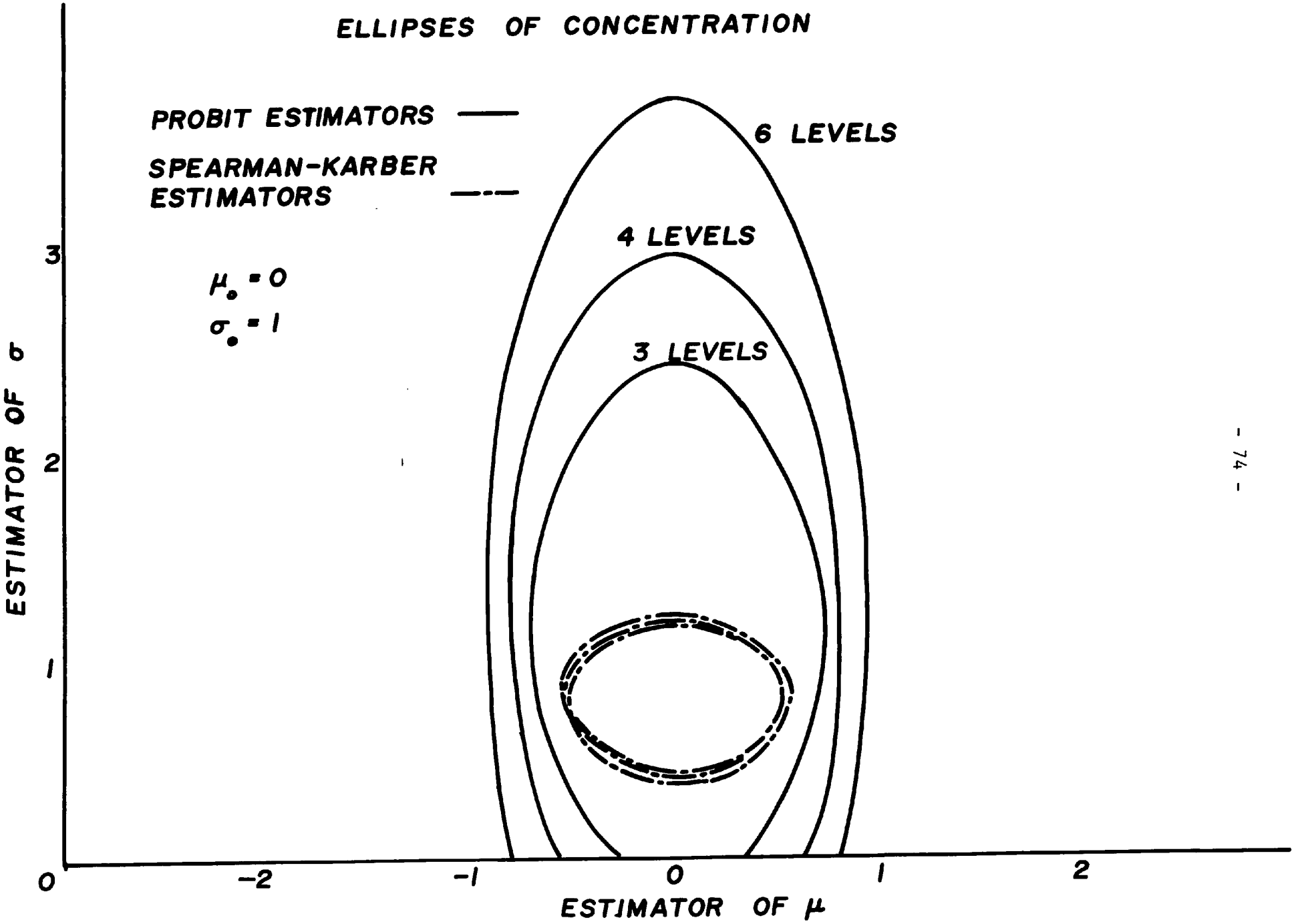


FIGURE 2


ELLIPSES OF CONCENTRATION
PROBIT ESTIMATORS
SPEARMAN-KARBER ESTIMATORS
$\mu_o = 0$
$\sigma_o = 1$
6 LEVELS
4 LEVELS
3 LEVELS
ESTIMATOR OF σ
ESTIMATOR OF μ
0
1
2
3
-2
-1
0
1
2

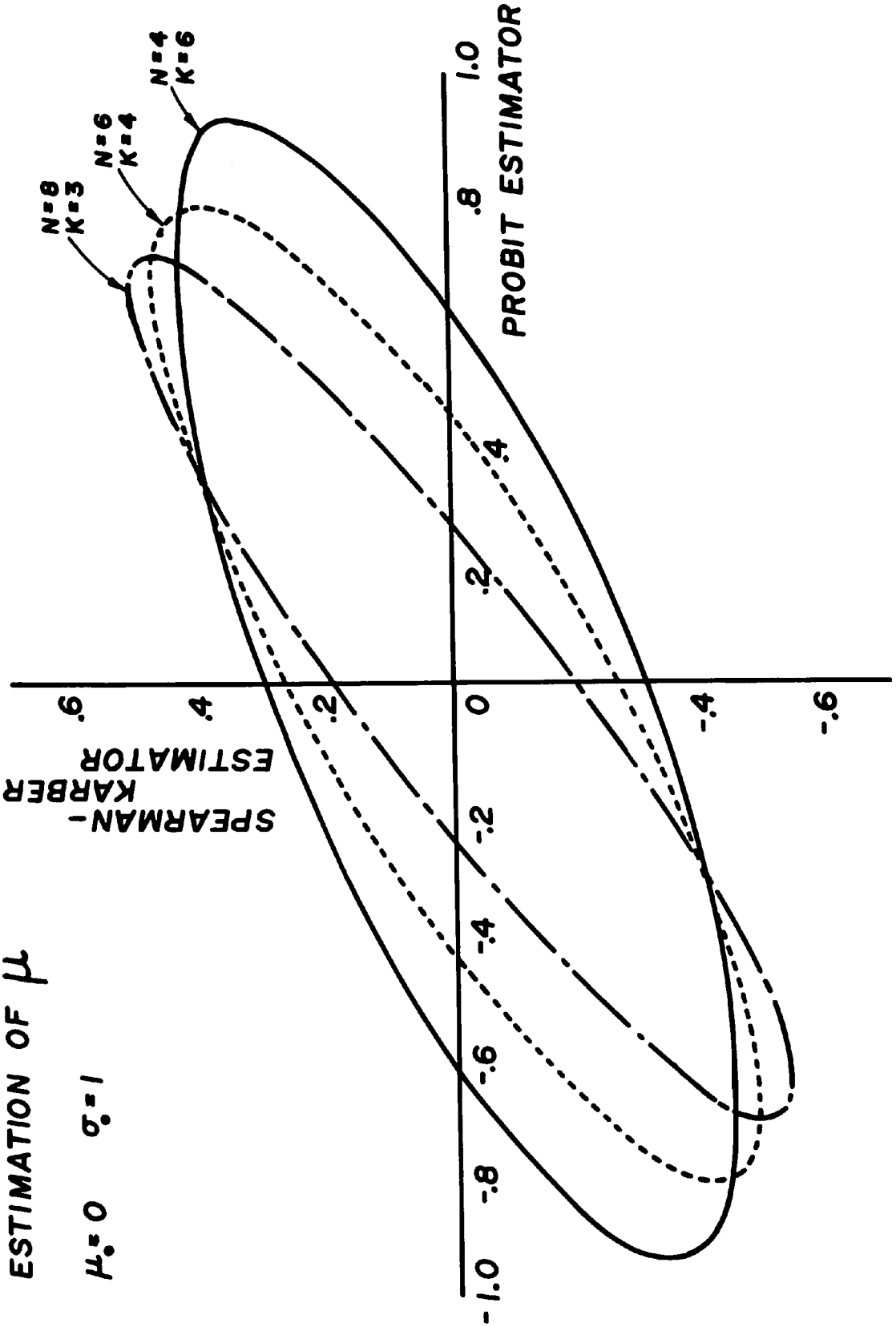


FIGURE 23
COMPARISON OF THREE FIXED STRATEGIES
ESTIMATION OF μ

$\mu_0 = 0 \quad \sigma_0 = 1$

Figure 24

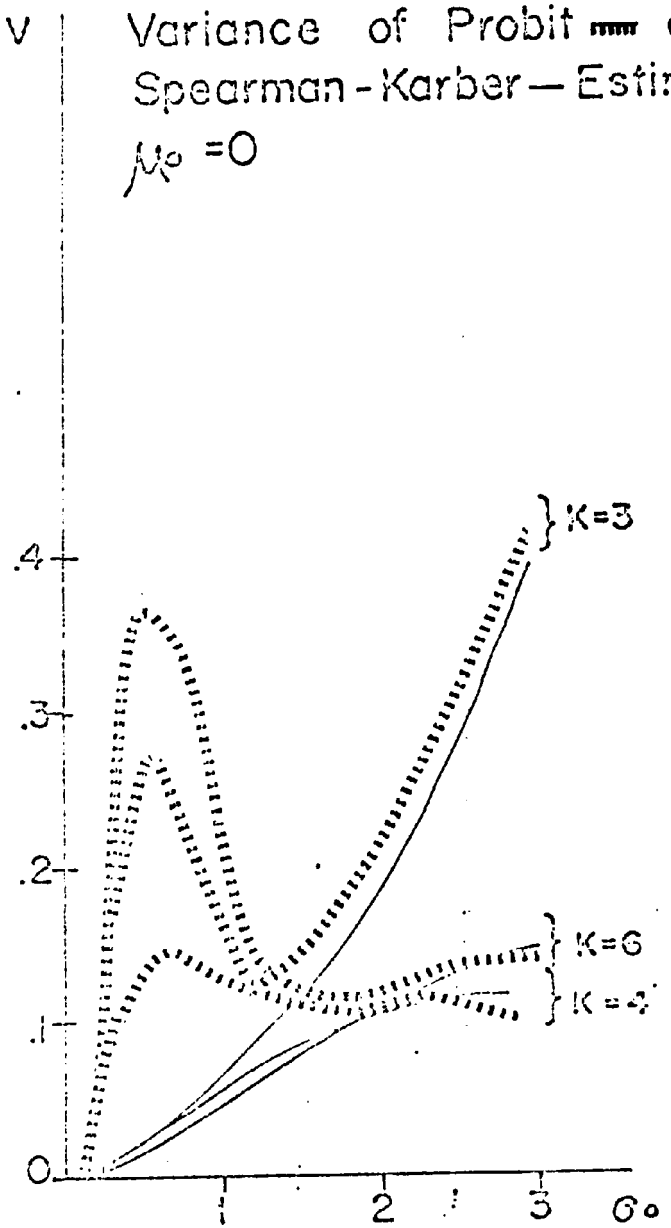
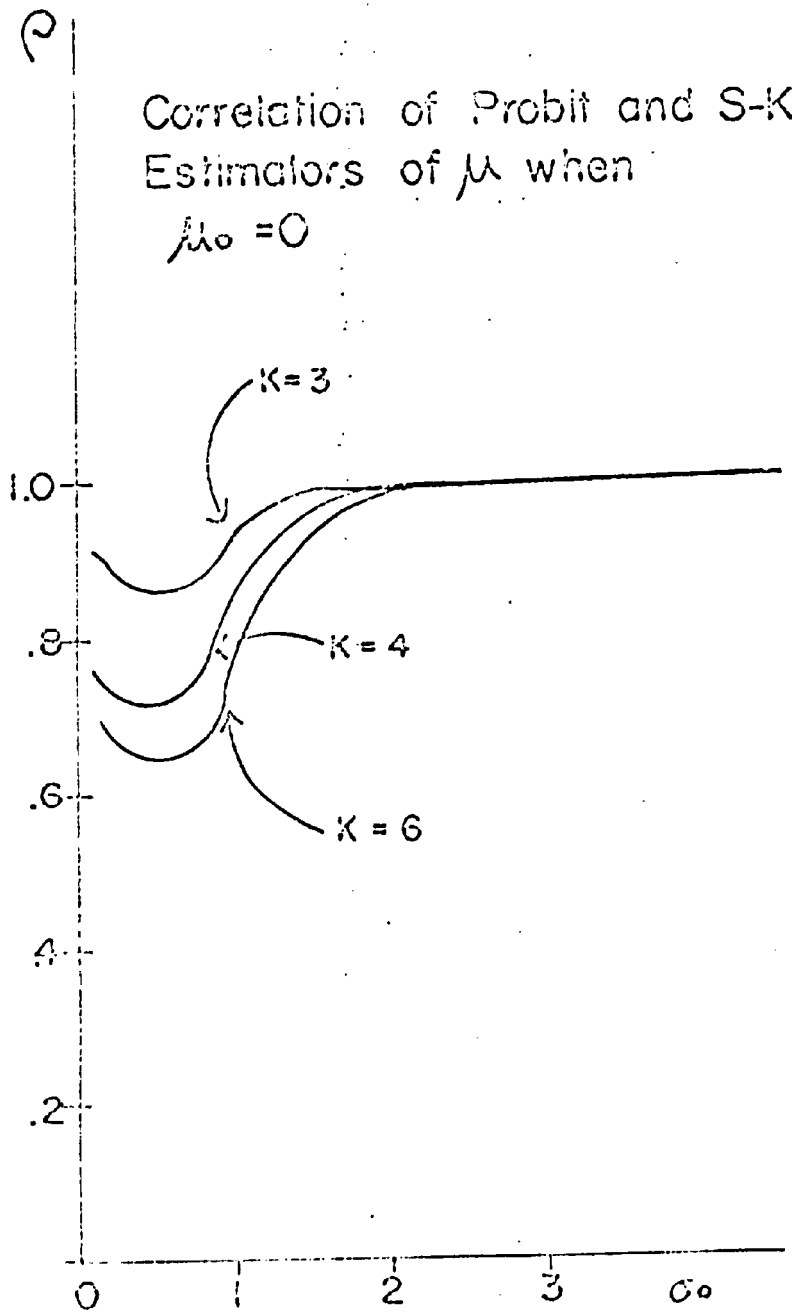


Figure 25



uninviting situation since the probability of guessing the mean exactly is infinitesimal.

From Figure 24 we confirm the fact that the variances of the two estimators behave rather differently as σ_0 is changed. Whereas the Spearman-Karber estimator has a variance which increases nearly monotonically with σ_0, the probit estimator's variance has a curious peak near $\sigma_0 = 1/2$. Thus if one were unlucky enough to guess σ too low by a factor of two, his estimator would become much more variable than might otherwise occur. The local minimum of the variance of the probit estimator in the range of σ_0 from one to two suggests that a nearly optimum fixed strategy would have a range of stimulus levels extending from $\mu_0 - 1.5\sigma_0$ to $\mu_0 + 1.5\sigma_0$ and that the prior estimate of σ_0 should err on the high end of the scale.

Figure 25 suggests that the correlation between the two estimators approaches one as σ_0 increases. Thus in the limit we would have

$$(4.1)\quad \hat{\mu}_p \rightarrow \mathcal{E}(\hat{\mu}_p) + \left(\frac{V(\hat{\mu}_p)}{V(\hat{\mu}_{sk})}\right)^{\frac{1}{2}} (\hat{\mu}_{sk} - \mathcal{E}(\hat{\mu}_{sk})) \quad \text{as} \quad \sigma_0 \rightarrow \infty$$

From Figure 24 we tentatively conclude that the ratio of variances tends to one and from Figures 18 through 22 it appears that the expectations tend to be equal as σ_0 increases. Thus for large values of σ_0, it would seem that the probit and Spearman-Karber estimators are nearly identical. Unfortunately, this fact will be of little assistance since as σ_0 increases the probability of a nondegenerate sample point tends to zero as was seen in section 4.1.

Figures 26 and 27 show the expectations and standard deviations of the estimators of σ. Although the Spearman-Karber estimator is biased,

Figure 26

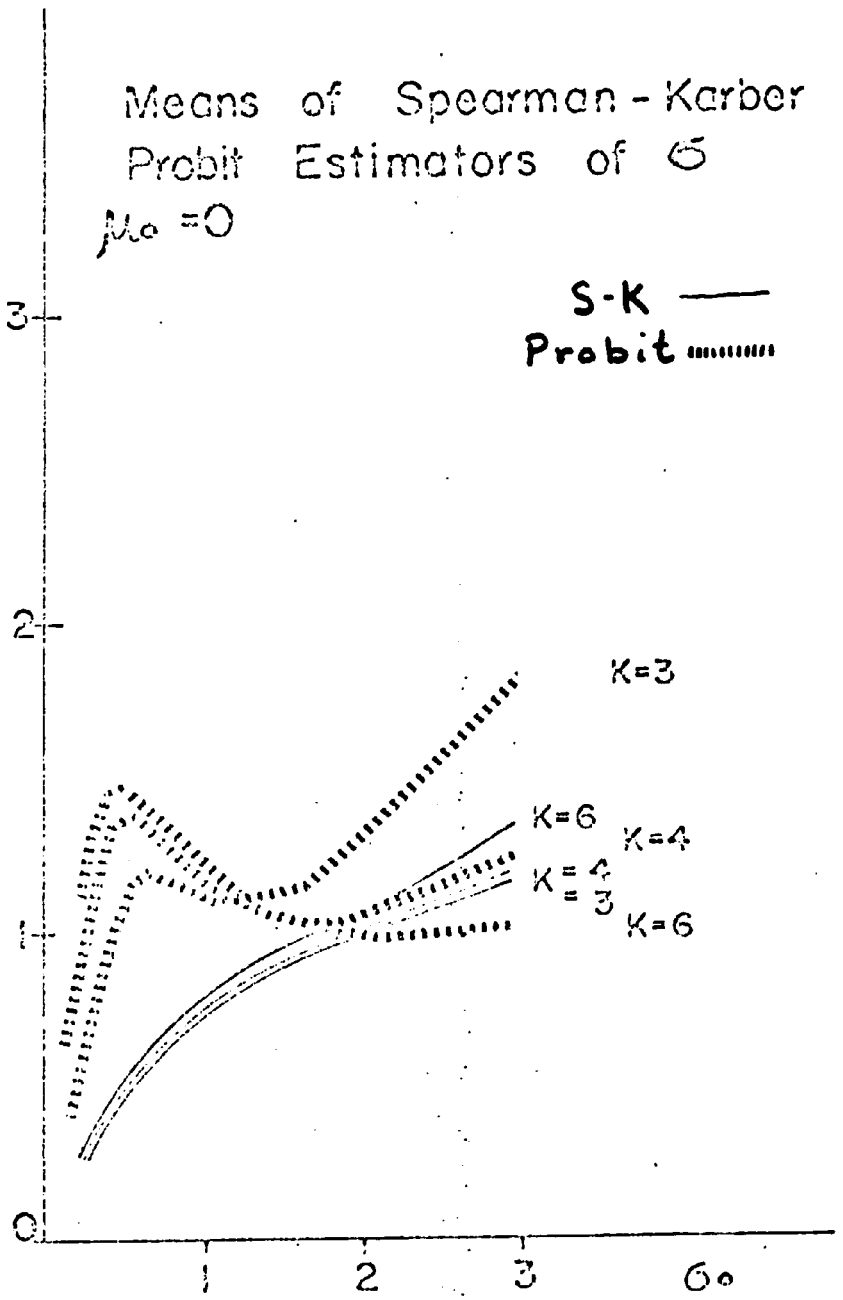
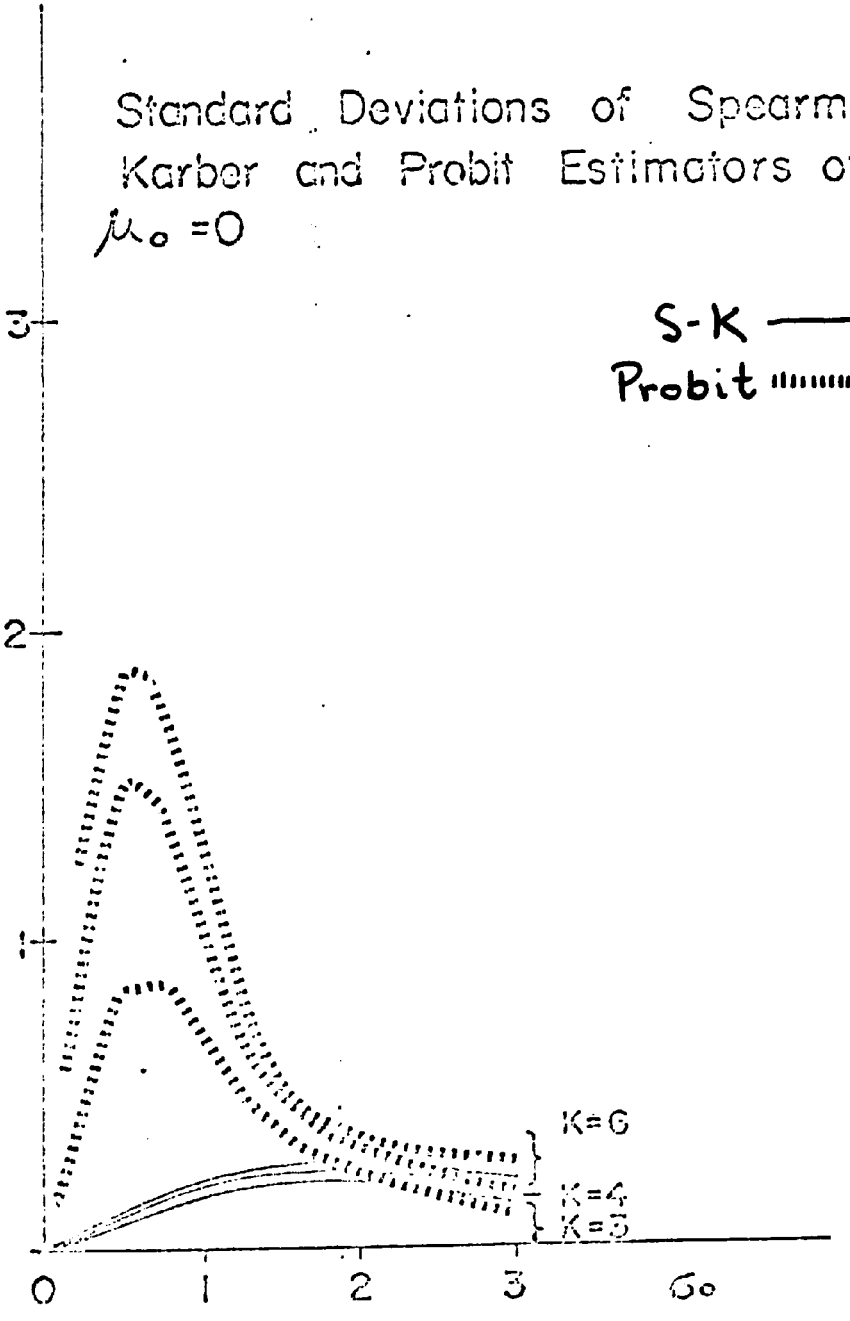


Figure 27



the regularity of the relationship between the expectation and σ_o, suggests that it might be possible to obtain a reasonable bias correction formula. Clearly the variability of the probit estimator makes it inferior in that respect although the bias correction for $\hat{\sigma}_{SK}$ might increase its variance.

Figures 28 through 31 show contour maps of the bias of the estimators of μ and σ to facilitate further comparisons. On the whole we consider that the additional computation required to obtain the probit estimators is not justified relative to the Spearman-Karber estimators.

The results in the literature [23],[104],[35] do not contradict ours, but give the impression that the differences between Spearman-Karber and probit estimation are much smaller than we have shown. This is due to attempts to summarize the differences in a single attribute, either the mean squared error or Bross's "worth." The differences we have seen are in both bias and sampling variance and are thus obscured by any simple description.

The extremely large variances of the probit estimators can be partially understood by reference to Figure 32. The points representing the most extreme values of the estimators in each method of estimation were connected with a smooth curve to indicate the "effective sample spaces" of the estimators for the strategy with three levels. While the very extreme values for the probit estimators have very small probabilities, the same sample points give rise to much less extreme values of the Spearman-Karber estimators. An additional methodological question arises when one realizes that much of the previous work has ignored sample points with small probabilities (or extreme values of the estimators) or has been based on Monte Carlo simulations in which such extreme values might well not appear since their probabilities are small. This consideration casts

Figure 28

Contours of Bias of Spearman-Karber Estimator of μ

Four Subjects at Six Levels

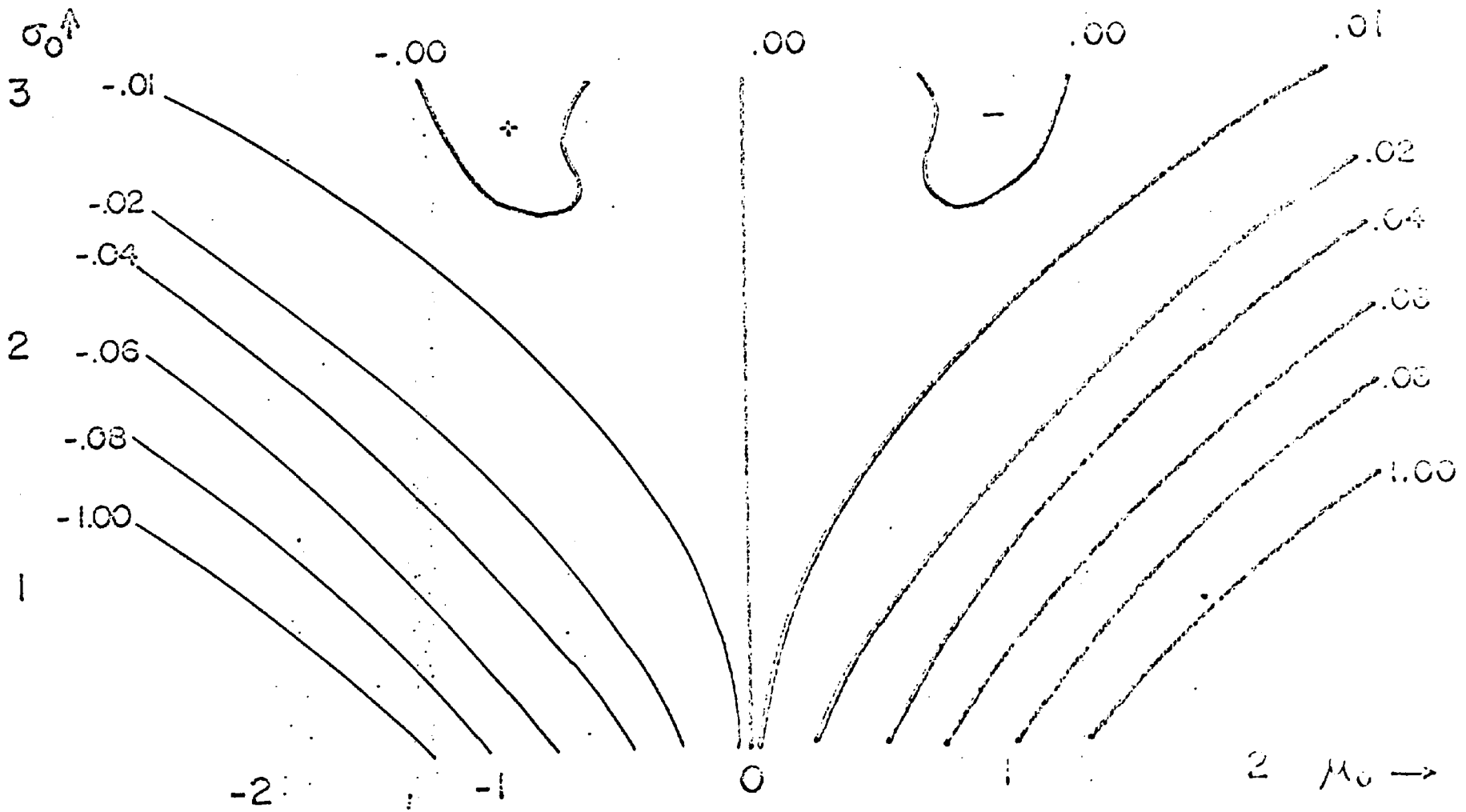


FIGURE 29

CONTOURS OF THE BIAS OF THE PROBIT ESTIMATOR OF μ

4 SUBJECTS AT EACH OF 6 LEVELS

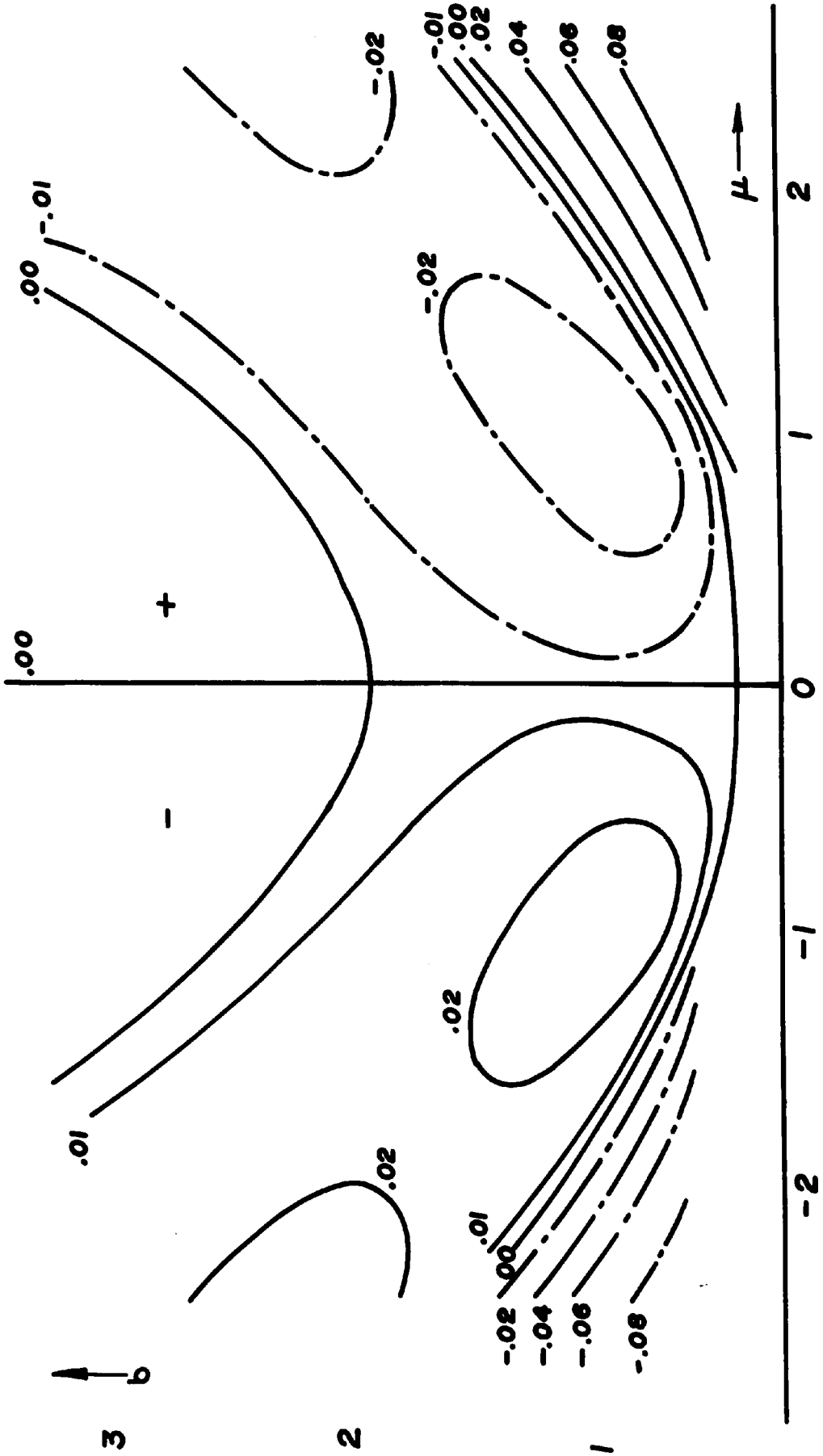


Figure 30

Bias of Spearman-Karber Estimator of σ; Four Subjects at Six Levels

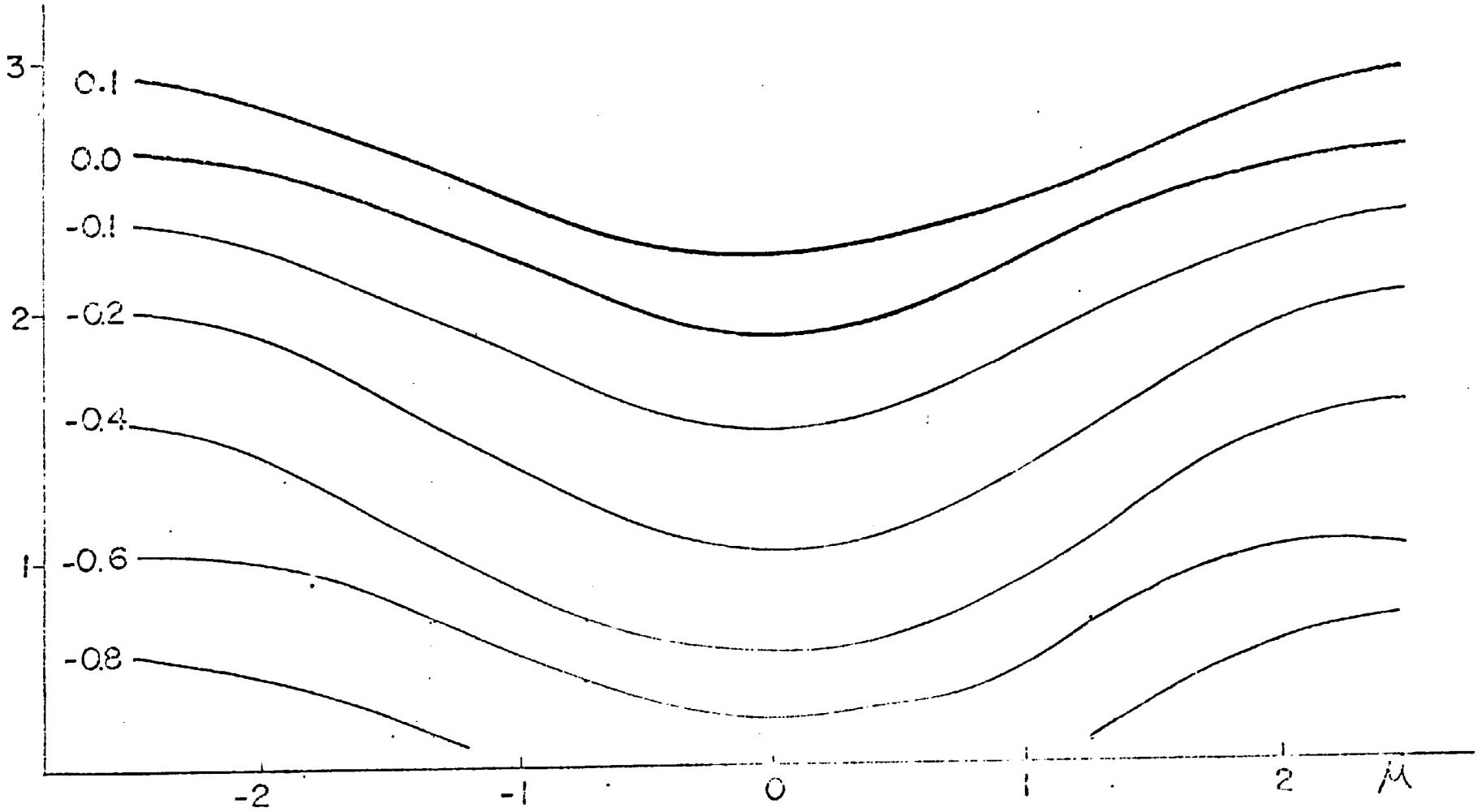


FIGURE 31

BIAS OF PROBIT ESTIMATOR OF σ

4 SUBJECTS AT EACH OF 6 LEVELS

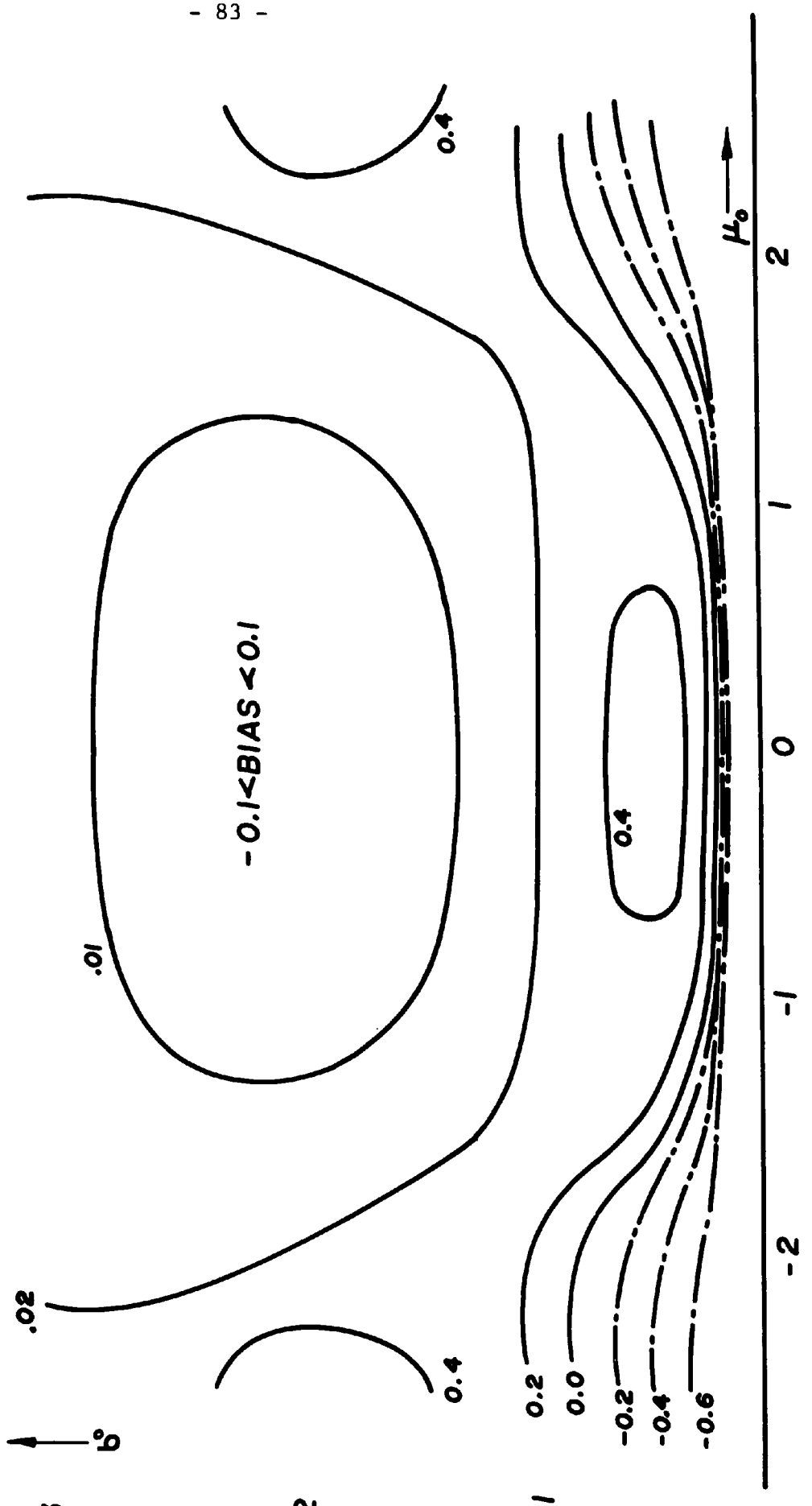
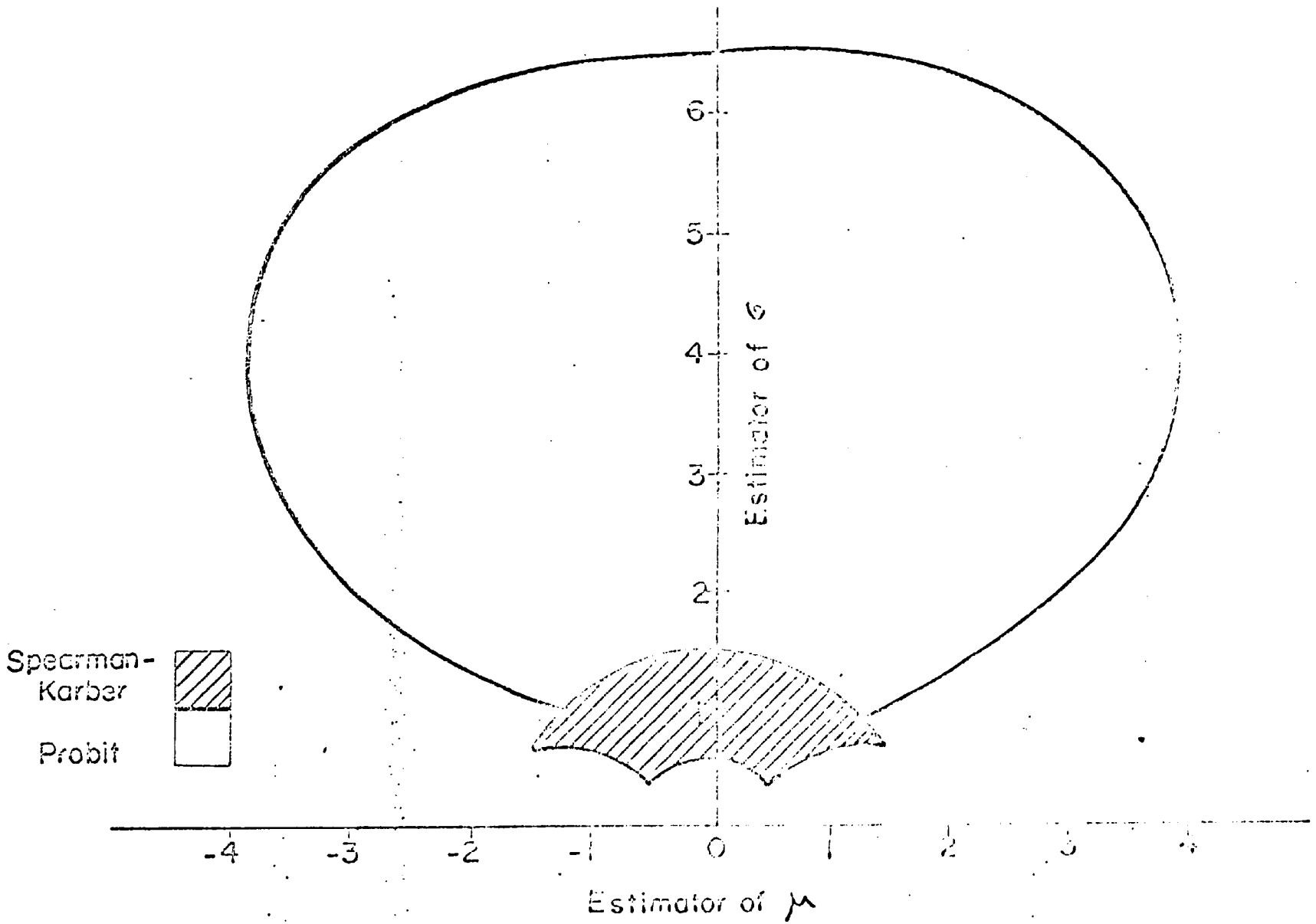


Figure 32 BOUNDARIES OF THE EFFECTIVE SAMPLE SPACES FOR THE PROBIT AND SPEARMAN-KARBER ESTIMATORS



severe doubt on the advisability of truncation of sample spaces or simple Monte Carlo investigations.

#4.3 Stochastic Strategies: Spearman-Karber Versus Dixon-Mood Estimation

In the discussion of the stochastic strategy results we will have to introduce some symbolic notation in order to eliminate possible confusion due to the necessity to use both the term "estimator" and the term "estimate" in the same phrase. We will denote the Spearman-Karber and the Dixon-Mood estimators of the parameters of the tolerance distribution by the Greek symbol representing the parameter (i.e., μ or σ) with a carat to indicate an estimation of the parameter and with subscripts (SK or DM) to indicate the method of estimation. Thus we have $\hat{\sigma}_{DM}$ denoting the Dixon-Mood estimator of the standard deviation of the tolerance distribution as one example. We will denote the expectation and variance of an estimator θ by $\mathcal{E}(\theta)$ and $V(\theta)$ respectively. To indicate the estimates of these moments of the distribution of an estimator from our simulated experiments, we will use a carat over the $\mathcal{E}$ or V. Hence we have the following:

$\hat{\mu}_{SK}$	Spearman-Karber estimator of μ
$\mathcal{E}(\hat{\mu}_{SK})$	theoretical mean of the sampling distribution of $\hat{\mu}_{SK}$
$\hat{\mathcal{E}}(\hat{\mu}_{SK})$	simulation estimate of $\mathcal{E}(\hat{\mu}_{SK})$

and similarly for other estimators.

The stopping rules used will be denoted as follows:

B	1(5)	continue until end of fifth run of like responses
C	1(10)	continue until end of tenth run of like responses
D	2(10)	continue until end of first run after ten trials
A	2(20)	continue until end of first run after twenty trials
E	3	continue until largest "nonlethal" level exceeds the smallest lethal level.

The random starts will be denoted by the Greek letters α through ϵ.

First let us consider the comparison of the estimators of μ with respect to bias. Table 9 shows the empirical F ratios for testing the hypothesis that the expectations of the two estimators are equal by μ_0 and σ_0. Since both estimators have symmetric distributions when μ_c is zero, it is not surprising that the hypothesis cannot be rejected when that is the case. Indeed we would be very suspicious if this hypothesis could be rejected when the experimenter is assumed to know μ exactly.

Table 10 gives the empirical F ratios for testing the hypothesis that $\mathcal{E}(\hat{\mu}_{SK})$ is zero. Again we would be concerned if this hypothesis could be rejected when μ_0 is zero, but no such evidence is found.

Table 11 shows the difference of the absolute values of the sample means of the estimators as functions of μ_0 and σ_0. Note the preponderance of negative values, suggesting that the Dixon-Mood estimator is frequently more biased than the Spearman-Karber estimator. Table 12 shows the results of the tests of the hypotheses mentioned above and the sign of $\mathcal{E}(\hat{\mu}_{SK}) - \mathcal{E}(\hat{\mu}_{DM})$ in coded form. The joint frequencies of the hypotheses are of interest. Table 13 gives a 2 x 2 contingency table for the results of testing Ho: $\mathcal{E}(\hat{\mu}_{SK}) = \mathcal{E}(\hat{\mu}_{DM})$ and Ho: $\mathcal{E}(\hat{\mu}_{SK}) = 0$.

The χ^2 test for association is significant at the .01 level and suggests the conclusion that the Dixon-Mood and Spearman-Karber estimates are usually both biased or both unbiased for values of μ_0 and σ_0 within the range of values studied here.

Table 9

Empirical F^* Ratios for Testing
Ho: $\mathcal{E}(\hat{\mu}_{SK}) = \mathcal{E}(\hat{\mu}_{DM})$

df = 1,99		Initial Stimulus				
		0	1	2	3	4
S S	1/8	<1	28.2	23.2	57.0	192.0
T E	1/4	<1	30.2	25.2	10.6	24.8
E Z	1/2	<1	1.22	14.2	2.54	79.5
P E	1	<1	3.35	3.06	10.7	<1.
	2	1.94	1201.0	1.19	500.0	<1.

$F_{1,99}$ (.90) = 2.77

$F_{1,99}$ (.95) = 3.96

$F_{1,99}$ (.99) = 6.96

$$*F = \frac{[\hat{\mathcal{E}}(\hat{\mu}_{SK}) - \hat{\mathcal{E}}(\hat{\mu}_{DM})]^2}{\hat{V}[\hat{\mathcal{E}}(\hat{\mu}_{SK}) - \hat{\mathcal{E}}(\hat{\mu}_{DM})]^2}$$

Table 10

Empirical F^* Ratios for Testing
Ho: $\mathcal{E}(\hat{\mu}_{SK}) = 0$

df = 1,99		Initial Stimulus				
		0	1	2	3	4
S S	1/8	2.22	129.	136.	342.	216.
T I	1/4	<1	199.	417.	20.2	44.2
E Z	1/2	2.17	3.2	<1	1.22	14.4
P E	1	<1	<1	<1	1.31	<1
	2	<1	26.0	4.6	40.4	<1

$$*F = \frac{[\hat{\mathcal{E}}(\hat{\mu}_{SK})]^2}{\hat{V}(\hat{\mu}_{SK})}$$

Table 11

Difference of Absolute Values

$$\left|\hat{\mathcal{E}}(\hat{\mu}_{SK})\right| - \left|\hat{\mathcal{E}}(\hat{\mu}_{DM})\right|$$

	Initial Stimulus				
	0	1	2	3	4
S S 1/8	+.007	-.152	-.142	-.643	+.561
T I 1/4	+.002	-.213	-.228	-.197	-.214
E Z 1/2	+.018	-.034	-.205	-.054	-.418
P E 1	+.008	-.010	-.096	-.056	-.021
2	-.034	-.865	+.005	-.829	-.003

Table 12

Relations Between $\mathcal{E}(\hat{\mu}_{SK})$ and $\mathcal{E}(\hat{\mu}_{DM})$

Summary of Tables 9, 10, and 11

	Initial Level				
	0	1	2	3	4
S S 1/8	= 0 +	≠ ∅ -	≠ ∅ -	≠ ∅ -	≠ ∅ +
T I 1/4	= 0 +	≠ ∅ -	≠ ∅ -	≠ ∅ -	≠ ∅ -
E Z 1/2	= 0 +	= ∅ -	≠ 0 -	= 0 -	≠ ∅ -
P E 1	= 0 +	= 0 -	= 0 -	≠ 0 -	= 0 -
2	= 0 -	≠ ∅ -	= ∅ +	≠ ∅ -	= 0 -

Symbol	Meaning
≠	$\mathcal{E}(\hat{\mu}_{SK}) = \mathcal{E}(\hat{\mu}_{DM})$ rejected at $\alpha \leq .01$
=	opposite of ≠
∅	$\mathcal{E}(\hat{\mu}_{SK}) = 0$ rejected at $\alpha \leq .01$
0	opposite of ∅
+	$\left\|\hat{\mathcal{E}}(\hat{\mu}_{SK})\right\| > \left\|\hat{\mathcal{E}}(\hat{\mu}_{DM})\right\|$
-	opposite of +

Table 13

Relation Between Hypotheses

$$\mathcal{E}(\hat{\mu}_{SK}) = \mathcal{E}(\hat{\mu}_{DM})$$
$$\mathcal{E}(\hat{\mu}_{SK}) = 0$$

	0	∅	
=	10	2	12
≠	2	11	13
	12	13	25

$\chi_1^2 \doteq 11.42$

Among those 13 cells for which the two estimators appear to have different expectations (according to the hypothesis test above), for 12 cells the sign of the difference between the absolute values of the estimated expectations is negative and for only one cell is the sign positive. Assuming that if $\mathcal{E}(\hat{\mu}_{SK}) \doteq \mathcal{E}(\hat{\mu}_{DM})$ then the probability of either sign in the sample should be approximately .5, the observed proportion of 1/13 is indicative of smaller biases for the Spearman-Karber estimator and would be significant at the .01 level or below ($\chi_1^2 = 9.307$).

Tables 14 through 21 give the analysis of variance tables for the results of the simulations treating the estimates of the parameters as response variables. As we shall see later, the variances of the estimators appear to vary systematically from cell to cell so that the F ratios which are shown cannot be assumed to follow exactly the distribution of F. The F ratios obtained can be interpreted cautiously however to indicate the relative importance of various aspects of the design of an up and down procedure and the choice of estimators.

If the up and down procedure is effective, the initial stimulus level should be relatively unimportant as a determinant of the expectation of the estimators of μ provided the experiment is sufficiently prolonged so as to allow the levels to approach (and pass) the true median of the tolerance distribution. The stopping rule should have the same kind of effect in that once the levels in the neighborhood of the true median are reached, subsequent trials serve only to refine the estimate beyond the gross improvement made from the initial stimulus (presumably the experimenter's best prior guess at μ). The step size will be important in determining the number of subjects necessary to make the gross improvement over μ_0 and in setting an upper limit on the precision with which the parameters can be estimated. The latter can best be illustrated with reference to the Spearman-Karber estimators. Since they are basically moment estimates whose expectations for "large" samples differ from the true parameters by the error due to approximation of an integral by a sum, the finer we make the lattice of stimulus levels, the smaller the bias we should obtain. We note, however, that for a design which terminates with probability one, some proportion of the subjects used will be involved in the movement from μ_0 to the neighborhood of the true mean. For small experiments this part of the sequence of trials may be the major portion of the experiment. Thus it may not be possible to observe the reduction in the error of approximation in our study.

In Table 14 for the Spearman-Karber estimator of μ we see that the largest F ratio (except for that attributed to the mean) is that due to the effect of various step sizes. From Table 15 and Figure 33 we see that the bias of the Spearman-Karber estimator of μ decreases with increasing step size. This effect may be due to the decreasing number

Table 14

Analysis of Variance
Spearman-Karber Estimator of μ

Source	SS	DF	MS	F ratio
Grand Mean	29.991	1	29.991	147.4
Initial Stimulus	17.644	4	4.411	21.7
Step Size	91.168	4	22.792	112.0
Stopping Rule	21.470	4	5.367	26.4
Random Start	7.044	4	1.761	8.7
Sequence Number*	.364	1	.364	1.8
Residual	505.108	2482	.204	
Total	672.789	2500	.269	

Table 15

Means by Treatment Level
Spearman-Karber Estimator of μ

Treatment	Level				
	1st	2nd	3rd	4th	5th
Initial Stimulus	-.032	.087	.103	.197	.193
Step Size	.449	.174	.042	-.030	-.087
Stopping Rule	.005	.070	.055	.280	.127
Random Start	.037	.074	.110	.194	.127

Grand Mean	.110
Regression on Sequence Number	-.0042

*Sequence number indicates the effect of order of simulation and is an implicit test of the random number generator.

Table 16

Analysis of Variance
Dixon-Mood Estimator of μ

Source	SS	DF	MS	F ratio
Grand Mean	47.975	1	47.975	207.9
Initial Stimulus	37.665	4	9.416	40.8
Step Size	245.893	4	61.473	266.4
Stopping Rule	117.844	4	29.461	127.7
Random Start	16.387	4	4.097	17.8
Sequence Number	.261	1	.261	1.1
Residual	572.790	2482	.23	
Total	1038.814	2500	.416	

Table 17

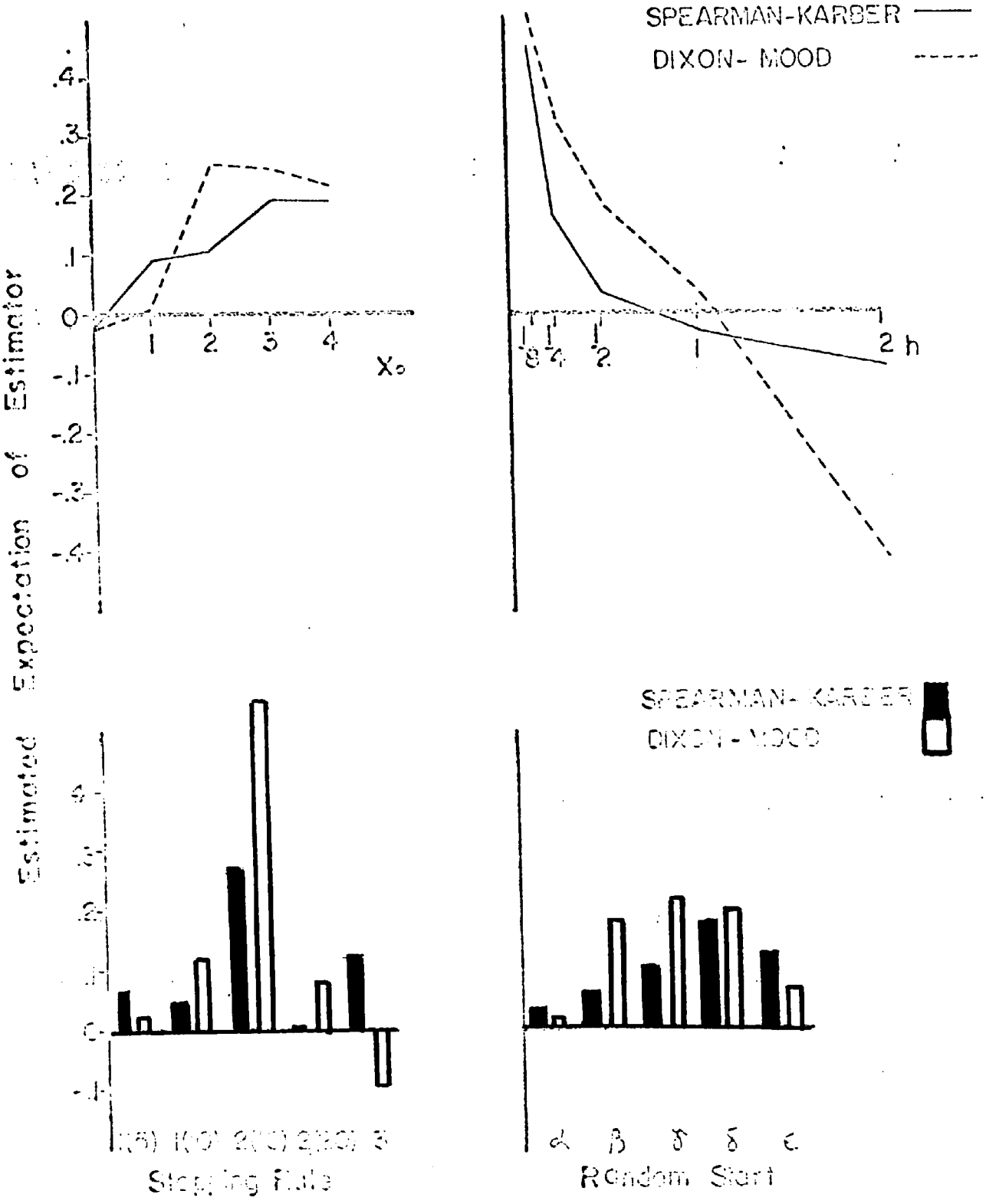
Means by Treatment Level
Dixon-Mood Estimator of μ

Treatment	Level				
	1st	2nd	3rd	4th	5th
Initial Stimulus	-.029	.008	.249	.246	.229
Step Size	.514	.345	.189	.051	-.407
Stopping Rule	.080	.020	.124	.550	-.082
Random Start	.016	.186	.222	.199	.069

Grand Mean	.139
Regression on Sequence Number	-.0004

Figure 33

Effect on Expectation of $\hat{\Delta}$ of Various Aspects of Stochastic Experimental Design



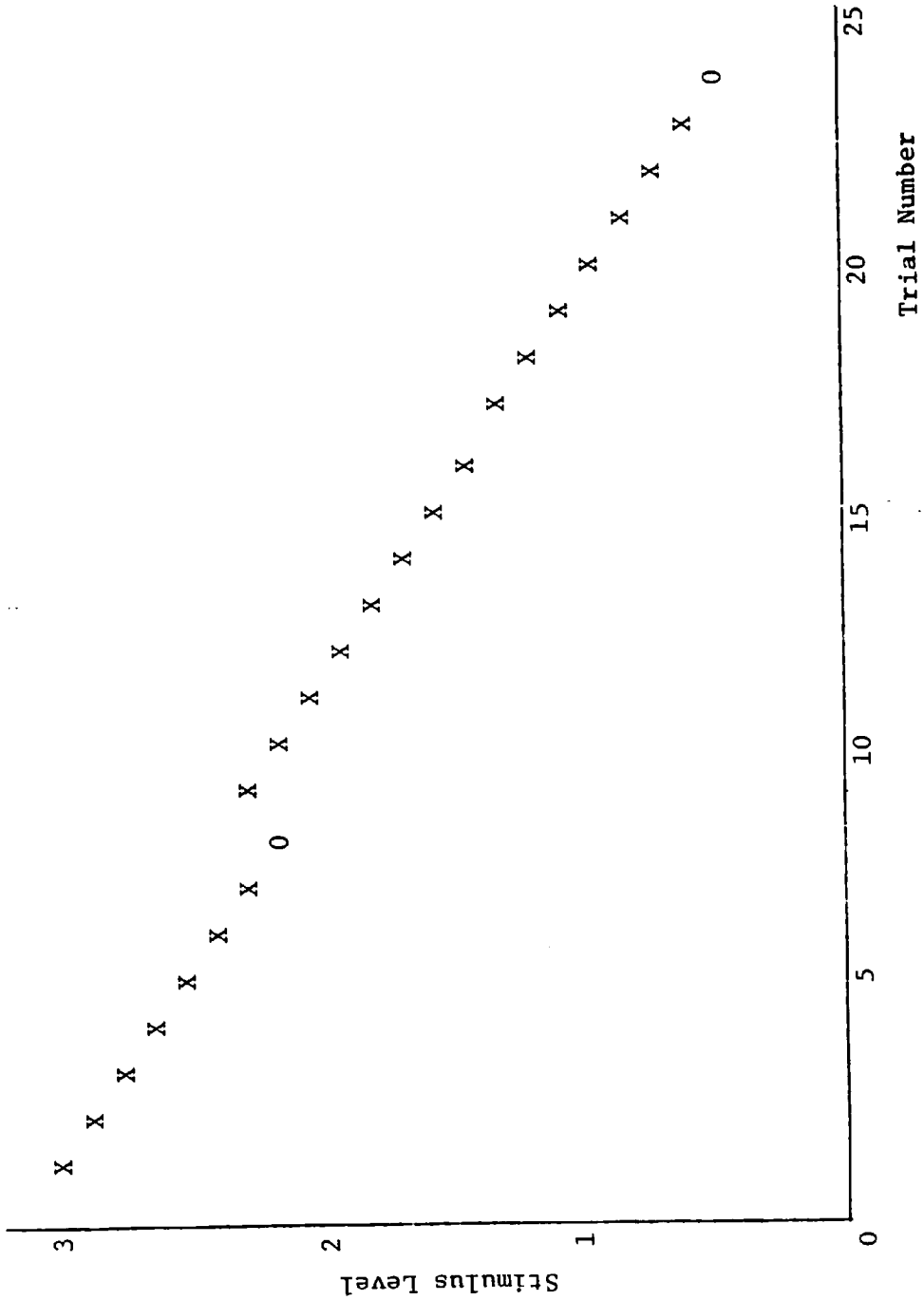
of steps required to reach the neighborhood of the mean. The initial stimulus level has an effect on the expectation of approximately the same order of magnitude as the stopping rule for the strategies we studied.

The large difference between the means for rules 2(10) and 2(20) is mainly due to the fact that for one strategy, namely $x_o = 3$, $h = 1/8$ and rule 2(10), the number of steps is limited to less than half the initial distance from the mean. This fact makes the modal outcome of the simulation clear. A run of successes is observed terminated by a failure, usually at a level somewhat above the true mean. Since an experiment with this type of outcome yields degenerate estimates of the scale parameter, it is discarded. Those experiments which were acceptable had to have a failure before the tenth trial and a continued run of successes following. Figure 34 shows the type of realization in a specific case. The crucial aspect is that the first failure must occur within the first ten trials in order to provide a nondegenerate estimate of σ when the stopping rule is satisfied. If we denote the level at which this first failure occurs by x_N and the level at which the second failure occurs by x_0 then we have the following as a typical record of such an experiment.

$$(4.2) \qquad p_i = \begin{cases} 1/1 \text{ if } & i > N \\ 1/2 \text{ if } & i = N \\ 1/1 \text{ if } & 0 < i < N \\ 0/1 \text{ if } & i = 0 \end{cases}$$

Figure 34

Typical Acceptable Outcome of an Up and Down Experiment with Initial Stimulus Level 3., Step Size 1/8, and Stopping Rule 2(10)



Applying the Spearman-Karber estimators to these results we obtain

$$(4.3)\quad \hat{\mu}_{SK} = \frac{X_N + X_{N+1}}{2}\left(\frac{1}{1} - \frac{1}{2}\right) + \frac{X_{N-1} + X_N}{2}\left(\frac{1}{2} - \frac{1}{1}\right) + \frac{X_0 + X_1}{2}\left(\frac{1}{1} - \frac{0}{1}\right) =$$

$$= \frac{X_N + X_{N+1} - X_{N-1} - X_N}{4} + \frac{X_0 + X_1}{2} = \frac{2h}{4} + X_0 + \frac{h}{2} = X_0 + h$$

In this situation the level at which the first failure occurs becomes irrelevant and the estimator takes on the value of the final stimulus level plus the step size.

Similarly we find the estimate of σ^2 by

$$(4.4)\quad \hat{\sigma}^2_{SK} = \left(\frac{X_N+X_{N+1}}{2} - X_0 - h\right)^2 \frac{1}{2} + \left(\frac{X_{N-1}+X_N}{2} - X_0 - h\right)^2 \left(-\frac{1}{2}\right) + \left(\frac{X_1+X_1}{2} - X_0 - h\right)^2 =$$

$$= \left(N - \frac{1}{2}\right)^2 \frac{h^2}{2} - \left(N - \frac{3}{2}\right)^2 \frac{h^2}{2} + \frac{h^2}{4} =$$

$$= \frac{h^2}{2}\left[N^2 - N + \frac{1}{4} - N^2 + 3N - \frac{9}{4} + \frac{1}{2}\right] =$$

$$= \frac{h^2}{2}\left[2N - \frac{3}{2}\right] = h^2\left[N - \frac{3}{4}\right]$$

When the bias and Sheppard's corrections are made, this becomes

$$(4.5)\quad \hat{\sigma}^2_{SK} = h^2\left[N + \frac{7}{12}\right]$$

and therefore

$$(4.6)\quad \hat{\sigma}_{SK} = h\sqrt{N + \frac{7}{12}}$$

For the Dixon-Mood estimators under the same conditions we find that

$$(4.7) \quad \hat{\mu}_{DM} = X_0 + \frac{N + 1}{2} h$$

and

$$(4.8) \quad \hat{\sigma}_{DM} = 1.620\ h((X_0 + \frac{Nh}{2}) \frac{N}{2} + .029)$$

Since the Spearman-Karber estimator of μ is independent of the stimulus level at which the first failure occurs while the Dixon-Mood estimator uses this part of the information, the latter will be more strongly influenced by the occasional abberrant failure at a high stimulus level. On the basis of this reasoning we are not surprised to note that the mean Spearman-Karber estimate of μ for the design starting at a stimulus of 3 and with a step size 1/8 is 1.062 compared to the mean Dixon-Mood estimate of 1.705.

Since the stimulus at which the second failure occurs is likely to be near zero, the comparison between the two estimators of σ is approximately that between $h\sqrt{N}$ and N^2h^2. We find that the mean of $\hat{\sigma}_{SK}$ is 0.643 compared to 7.588 for $\hat{\sigma}_{DM}$. On the basis of this extreme sensitivity of the Dixon-Mood estimators to the prior information and the stopping rule, we conclude that if this estimator is to be used, a stopping rule which does not depend on the number of trials should be used.

This particular strategy has increased the estimates of treatment means for each of the treatments applied to it and therefore must be kept in mind when considering the results of the simulations.

Returning to Figure 34 we see that each of the two estimators of are affected in the same gross fashion by changes in the initial stimulus level and the step size. While stopping rules depending on the number

of trials appear to favor the Spearman-Karber estimator, the comparison between the effects of rules 1(5) and 1(10) on the Dixon-Mood estimator is confused. The latter rule should in general cause longer sequences of trials and yet the estimator does not seem to take advantage of the additional information available in the longer experiments.

It is interesting that the mean of the Spearman-Karber estimates appears to have a hyperbolic type of relationship with the step size while the relationship of the mean of the Dixon-Mood estimates to the step size is less clear. In Figure 35 we have plotted the same quantities with a log base 2 and an inverse scale for the step size. Except for the point at step size two the Dixon-Mood estimator appears to have an expectation linearly related to the log of the step size. On the other hand, the mean of the Spearman-Karber estimator appears to be linearly related to the inverse of the step size.

Tables 18 and 20 give the observed sample variances of the Spearman-Karber and Dixon-Mood estimates by the initial stimulus level and step size used in the simulations. Tables 19 and 21 give the pooled estimates by strategy characteristics. Several points of interest should be noted. First, the variance of the Spearman-Karber estimator is larger than that of the Dixon-Mood estimator in 20 of the 25 configurations. The ratio of the former to the latter ranges from about .75 to 3. with most of the configurations yielding a ratio of about 1.1. Second we note that both estimators are extremely variable for the configuration with initial stimulus 0 and step size 2. We note that the stopping rule in this configuration was 2(10), the same rule which gave extreme values of the estimates for initial stimulus 3 and step size 1/8. Since the stimulus levels most likely to be used in such an experiment are -2, 0, and 2 this

Figure 35

Relationship of Estimated Mean of Estimator of μ to Logarithm and Inverse of Step Size

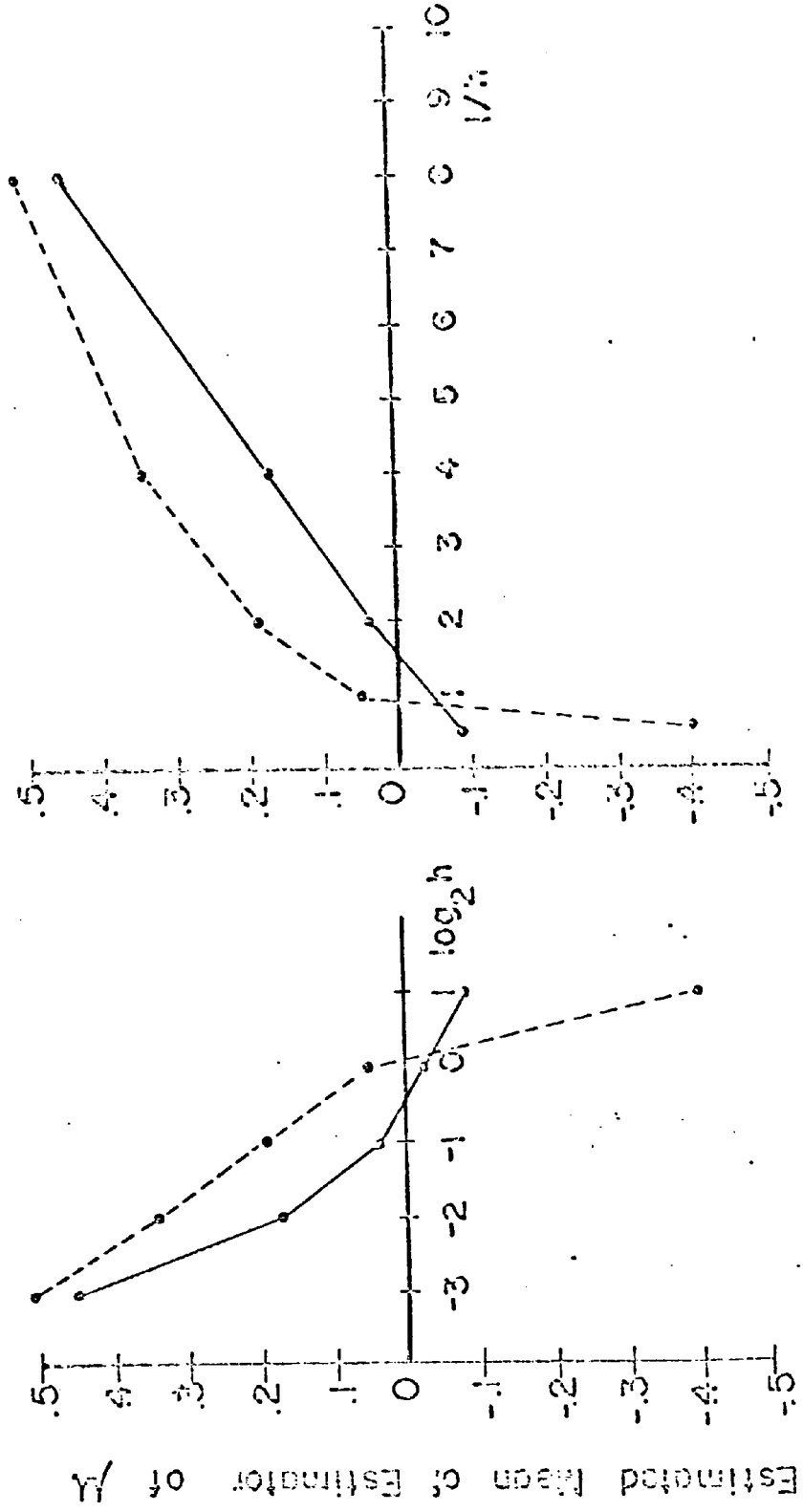


Table 18

Sample Variances of Spearman-Karber Estimates of μ from Stochastic Strategies

		Initial Stimulus Level				
		0	1	2	3	4
S	1/8	.046	.082	.074	.323	.147
T	1/4	.079	.141	.192	.132	.156
E	1/2	.256	.084	.210	.111	.217
P	1	.224	.143	.253	.300	.166
	2	.687	.095	.214	.116	.283

Table 19

Pooled Estimates of Variance of $\hat{\mu}_{SK}$ by Strategy Characteristics

Factor	Treatment Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.258	.109	.189	.196	.194
Step size	.134	.140	.176	.217	.279
Stopping rule	.128	.158	.138	.324	.198
Random start	.143	.201	.260	.175	.167

Total Estimate .189

Table 20

Sample Variances of Dixon-Mood Estimates of μ from Stochastic Strategies

		Initial Stimulus Level				
		0	1	2	3	4
S S	1/8	.036	.060	.081	.102	.197
T I	1/4	.059	.109	.186	.150	.180
E Z	1/2	.108	.076	.192	.097	.163
P E	1	.172	.132	.215	.239	.133
	2	.490	.104	.197	.068	.265

Table 21

Pooled Estimates of Variance of $\hat{\mu}_{DM}$ by Strategy Characteristics

Factor	Treatment Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.170	.096	.174	.133	.188
Step size	.095	.137	.127	.198	.225
Stopping rule	.118	.134	.127	.216	.167
Random start	.117	.160	.213	.118	.155

Total Estimate .152

type of configuration tends to result in estimates similar to those of a fixed experiment with three levels. As we have noted earlier, this fixed design would rarely be selected a priori since the experimenter knows that the probability of a degenerate estimate of the scale parameter is high. Similarly, we are not surprised to see that the variance of both estimators is high for such experiments.

Due to the interactions between initial stimulus, step size, and the stopping rule it is difficult to make any hard and fast conclusions about the relationship between the variances of the estimators and the initial stimulus level, but it does seem clear from Figure 36 that the variances of both estimators increase with increasing step size.

Tables 22 through 25 describe the results of the simulation experiments with respect to the estimates of σ. Figure 37 shows the relations between the estimated expectation of the estimators of σ and the characteristics of the strategy. First we note that the Spearman-Karber estimator of σ is apparently unaffected by the initial stimulus level while the expectation of the Dixon-Mood estimator appears to increase with increasing starting stimulus. The exaggerated rise for $x_o = 3$ is due to the extremely sensitive behavior of the Dixon-Mood estimator to the peculiar type of sequence for $x_o = 3$, $h = 1/8$ and rule 2(10). The Spearman-Karber estimator has expectation approximately linear in the step size especially for $h \leq 1$. Since only one value of h greater than one was used, it is impossible to say anything conclusive about the relation beyond $h = 1$ except that it appears to be monotonic.

Figure 36

Effect on Variance of $\hat{\mu}$ of Various Aspects of Stochastic Experimental Design

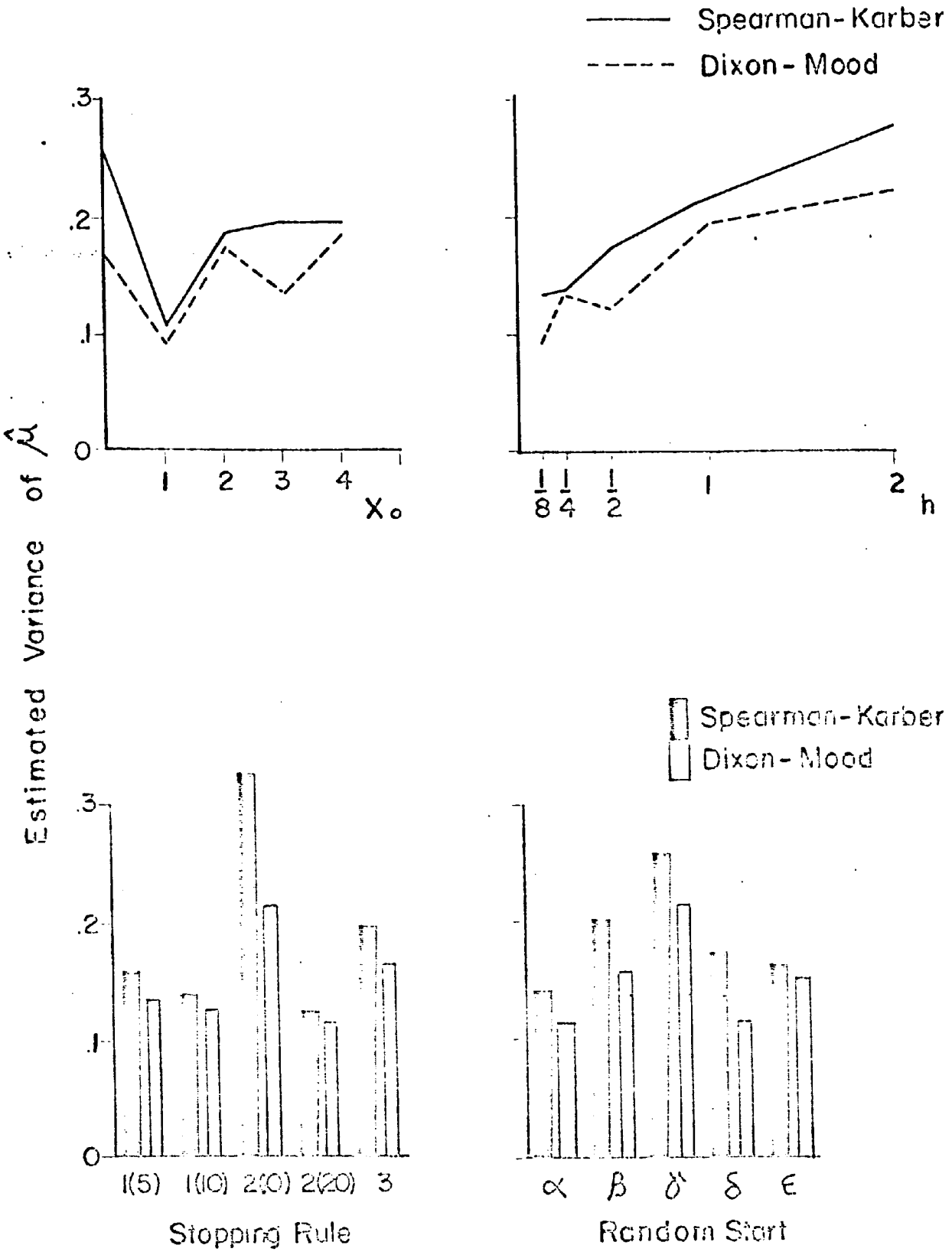


Table 22

Analysis of Variance
Spearman-Karber Estimator of σ

Source	SS	DF	MS	F ratio
Grand mean	2512.834	1	2812.834	48314.4
Initial stimulus	.752	4	.188	3.6
Step size	404.943	4	101.236	1937.4
Stopping rule	5.539	4	1.385	26.5
Random start	2.575	4	.644	12.3
Sequence number	.045	1	.045	.9
Residual	129.694	2482	.05201	
Total	3056.385	2500	1.2226	

Table 23

Means by Treatment Level
Spearman-Karber Estimator of σ

Treatment	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	1.008	.977	1.024	1.015	.989
Step size	.654	.703	.831	1.070	1.754
Stopping rule	.965	1.048	1.007	1.058	.935
Random start	.993	1.005	1.063	.975	.977

Grand Mean 1.003
Regression on Sequence Number .0002

Table 24

Analysis of Variance
Dixon-Mood Estimator of σ

Source	SS	DF	MS	F ratio
Grand mean	5394.114	1	5394.114	2019.5
Initial stimulus	837.081	4	209.270	78.3
Step size	723.765	4	180.941	67.7
Stopping rule	913.223	4	228.306	85.5
Random start	564.365	4	141.091	52.8
Sequence number	.591	1	.591	.2
Residual	6629.453	2482	2.6710	
Total	15062.592	2500	6.0250	

Table 25

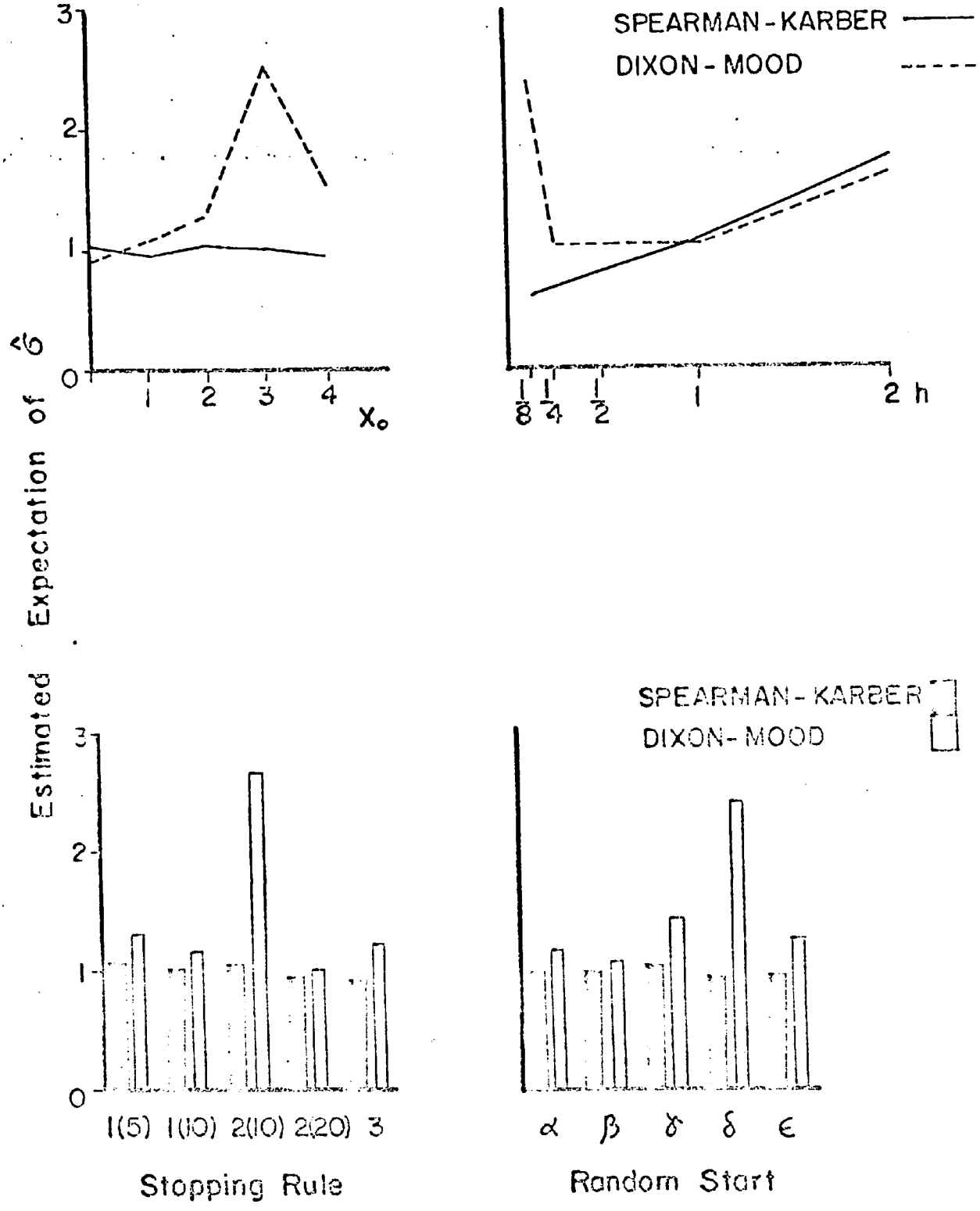
Means by Treatment Level
Dixon-Mood Estimator of σ

Treatment	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.910	1.058	1.305	2.547	1.534
Step size	2.435	1.076	1.083	1.064	1.687
Stopping rule	1.000	1.307	1.154	2.661	1.222
Random start	1.177	1.099	1.408	2.397	1.263

Grand Mean	1.469
Regression on Sequence Number	-.0005

Figure 37

Effect on Expectation of $\hat{\sigma}$ of Various Aspects of Stochastic Experimental Design



For $h \leq 1$ the relationship can be approximated by

$$(4.9) \quad E\left(\frac{\hat{\sigma}_{SK}}{\sigma}\right) - 1 \doteq .4\left(\frac{h}{\sigma} - 1\right)$$

or equivalently

$$(4.10) \quad E(\hat{\sigma}_{SK}) \doteq .6\sigma + .4h$$

This suggests a crude correction for bias of the form

$$(4.11) \quad \hat{\sigma}^{*}_{SK} = (5\hat{\sigma}_{SK} - 2h)/3$$

for $\hat{\sigma}_{SK} > h$. This correction bears further investigation as well as does the question of a possible correction for $\hat{\sigma}_{SK} < h$.

The sensitivity of the Dixon-Mood estimator is such as to make conclusions from our results risky, but it might be reasonable to suggest that basically it is less dependent on h than on x_o. This question also requires further investigation.

Table 26 shows the logarithm of the ratio of the sample variances of the estimators of σ with that of the Dixon-Mood estimator in the numerator. Table 26 gives the means of this quantity by various aspects of the design. As can be seen by reference to the residuals of Tables 22 and 24 the variances of the estimators are hardly commensurate with each other. For example, the residual mean square of the Spearman-Karber estimator is only 1/50 of that for the Dixon-Mood estimator. The smallest log ratio observed was .053 corresponding to a ratio of approximately 11/10. Clearly, the Dixon-Mood estimator seems unacceptable on this basis. However, if the bias correction suggested above for the Spearman-Karber estimator is made, its variance becomes

$$(4.12) \quad V(\hat{\sigma}^{*}_{SK}) = \frac{25}{9} V(\hat{\sigma}_{SK}) \doteq 2.78 V(\hat{\sigma}_{SK})$$

Table 26

Log Ratio of Variances of Estimators of σ
Log $V(\hat{\sigma}_{DM})/V(\hat{\sigma}_{SK})$

	Initial Stimulus Level				
	0	1	2	3	4
S S 1/8	.053	1.400	1.696	3.922	2.702
T I 1/4	.330	1.363	1.860	1.696	2.130
E Z 1/2	.581	.527	1.196	.756	1.881
P E 1	.371	.220	.560	.620	.433

Table 27

Mean Log Ratio of Variances by
Strategy Characteristic

Factor	Treatment Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.309	.799	1.100	1.496	1.453
Step size	1.955	1.476	.988	.441	.299
Stopping rule	.580	1.117	.624	1.587	1.249
Random start	.900	.871	1.037	1.273	1.576

Grand Mean 1.032

and the comparison would then be given by the values of Tables 26 and 27 reduced by .443. Only 17 of the 25 entries in Table 26 exceed this quantity, so that the Spearman-Karber estimator would still appear preferable but to a much smaller degree.

Figure 38 gives a graphical presentation of the relationships to the design characteristics. Note that the variance of the Dixon-Mood estimator increases more rapidly than that of the Spearman-Karber alternative with increasing initial stimulus whereas the relationship is reversed for increasing step size.

Tables 28 and 29 show the sample variances of the Spearman-Karber estimator and the pooled estimates of the variance by design characteristic. The variance of the estimator is shown as a function of the design characteristics in Figure 39. The relationship to the step size is clear but there is some question as to the relationship to initial stimulus.

Overall, we would prefer the Spearman-Karber estimator of σ over the Dixon-Mood estimator due to its smaller variance and an expectation apparently independent of both the initial stimulus level and the stopping rule. With regard to estimators of μ, our preference is less strong, but also favors the Spearman-Karber estimator since its expectation seems to be less severely affected by extremely poor prior information although its variability is on the whole slightly larger than that of the Dixon-Mood estimator.

4.3.3 Size of stochastic experiments. Table 27 shows the mean sample size for the stochastic experiments simulated and the means for the various estimated marginal effects. Since for each (x_o, h) combina-

Figure 38

Effect on log $\hat{V}(\hat{\sigma}_{\bar{x}_0})$ - log $\hat{V}(\hat{\sigma}_{\bar{x}_h})$ of Various Aspects of Stochastic Experimental Design

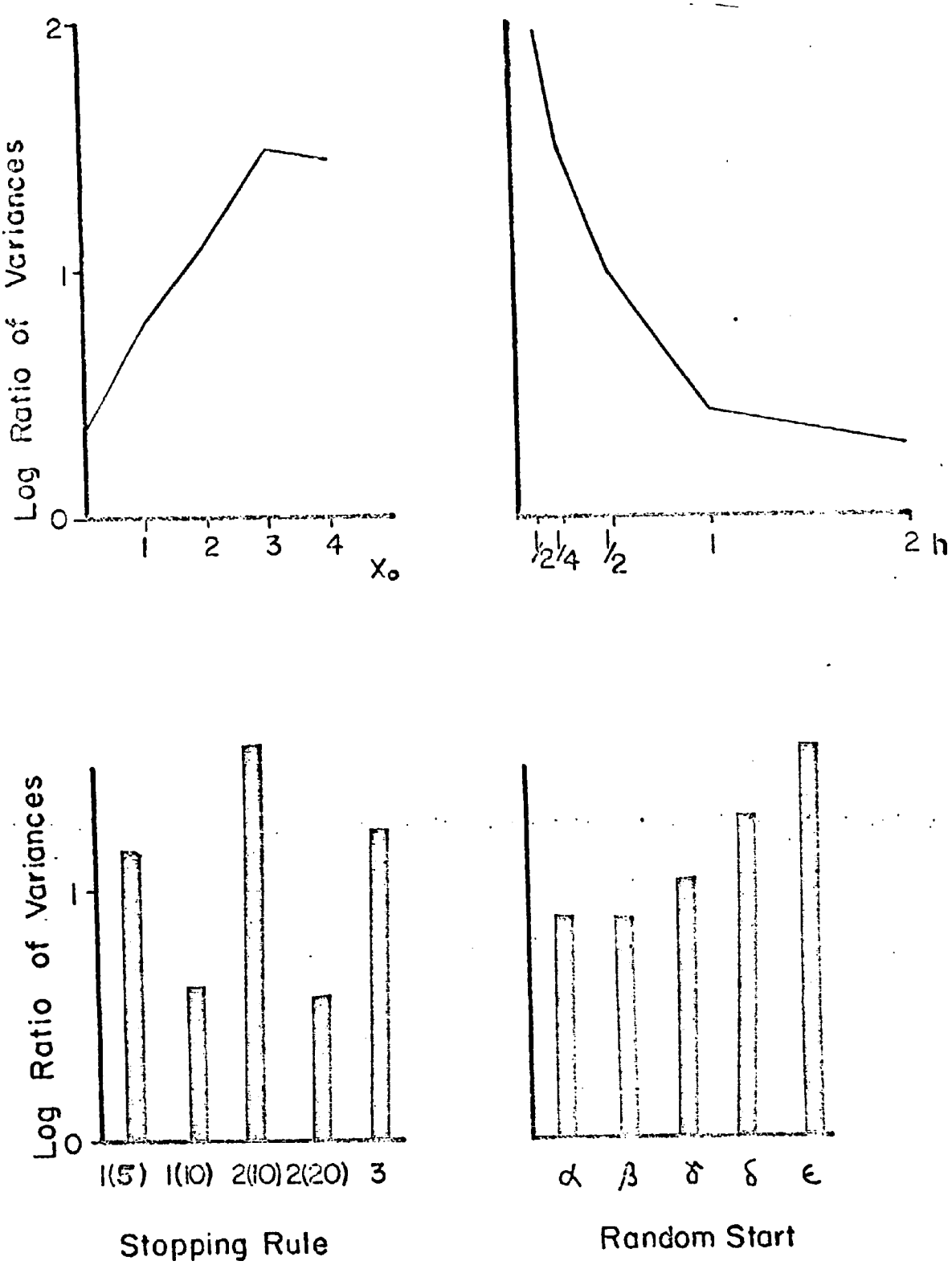


Table 28

Sample Variances of Spearman-Karber Estimates of σ by Initial Stimulus and Step Size

		Initial Stimulus				
		0	1	2	3	4
S S	1/8	.041	.023	.051	.004	.013
T I	1/4	.054	.031	.017	.046	.035
E Z	1/2	.045	.069	.047	.080	.019
P E	1	.052	.061	.058	.069	.093
	2	.129	.074	.047	.074	.043

Table 29

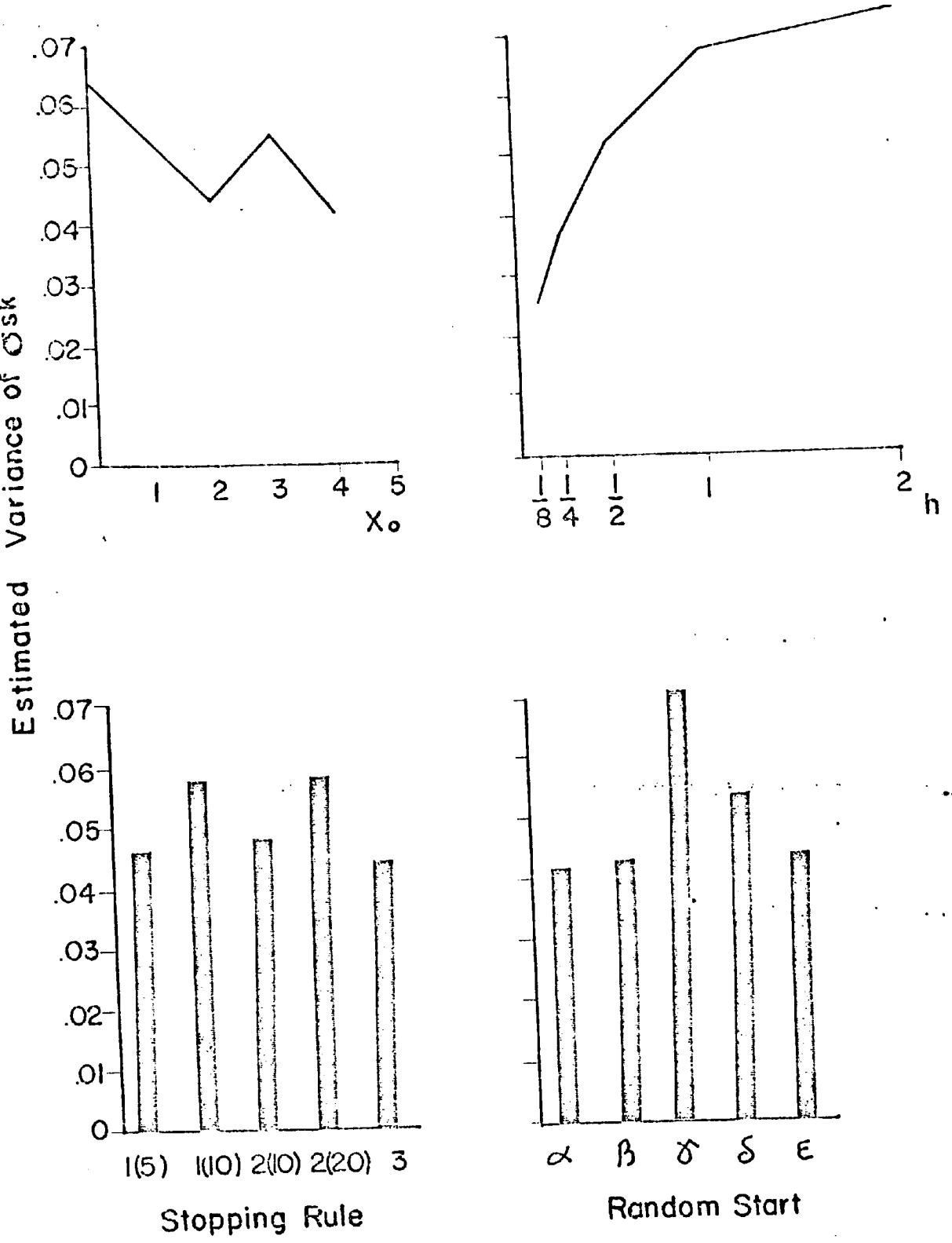
Pooled Estimates of Variance of Spearman-Karber Estimator of σ by Design Characteristics

Treatment	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	.064	.052	.044	.055	.041
Step size	.026	.037	.052	.067	.073
Stopping rule	.059	.046	.058	.048	.044
Random start	.042	.043	.071	.054	.044

Grand Mean .051

Figure 39

Effect on Variance of $\hat{\sigma}_{sk}$ of Various Aspects of Stochastic Experimental Design



tion some number of experiments will be used in approaching the mean of the tolerance distribution, it seems appropriate to reduce these means by some value which reflects the initial distance from the tolerance mean. Initial levels of two or more standard deviations from the tolerance mean are very unlikely to show negative responses and contribute little information (see Figure 1). We therefore chose to use

$$d = \frac{|x_o - \mu| - \sigma}{h}$$

as an approximation to the number of subjects required to complete the initial run from x_o to a level near $\mu \pm \sigma$. By reducing the values of Table 27 by the appropriate values of d we obtain Table 28 where we see that the "effective sample size" is relatively unaffected by x_o, h, or the random starts compared to the effects of the stopping rules. This is as it should be, if our adjustment is appropriate.

We note that the cell which demonstrated the interaction of prior information and stopping rules has only 3.56 effective observations by this adjustment. This serves to confirm our conjecture that d is a reasonable approximation to the number of "informationless" trials.

#4.4 Mixed Strategies: Two Stage Estimation

4.4.1 Design considerations. In designing a mixed experiment the experimenter must make the same kinds of choices as if he were designing both a stochastic and a fixed experiment. The criteria for making these decisions can not be applied independently to each experiment. Presumably the experimenter wishes to keep the stochastic stage experiment as small as possible in order to avoid the length of time required to execute it. Depending on how sure he is of his prior scale parameter estimate,

Table 30

Mean Number of Subjects,
By Design Characteristics

Treatment	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	14.56	15.25	17.25	17.71	21.19
Step size	23.25	17.58	15.78	14.78	14.56
Stopping rule	20.65	13.78	21.41	12.69	17.42
Random start	14.69	14.73	19.72	17.28	19.55
Overall mean	17.19				

Table 31

Mean Effective Sample Size,
By Design Characteristics

Treatment	Level				
	1st	2nd	3rd	4th	5th
Initial stimulus	14.56	15.25	14.06	11.51	11.79
Step size	13.65	12.79	13.39	13.58	13.77
Stopping rule	18.25	10.79	18.62	8.10	11.42
Random start	12.49	12.53	15.32	13.08	13.75
Overall mean	13.43				

FIGURE 40

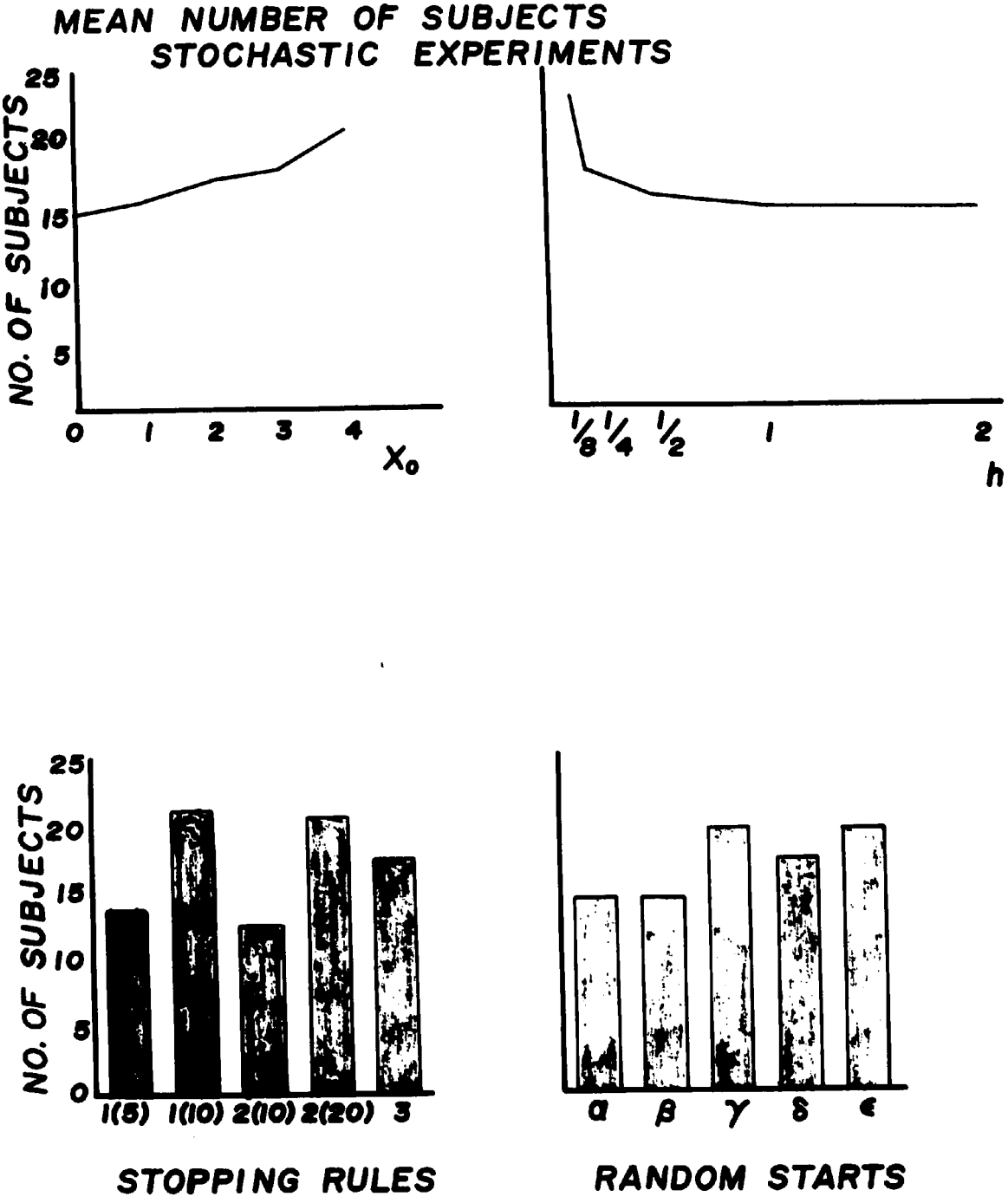
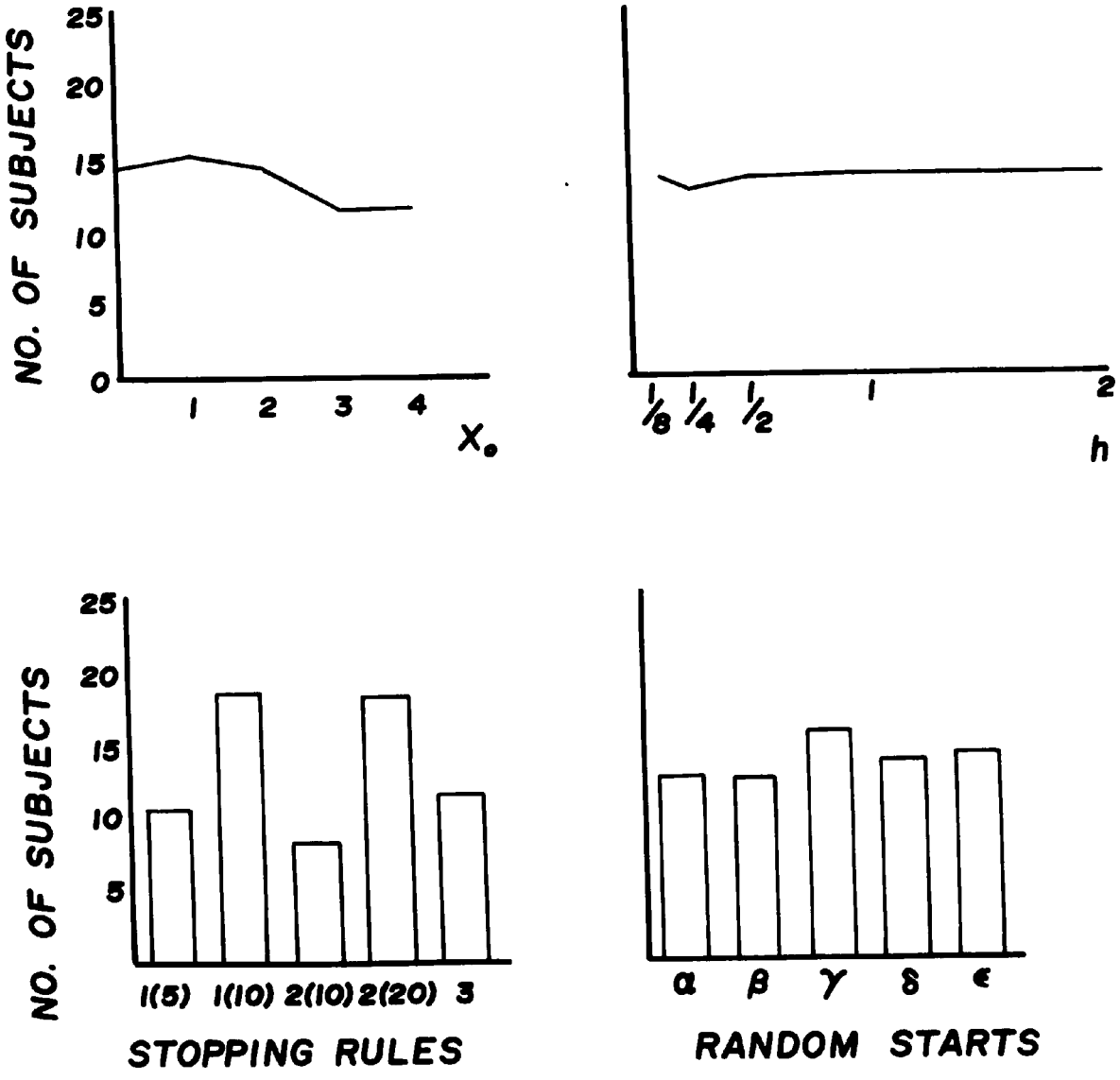

MEAN NUMBER OF SUBJECTS
STOCHASTIC EXPERIMENTS
NO. OF SUBJECTS
25
20
15
10
5
0
1
2
3
4
X_0
1/8
1/4
1/2
1
2
h
NO. OF SUBJECTS
1(5)
1(10)
2(10)
2(20)
3
STOPPING RULES
α
β
γ
δ
ϵ
RANDOM STARTS

FIGURE 41

MEAN EFFECTIVE SAMPLE SIZE STOCHASTIC EXPERIMENTS



he may be satisfied with nothing more than bracketing the mean of the tolerance distribution or he may require an estimate of the scale parameter which is more accurate (and precise) than his prior estimate. In the former case, several runs may be satisfactory and stopping rule 1 would be appropriate. The problem of degenerate first stage estimates can be avoided by simply accepting the prior estimate of the scale parameter in case the first stage experiment yields a degenerate estimate. Our concern is for the more difficult situation in which the experimenter's prior information is either meager or of doubtful reliability. In such cases the full mixed strategy experiment would seem to be required.

In specifying the stochastic strategy to be employed the experimenter must determine the stopping rule to be used. For reasons indicated above (see #4.3) a stopping rule based solely on the number of subjects tested seems inadvisable. We feel that rule 3 should be a minimal requirement so that a nondegenerate estimate of the scale parameter may be obtained. Additional requirements for stopping might lengthen the experiment but would provide more precise estimation for the first stage.

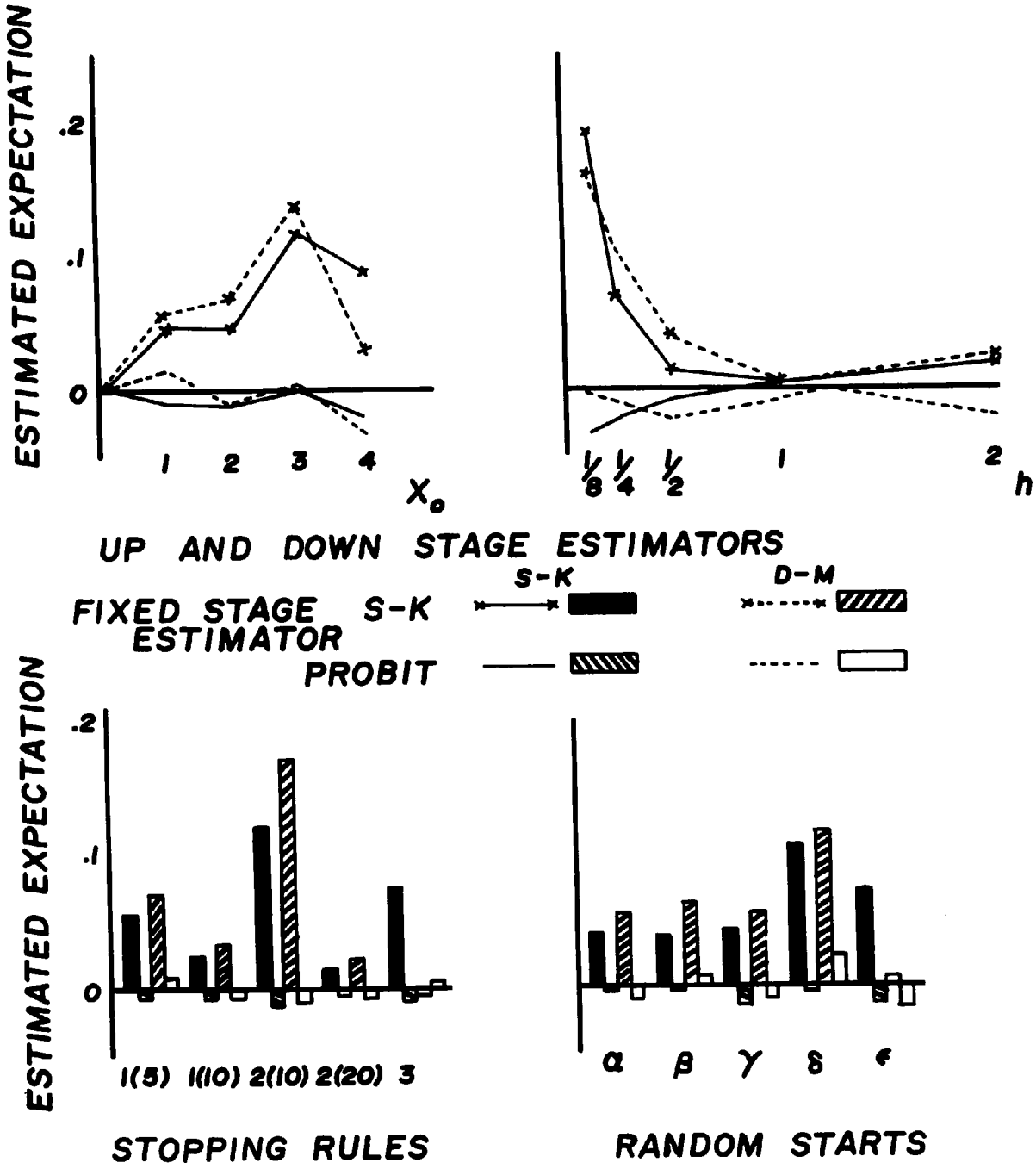
When the choice of stochastic stage estimators is made several criteria must be applied. Since the first stage estimates will be used to design the fixed experiment, we must consider the effects of various kinds of errors. As far as the choice of an estimator of μ is concerned, the "closeness" to the true tolerance mean is paramount in order to make possible precise estimation and to lower the probability of a degenerate estimate. There seems to be little reason to prefer either the Dixon-Mood or Spearman-Karber estimator of μ as the center level of the fixed levels. The specification of the range of the fixed levels depends on

the number of levels to be used and thus ultimately on the risk of degenerate estimates the experimenter is willing to assume. If a larger number of levels is used, then to obtain a minimal bias and variability for the final estimate of σ, a range of levels of three to five standard deviations should be the goal. Although the variance of the estimator increases with the number of levels, the probability of degenerate estimates is much lower for a design with six levels than one with three levels.

4.4.2 Estimation in mixed experiments. We saw in section 4.1 the improvement in the probability of nondegenerate estimates in a mixed experiment over stochastic and fixed experiments. In this section we shall discuss the results of our mixed experiment study with respect to the estimators of μ and σ. Figures 42 to 44 show the estimated expectations of the estimators of μ in mixed experiments. The effect of the interaction between x_o, h, and stopping rule 2 is evident in those estimators using Spearman-Karber estimation in the fixed stage but not for probit estimation. On the whole the bias resulting from probit estimation is very small compared to Spearman-Karber estimation in the fixed stage. First stage Spearman-Karber estimation is only slightly better than Dixon-Mood estimation regardless of the fixed stage estimator. Comparisons of the several fixed strategy designs show that the three level experiment produces smaller biases than either the four or six level experiment. This will have to be counterbalanced with the increased probability of degenerate sample points in the three level experiment. From Figures 45 to 48 we see that the variance is smallest when Spearman-Karber estimation is used at both stages. The variance of estimators with probit

FIGURE 42

ESTIMATED EXPECTATIONS OF ESTIMATORS OF ED50 (μ) MIXED EXPERIMENTS 3 LEVELS IN FIXED STAGE



FIGURE

ESTIMATED EXPECTATIONS OF ESTIMATORS OF ED50 (μ) MIXED EXPERIMENTS 4 LEVELS IN FIXED STAGE

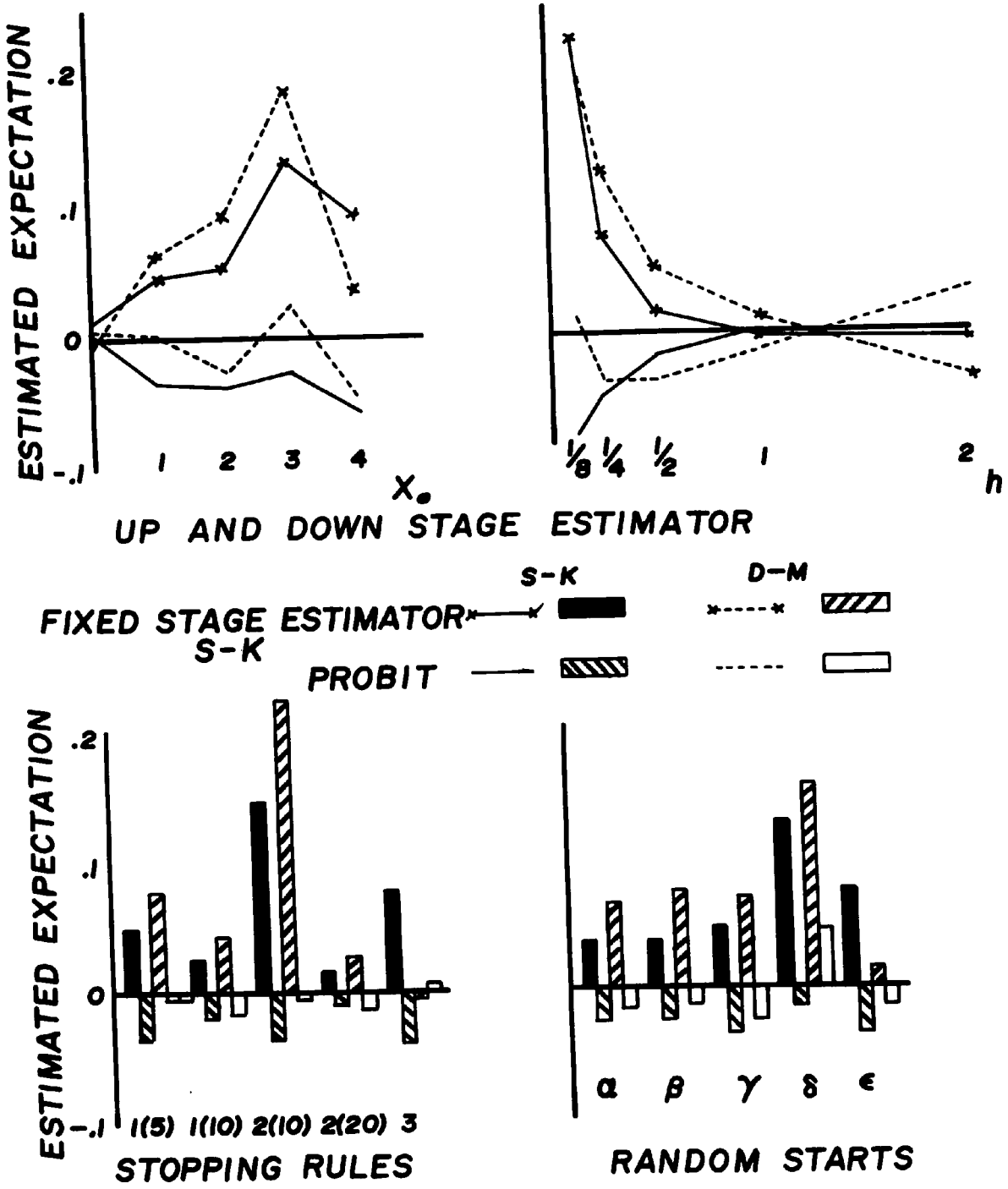


FIGURE 4 1

ESTIMATED EXPECTATIONS OF ESTIMATORS OF ED50 (μ) MIXED EXPERIMENTS 6 LEVELS IN FIXED STAGE

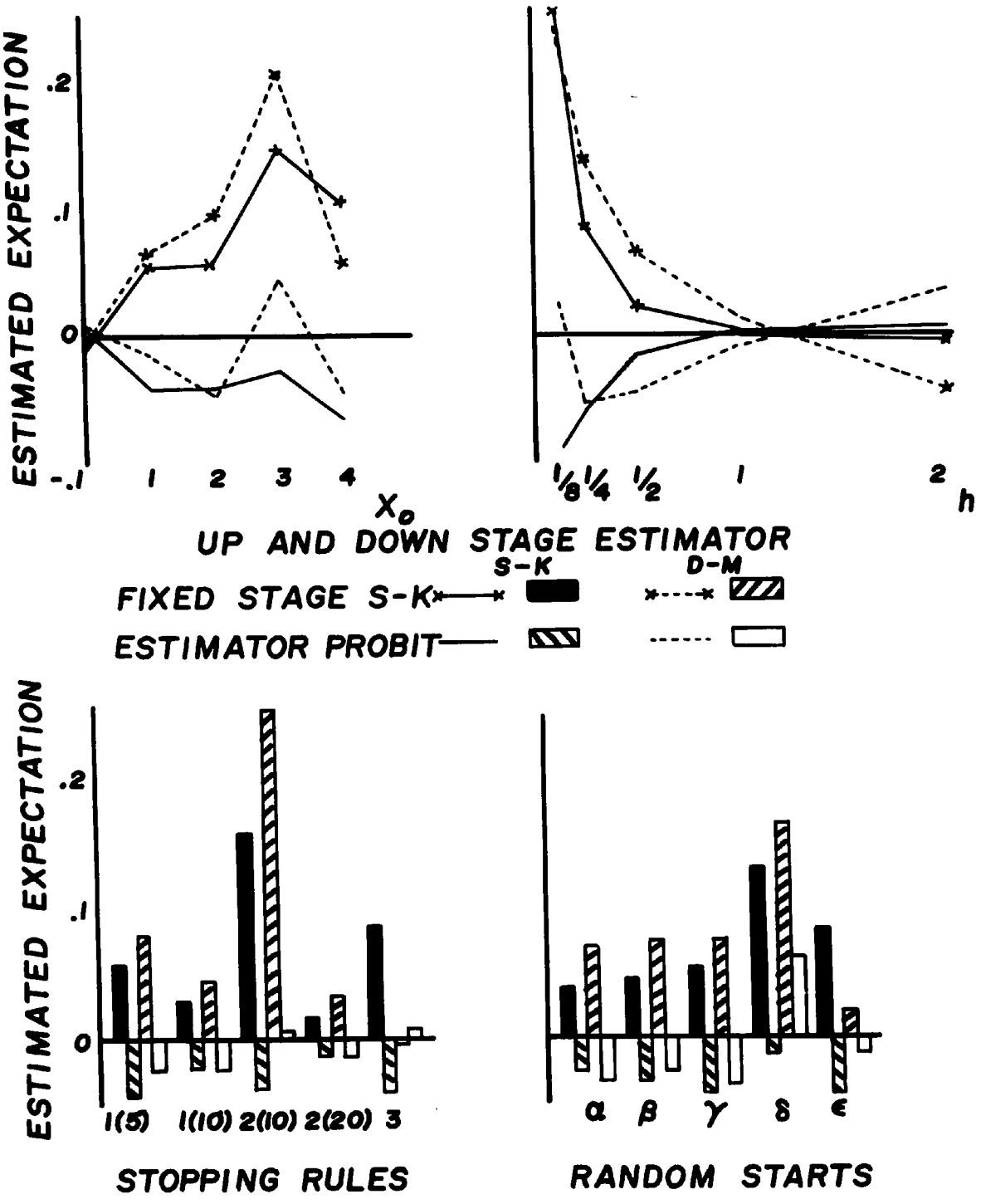


FIGURE 45

ESTIMATED VARIANCES OF ESTIMATORS OF ED50 (μ)
MIXED EXPERIMENTS 3 LEVELS IN FIXED STAGE

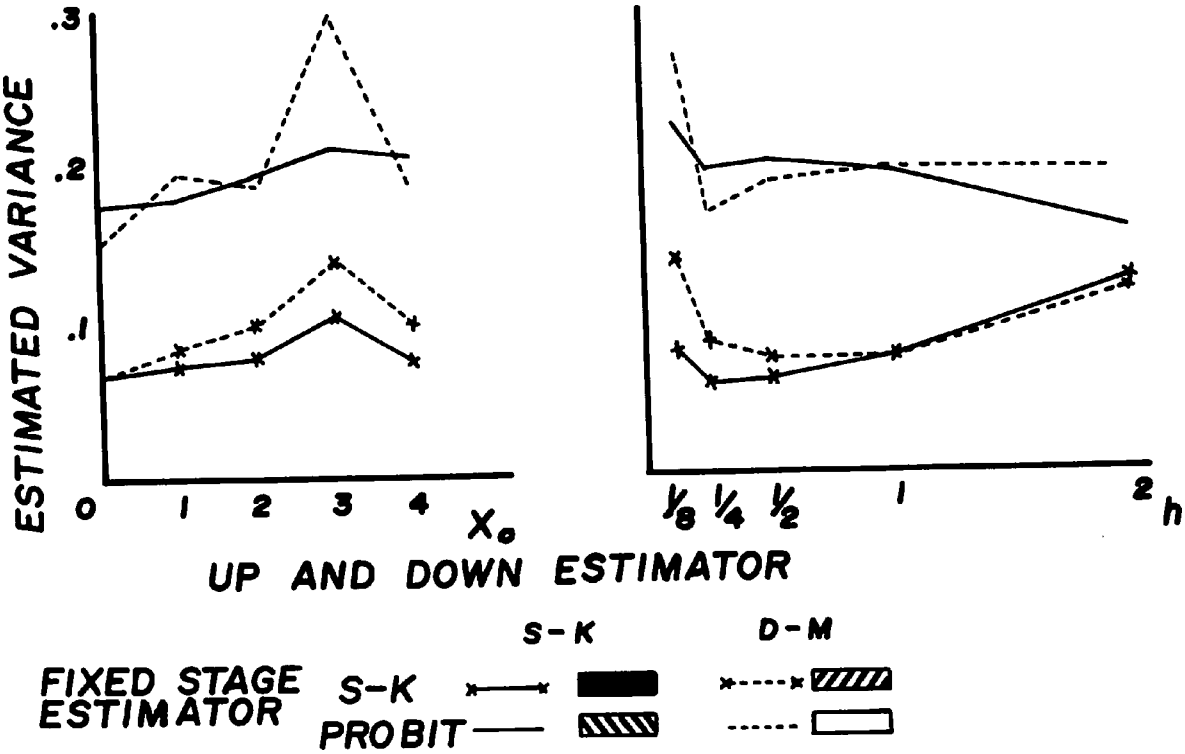


FIGURE 46

ESTIMATED VARIANCES OF ESTIMATORS OF ED50 (μ)
MIXED EXPERIMENTS 4 LEVELS IN FIXED STAGE

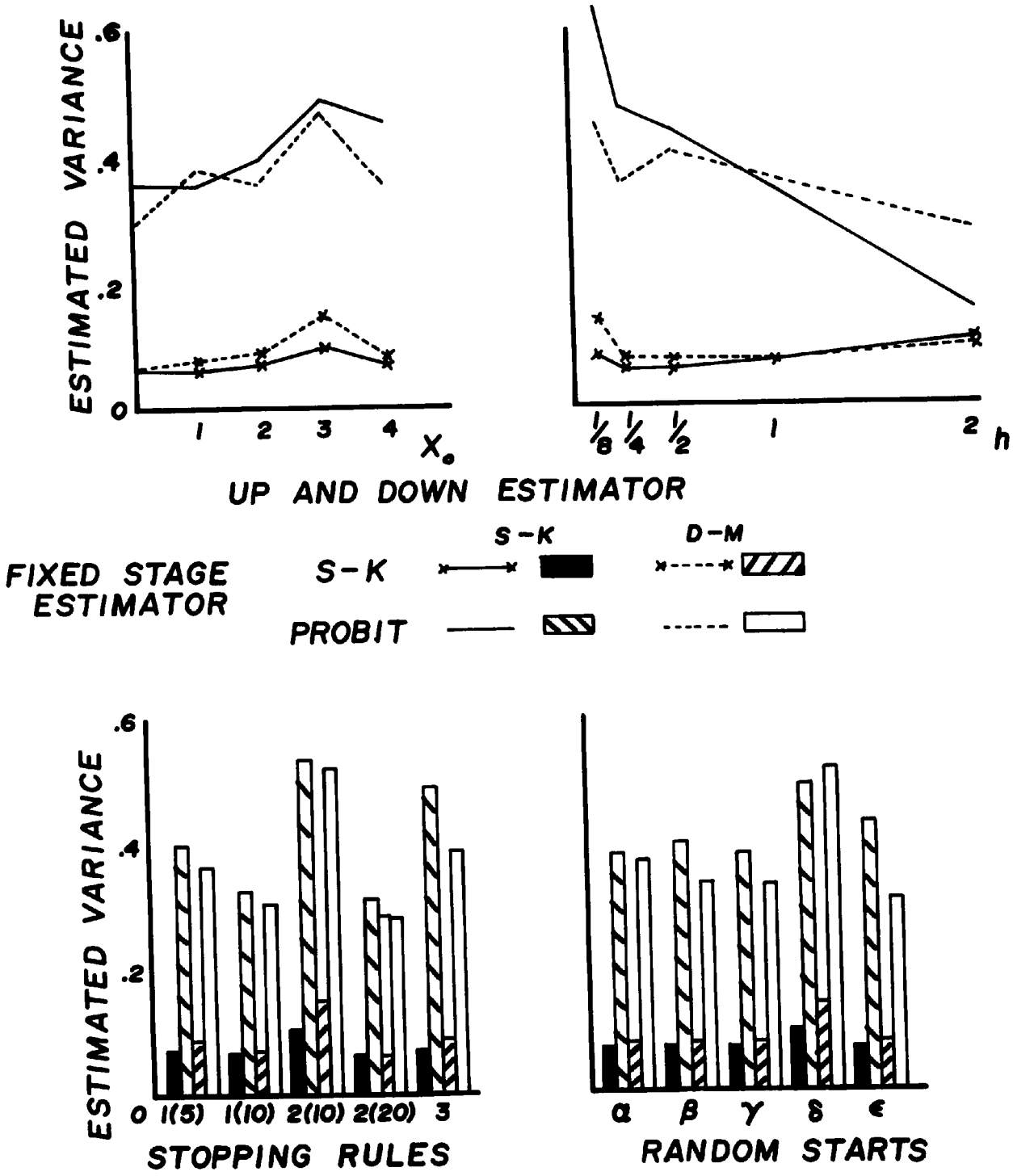
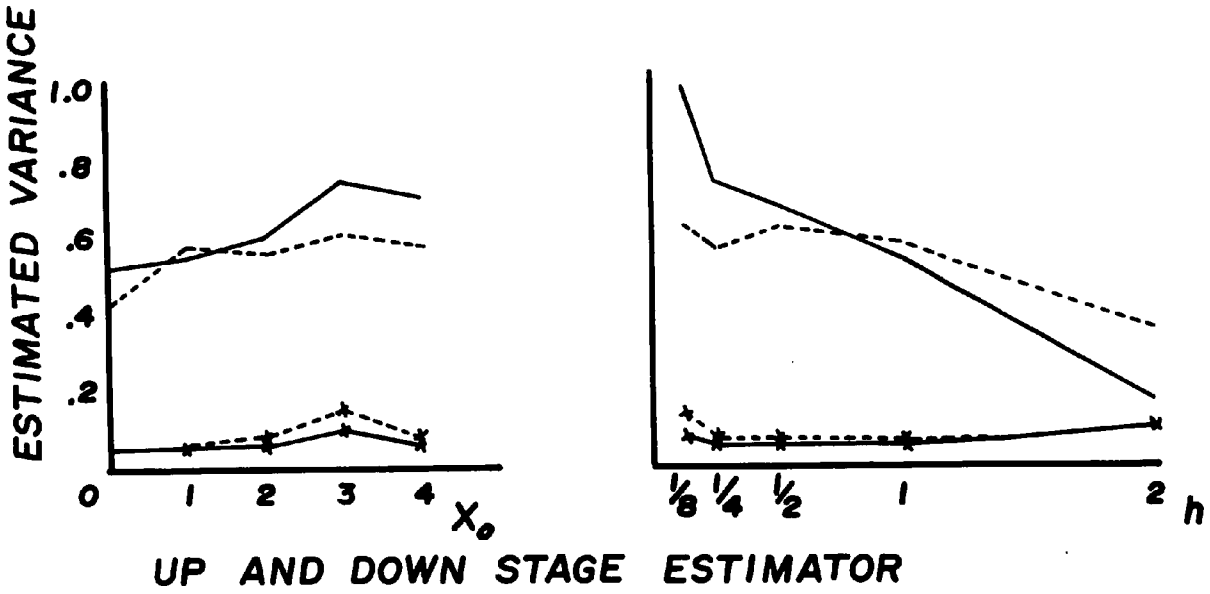
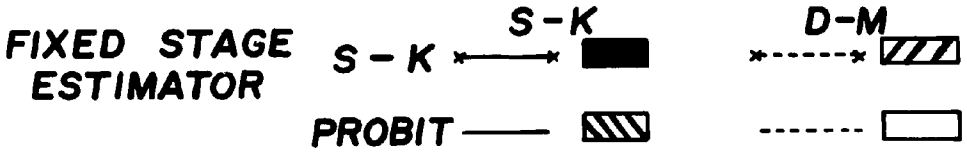


FIGURE 47

ESTIMATED VARIANCES OF ESTIMATORS OF ED50 (μ)
MIXED EXPERIMENTS 6 LEVELS IN FIXED STAGE





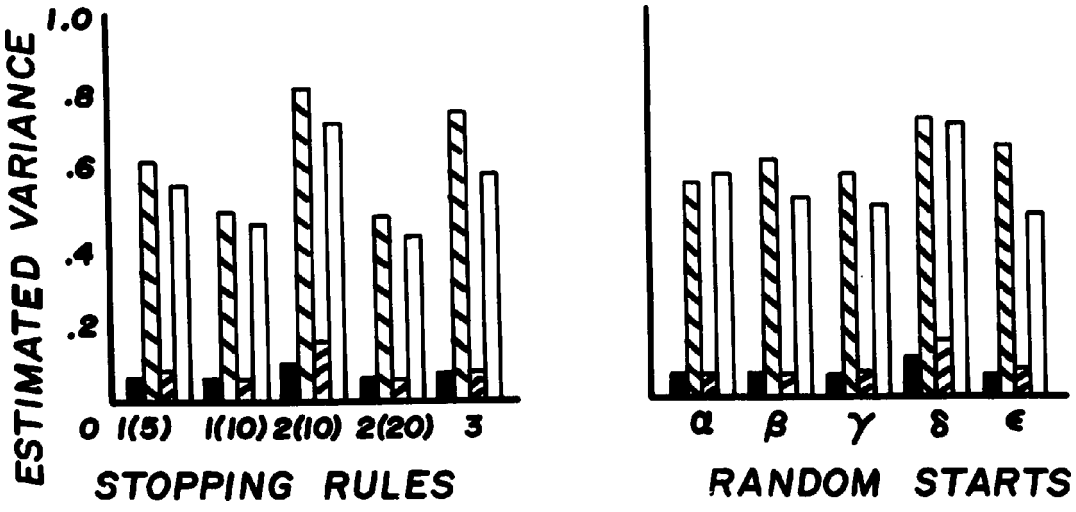
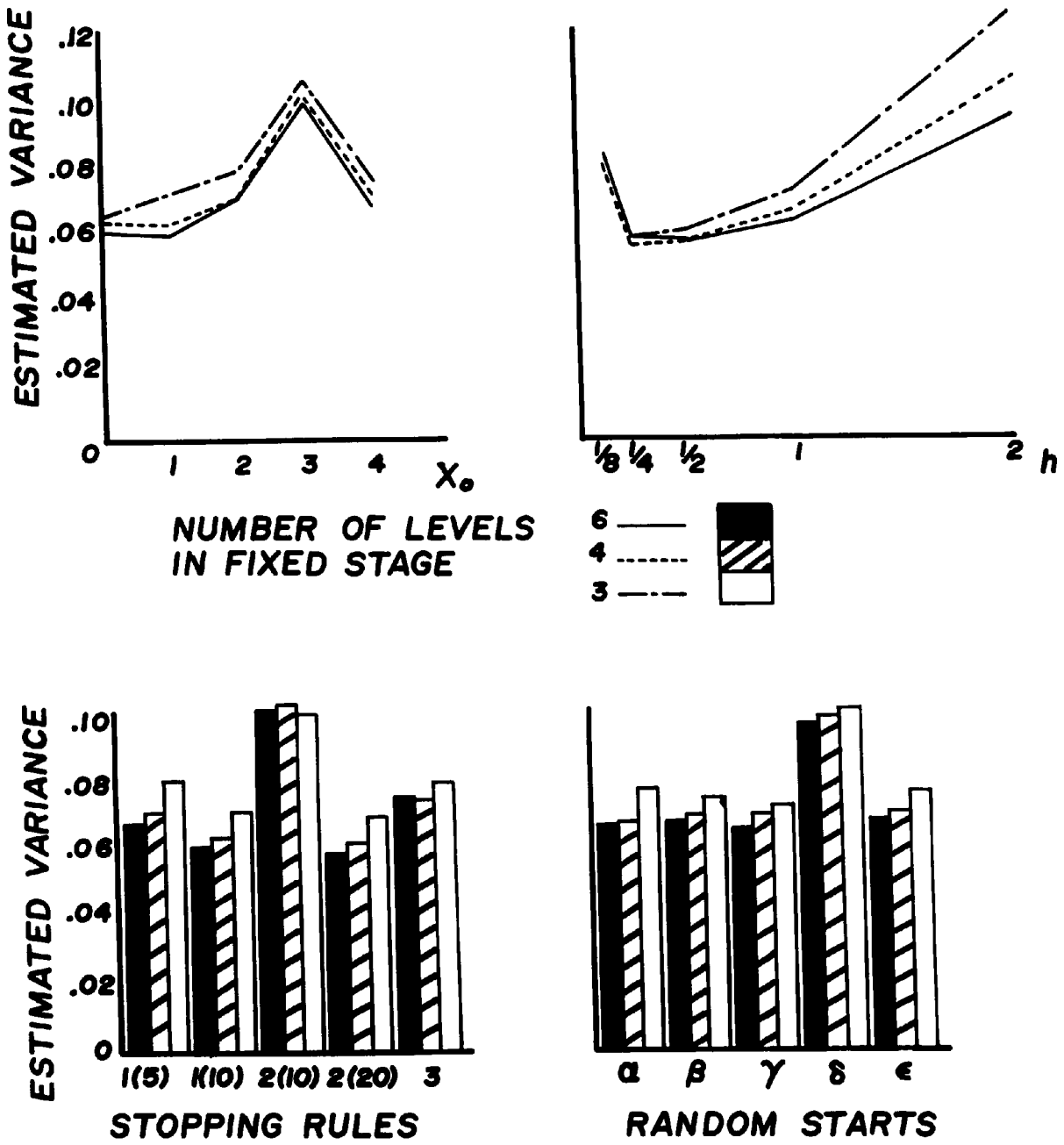


FIGURE 43

ESTIMATED VARIANCES OF SPEARMAN-KARBER ESTIMATOR OF ED50 (μ) MIXED EXPERIMENTS



estimation at the second stage increases rapidly with increasing number of levels used in the second stage. Note that the scales used in this set of figures increases from one to another in order to portray the relationship between probit and Spearman-Karber estimation. Thus in order to see the change in the variance of Spearman-Karber estimators with the number of levels we must turn to Figure 48. We see that the variance in the three level experiment tends to be larger than that in the six level experiment with the four level experiment falling in the middle. The differences are certainly minor compared to those encountered when probit estimation is considered.

With regard to estimation of σ, all estimators appear to be biased as can be seen from Figures 49 to 51. None is appreciably affected by the error in the prior estimate of μ or the stopping rule used. If Spearman-Karber estimation is used in the fixed stage experiment, we see the nearly linear relationship of $E(\hat{\sigma})$ to h encountered in the stochastic stage. The fixed stage probit estimators with stochastic stage Spearman-Karber estimation have a positive bias apparently independent of h in the three level fixed stage configuration, but with more levels the bias decreases with increasing step size. Some approximate bias corrections are given below in Table 32. These were obtained by fitting "by eye" linear relations between the estimated expectations of estimators and the step size used in the stochastic stage and solving the resulting relation for σ. If we assume

$$E\left(\frac{\hat{\sigma}}{\sigma}\right) = a + b\left(\frac{h}{\sigma} - c\right)$$

then we can obtain

$$\sigma = (E(\hat{\sigma}) - bh)/(a - bc)$$

FIGURE 43

ESTIMATED EXPECTATIONS OF ESTIMATORS OF σ MIXED EXPERIMENTS 3 LEVELS IN FIXED STAGE

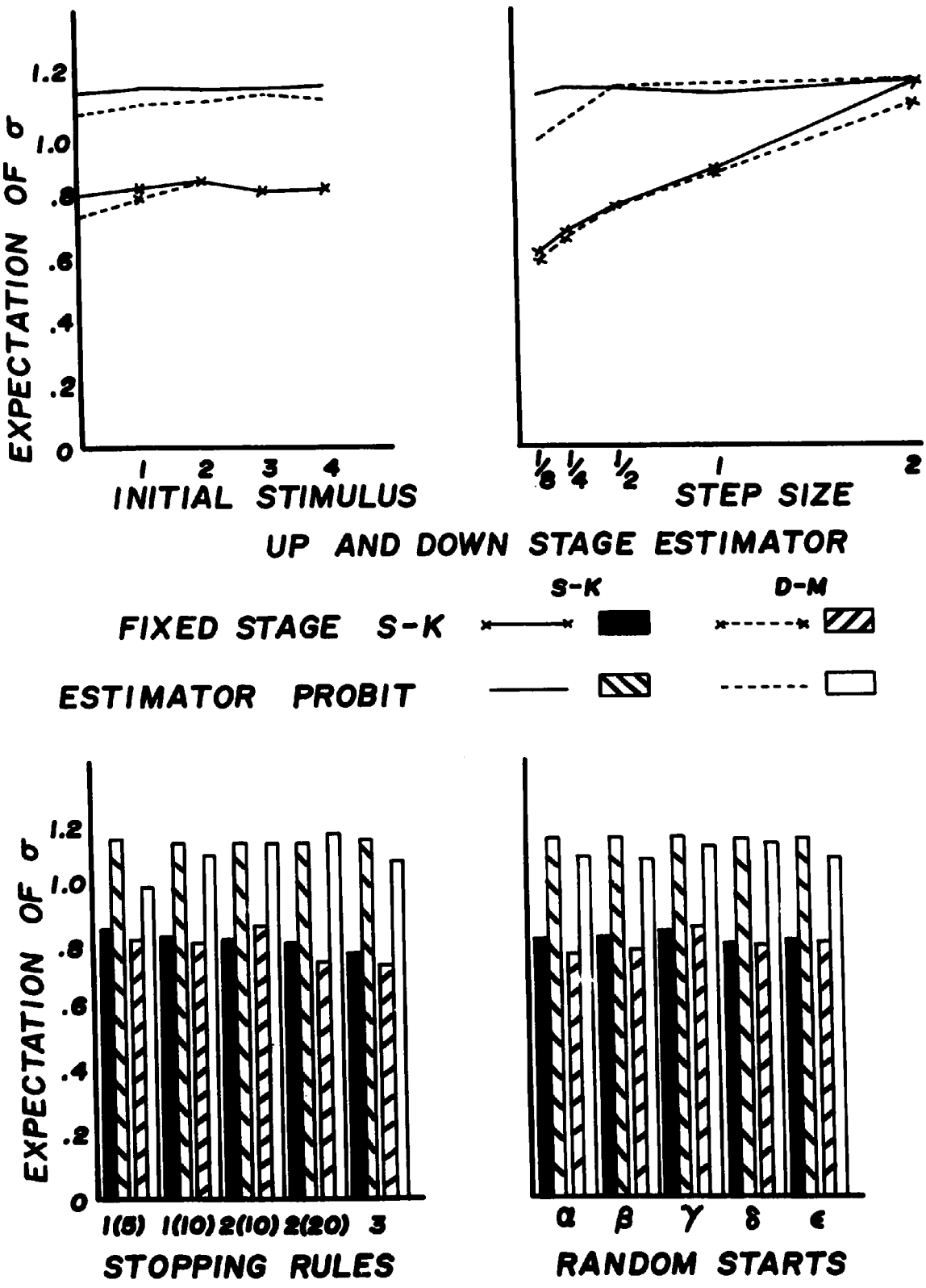
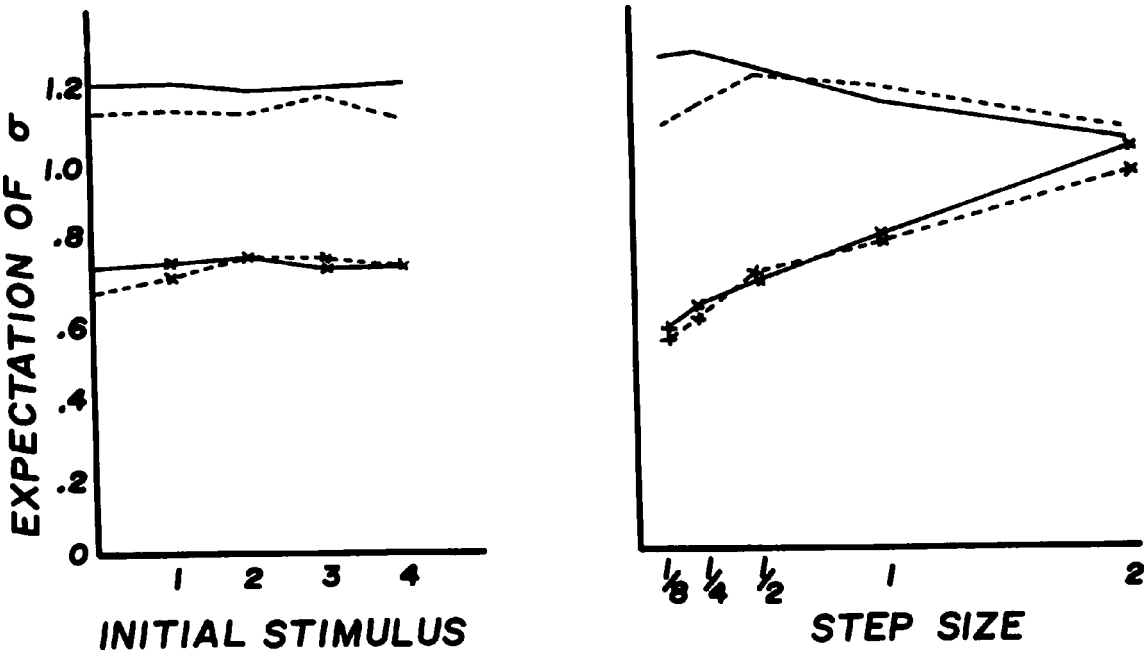
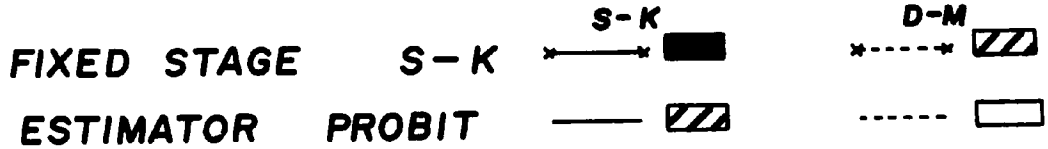


FIGURE 59

ESTIMATED EXPECTATIONS OF ESTIMATORS OF σ MIXED EXPERIMENTS 4 LEVELS IN FIXED STAGE



UP AND DOWN STAGE ESTIMATOR



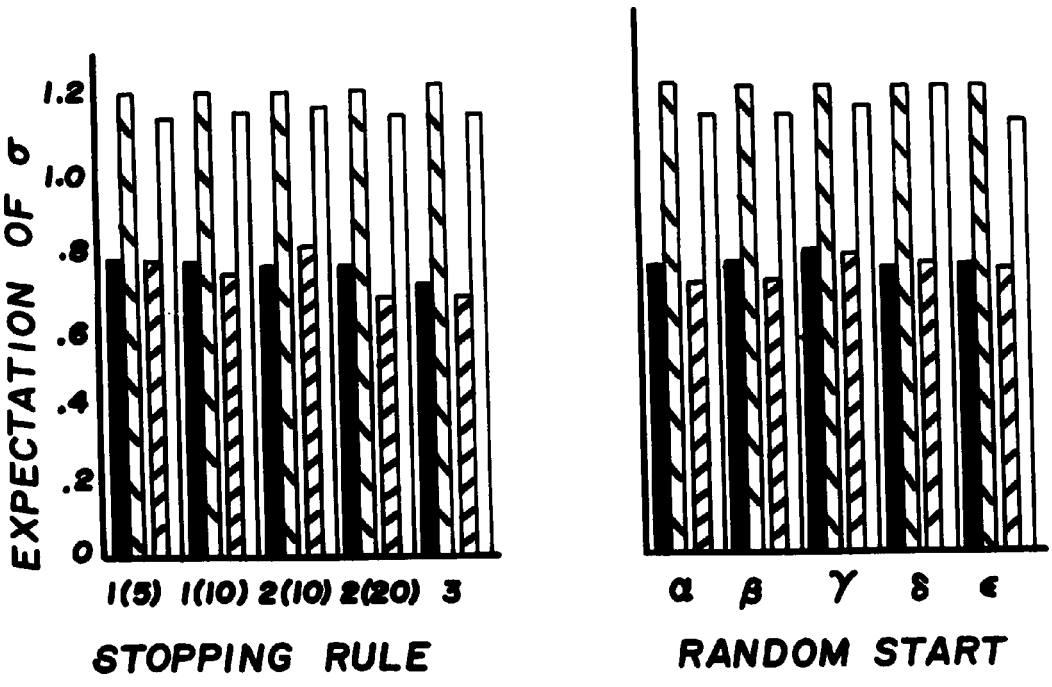
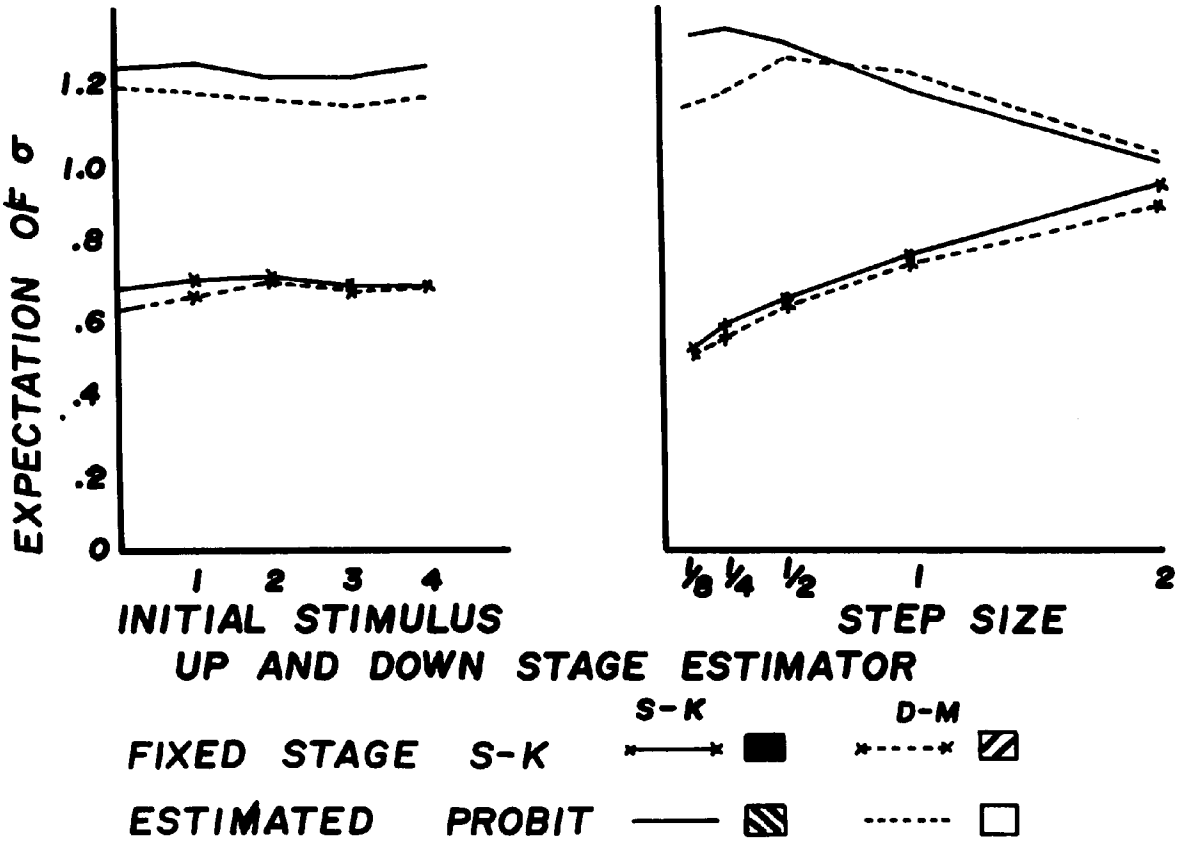


FIGURE 5

ESTIMATED EXPECTATIONS OF ESTIMATORS OF σ

MIXED EXPERIMENTS 6 LEVELS IN FIXED STAGE



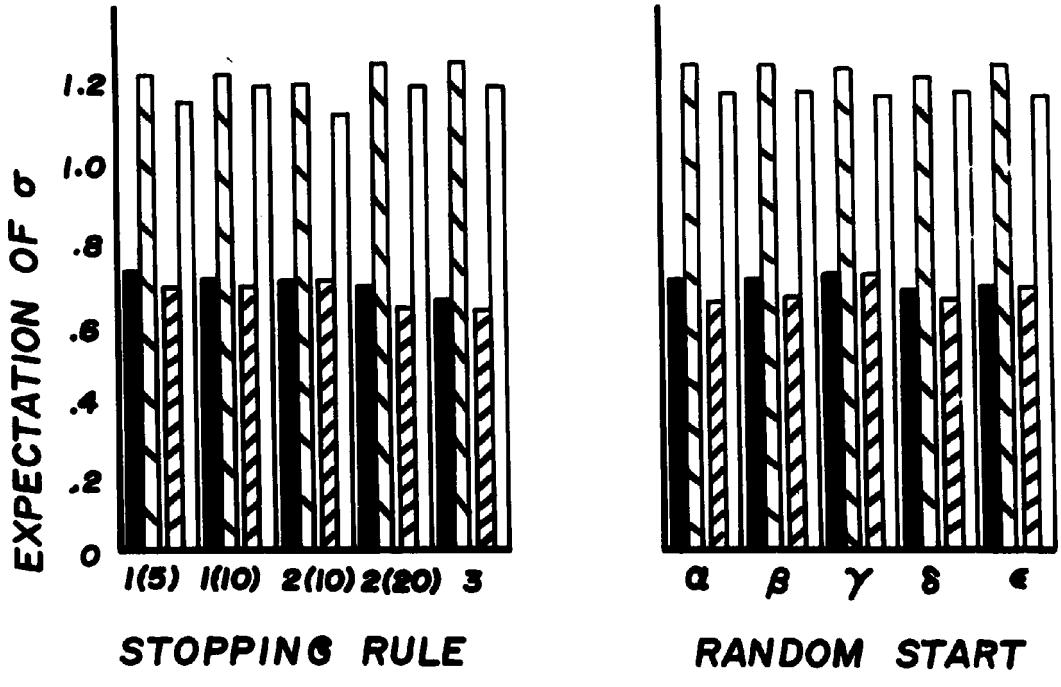


Table 32

Approximate Bias Corrections for
Mixed Experiment Estimators of σ

Fixed Experiment		Up and Down Estimator	Approximate Bias Correction	Approximate Variance
Levels	Estimator			
3	S-K	S-K	$(\hat{\sigma} - .28h)/ .62$	.10 - .20
		D-M	$(\hat{\sigma} - .24h)/ .63$	.15 - .30
	Probit	S-K	$\hat{\sigma}/1.14$	.10 - .40
		D-M $h<\sigma/2$	$(\hat{\sigma} - .4h) / .94$	.10 - .60
		$h>\sigma/2$	$\hat{\sigma}/1.14$	??
4	S-K	S-K	$(\hat{\sigma} - .24h)/ .56$	.10 - .20
		D-M	$(\hat{\sigma} - .17h)/ .63$	.15 - .30
	Probit	S-K	$(\hat{\sigma} + .08h)/1.22$	.10 -1.20
		D-M $h< \sigma/2$	$(\hat{\sigma} - .35h)/1.05$	.20 - .30
		$h> \sigma/2$	$(\hat{\sigma} + .10h)/1.28$	??
6	S-K	S-K	$(\hat{\sigma} - .18h)/ .58$	.10 - .20
		D-M	$(\hat{\sigma} - .15h)/ .59$	.15 - .25
	Probit	S-K	$(\hat{\sigma} + .18h)/1.37$	.15 -1.50
		D-M $h<\sigma/2$	$(\hat{\sigma} - .36h)/1.09$	.20 -1.10
		$h>\sigma/2$	$(\hat{\sigma} + .20h)/1.44$	??

and use $\sigma^* = (\hat{\sigma} - bh)/(a - bc)$ as an approximately unbiased estimator of σ. We then have

$$V(\sigma^*) = V(\hat{\sigma})/(a - bc)^2$$

which was used together with the maximum and minimum variances over the range of h from 1/8 to 2 as shown in Figures to to obtain crude approximations to the variances of the several corrected estimators. These bias corrections and corresponding variances require much further study to establish their validity but we feel that in the absence of more definitive results they may give some guidance in the selection of an estimation procedure if used cautiously. From the estimated variances of the uncorrected estimators, one would conclude that the probit estimators are decidedly inferior due to their variances being orders of magnitude larger than those corresponding to the Spearman-Karber estimators. However, when the approximate bias corrections are made these differences are reduced considerably since the variances of probit estimators are reduced and those of Spearman-Karber estimators are increased. It should be noted however that the variances for estimation at both stages by the Spearman-Karber procedure are still the smallest for each number of levels investigated. Whether these approximations are sufficiently accurate to warrant such conclusions is a question which can only be answered by further research.

All things taken together, we would prefer the use of Spearman-Karber estimation at both stages and a fixed stage experiment with at least four stimulus levels with a range set at about three standard deviations. It seems that this type of design should give moderate protection against degenerate estimates and reasonably precise estimation of both scale and location parameters.

FIGURE 52

ESTIMATED VARIANCES OF ESTIMATORS OF σ MIXED EXPERIMENTS 3 LEVELS IN FIXED STAGE

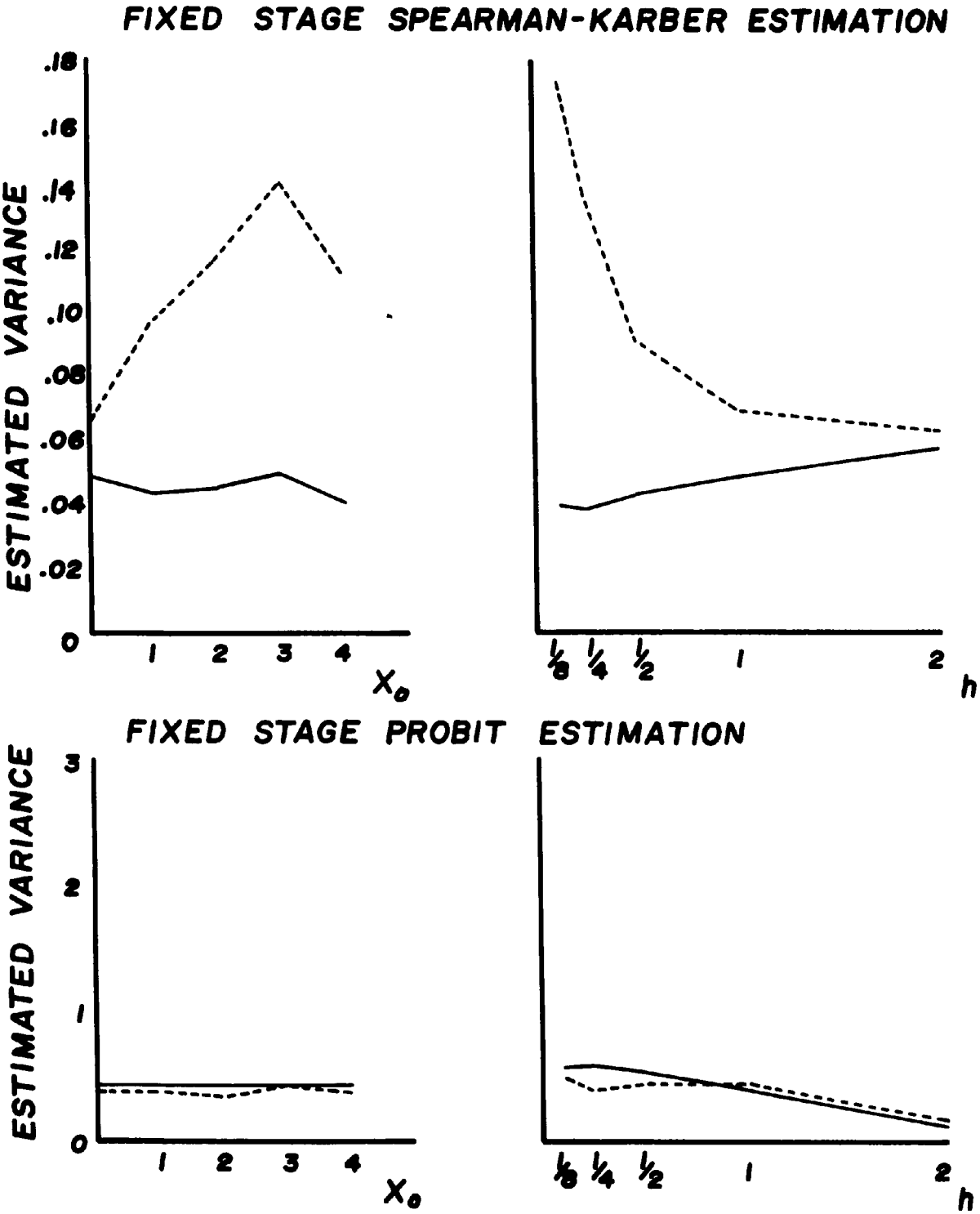


FIGURE 53

ESTIMATED VARIANCES OF ESTIMATORS OF σ
MIXED EXPERIMENTS 4 LEVELS IN FIXED STAGE

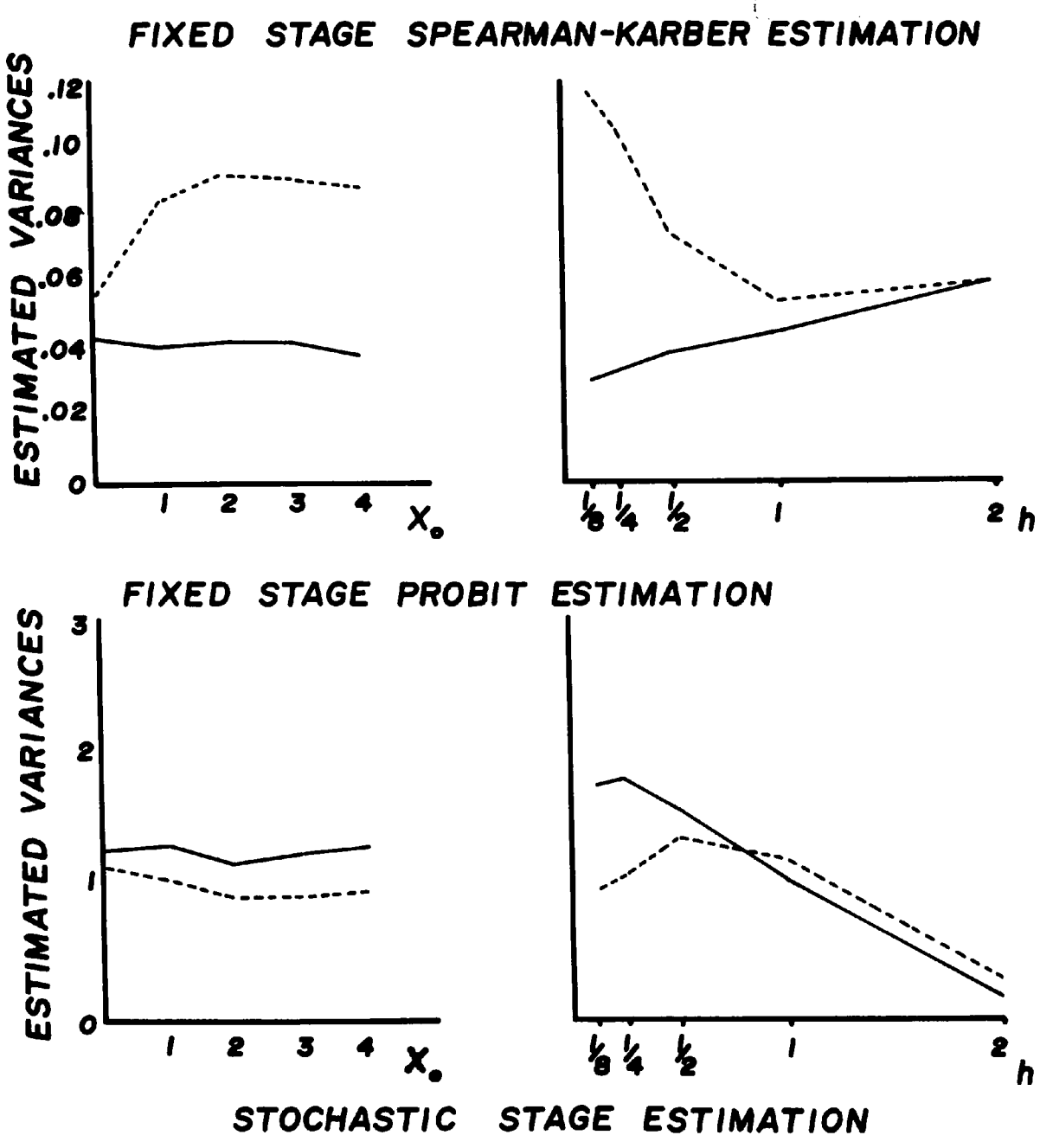
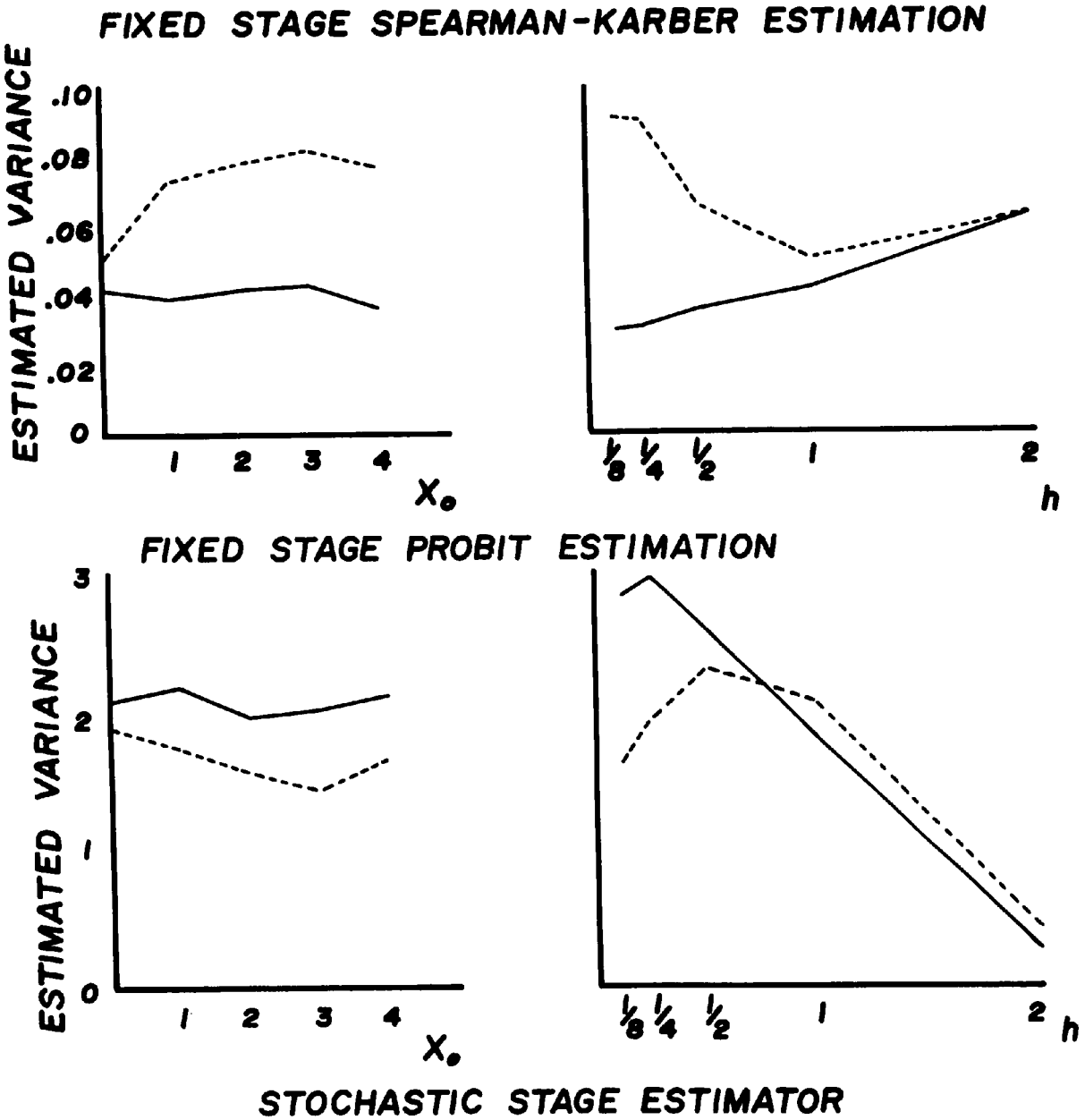


FIGURE 5.4

ESTIMATED VARIANCES OF ESTIMATORS OF σ MIXED EXPERIMENTS 6 LEVELS IN FIXED STAGE



#4.5 Comparisons of Strategies and Recommendations

As an aid to the exposition of this section we will introduce certain qualitative distinctions between states of prior information available to the experimenter. These are analogous to the classical formulation of the problem of estimation from data which follow the Gaussian distribution. In this formulation we usually set forth three situations: μ unknown and σ known, μ known and σ unknown, and both unknown. To correspond to the situation in which a parameter is known, we will say that prior information on a parameter is "good" if the prior estimate is "close" to the true value and if the experimenter is certain enough of his prior estimate that he is willing to risk the cost of experimentation on that prior estimate. This is a rather imprecise statement but one which could be quantitated by reference to a subjective probability distribution for the parameter in question. In Bayesian terms the experimenter must be willing to bet the expected cost of the experiment against the possibility that his prior estimate of the parameter is so far from the true value that his expected losses resulting from subsequent actions are unchanged or increased.

Although we will not attempt to carry out an analysis in these Bayesian terms in this dissertation, the logical framework provided suggests an approach to the problem which should be considered for further research. Here we will be content to distinguish between "good" and "poor" prior information for a parameter. Thus the experimental situations to which we shall address ourselves are: a) poor information on μ, good information on σ (estimation of μ), b) good information on μ, poor information on σ (estimation of σ), c) poor information on both parameters (estimation of μ and σ), and d) good information on

both μ and σ. This last has no analogue in the classical inference problem but one can consider it as the situation in which one experimenter is attempting to confirm the results of another by replication. In this case one is attempting to refine a previously obtained estimate using this latter to design the current experiment.

4.5.1 Estimation of μ. With a good prior estimate of σ the experimenter can design a fairly efficient up and down experiment and estimate μ with either the Dixon-Mood or the Spearman-Karber estimator. The former has been found to be slightly the less variable but its expectation is the more strongly influenced by events of low probability. Occasionally, the Dixon-Mood estimation procedure will require an iterative solution while the Spearman-Karber estimator can always be obtained in closed form. The latter is appropriate for any tolerance distribution for which the grouped mean and variance are defined,* while the Dixon-Mood estimator relies upon an assumption of a Gaussian tolerance distribution. It is not known what effect departures from this assumption may have on the estimator.

If the time required to execute a complete up and down experiment is excessive, a short sequence followed by a fixed experiment in a region where both positive and negative responses have been observed seems appropriate. If probit estimation is to be used in this fixed stage, then the subjects used should be concentrated at a few levels. If the Spearman-Karber estimator is to be used, rather more closely spaced levels should be used with fewer subjects per level. The use of Spearman-Karber estimates as starting points for the probit estimation is quite satisfactory, thus making completely automatized statistical analysis possible. For narrow spacings the Spear-

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*(perhaps by the truncation of tails of the distribution)

man-Karber estimator is considerably the less variable so that probit estimation seems unnecessary in this case.

4.5.2 Estimation of σ. No procedure which we have studied seems quite adequate without modifications. The probit estimator either in a fixed experiment or as the second stage of a mixed experiment has so great a variance compared to that of the Spearman-Karber estimator that we would be hesitant to recommend it. On the other hand, the bias corrections we have suggested are quite crude and require validation before we would be satisfied that the Spearman-Karber estimator would be satisfactory. Another line of attack would be to attempt to design a sequential experiment where one could have as the end product a set of stimuli and associated responses which would permit precise unbiased estimation of σ. This should include a stochastic determination of the spacing between range of levels.

4.5.3 Estimation of both parameters. In the same vein as the previous section we are concerned about the problem of estimation of σ. Again the type of experiment desired should permit early information obtained about σ to influence the spacing of subsequent levels. It should also incorporate the up and down type of concentration of levels near μ so as to increase the information per subject used. Again we must leave this topic to future research.

4.5.4 Refinement of good prior estimates. This is the only situation in which we would recommend the use of the fixed experiment without reservations. Provided one has prior estimates which are known to be quite close to the true values of the parameters, an efficient fixed ex-

periment can be designed. Spearman-Karber estimation would be our choice except for the bias of the estimator of σ. In any case, only large experiments can provide estimates which satisfy rigid precision requirements and the experimenter who makes such demands must be prepared to pay the price.

#4.6 Methodological Findings

4.6.1 Implications of extreme sample points with small probabilities. As we have seen in the discussion of the effective sample space for the fixed experiment, there exists a set of sample points which yield extreme estimates of the parameters. For an experiment with reasonably accurate prior information, these sample points have small probabilities. This fact causes some concern for those numerical studies of the quantal response problem which exclude extreme estimates since the variances so computed will be smaller than the true values for the probit estimators. Simulation studies which employ small random samples could frequently fail to observe any of these sample points thus leading to underestimates of the variances. Presumably, the characteristic of extreme estimates with small probabilities may be shared with stochastic experiments. If this is so, our estimates of variances of the Dixon-Mood estimators may be suspected of the same fault. Bross's "worth" [23] would appear to be affected by such a strategem if such sample points are ignored or if any arbitrary type of assignment of the corresponding probabilities is made.

For studies which calculate parameters of exact sampling distributions our only recommendation would be that all sample points be included regardless of their probabilities. In simulation studies, some form of stratified sampling which allows for oversampling among the extremes of

the distribution of the estimators would seem to be appropriate.

4.6.2 Combination of results. The separation of mixed experiments into fixed and sequential subexperiments and using the theory of conditional distribution is a natural step. Aside from the logical appeal of such an approach, there can be some rather practical advantages. From an operational standpoint, one advantage is that one can check results from each stage separately. A second advantage is that it could be possible to use intermediate results for other studies. By obtaining intermediate results in a form which can be used in the computer directly, it should be possible to communicate results between researchers at a level which can lead to economy in research effort. Due to the absence of this approach by others we have had to duplicate parts of the work of some other researchers. For instance, if moments of the joint distribution of probit and Spearman-Karber estimators are needed in the future for other investigations, these are available in a form in which they can be used directly in computers without the necessity of recomputation or copying from printed tables. It would seem that in the absence of coordinated attacks on theoretical problems, the researcher should make a reasonable attempt to carry out his work consistent with the goal of economy of effort.

CHAPTER 5

RECOMMENDATIONS FOR FURTHER RESEARCH

#5.1 Modifications of Spearman-Karber Estimators

From the results of the studies conducted, it appears that the bias of the Spearman-Karber estimator of σ has a sufficiently well defined relation to the errors of the prior estimates of the parameters as to make corrections for this bias feasible in all of the strategies. These possibilities should be explored more thoroughly and exploited.

#5.2 Economic and Bayesian Analysis

The study should be extended to consider more formally the various cost factors and goals of experimentation as well as the prior information. One approach would be the specification of loss functions in terms of the expectations and variances of the estimators and the use of subjective distributions of the parameters. With this kind of framework, certain recommendations could be made more specific.

#5.3 Other Mixed and Stochastic Strategies

Most of the stochastic strategies which have been proposed utilize only the information on μ gained in the course of the experiment. Strategies could be designed to modify the step size according to the observa-

tions obtained. It may be that information on σ gained in the experiment may be used in this fashion. The study of such strategies has heretofore been quite limited. [106] We feel that this type of strategy is a natural extension of the up and down and Robbins-Monro type experiments and that it merits further investigation.

#5.4 Alternative Tolerance Distributions

The Spearman-Karber estimators are estimators of moments. They would not be expected to perform satisfactorily for tolerance distributions without moments as estimators of other meaningful scale and location parameters are defined. The question of estimation from observations on such tolerance distributions needs investigation.

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APPENDIX

EXHIBIT A Flow chart and program listing for calculation of moments for fixed experiment estimators.

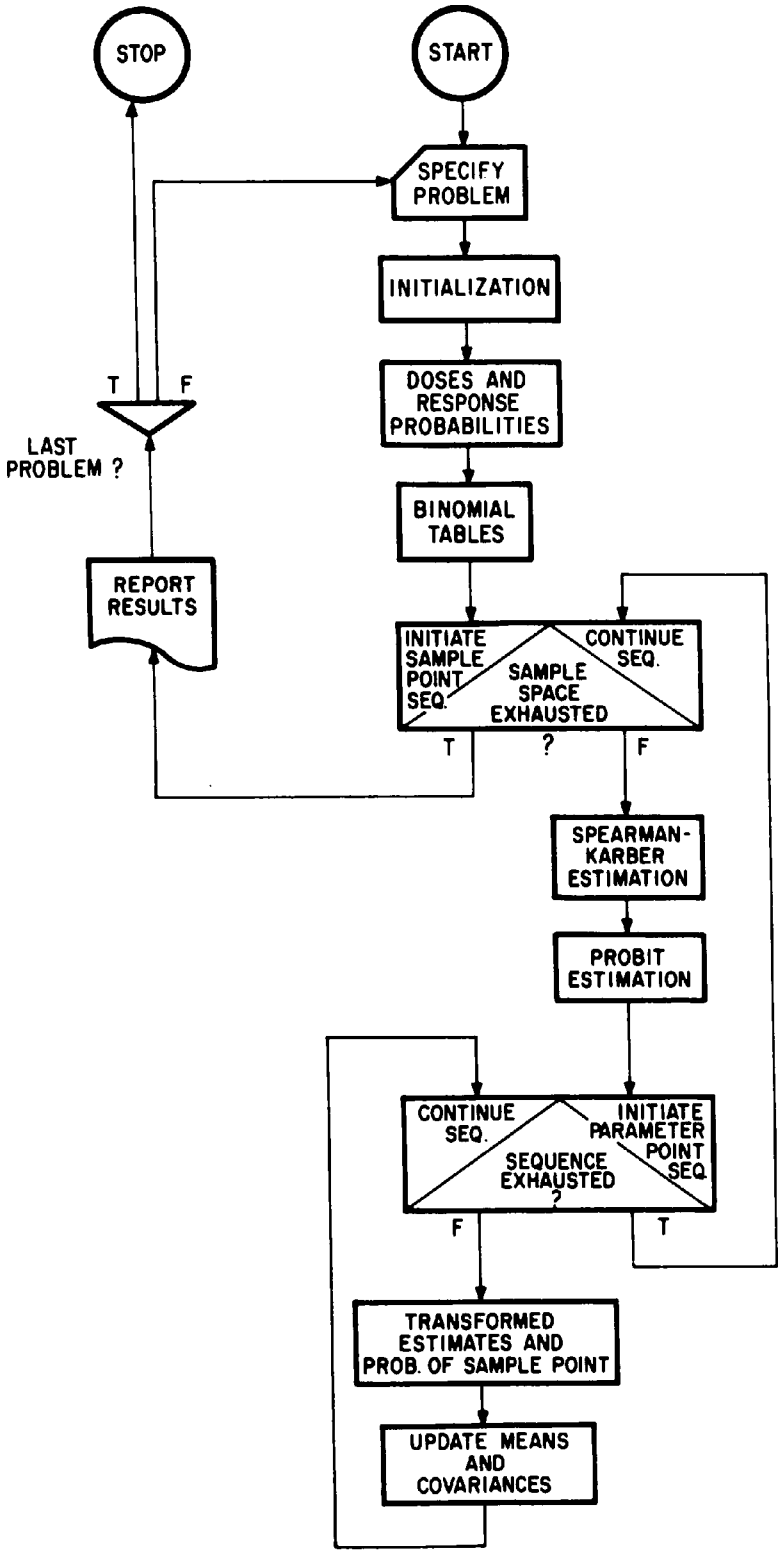
EXHIBIT B Flow chart and program listing for simulation of stochastic experiments.

EXHIBIT C Flow chart and program listing for estimation of moments of mixed experiment estimators.

EXHIBIT D Description of GRAFIX program.

EXHIBIT A

COMPUTATION OF JOINT FIRST AND SECOND MOMENTS
OF SPEARMAN-KARBER AND PROBIT ESTIMATORS
IN FIXED EXPERIMENT



```
$ASSEMBLE,PUNCH OBJECT, EXECUTE
****** MACRO PACKAGE
****** MACROS TO SAVE AND RESET INDEX REGISTERS 1,2, OR 4
SAVE    MACRO   T,A,XRT
        IFF     1,/CRS/T,8
        IFF     1,/CRS/A,5
        SXA     XRT,T
XR-T-A  MACRO
XRT     AXT     **,T
XR-T-A  ENDM
        SKIP
        SXA     XR-T,T
        SKIP
        STO     AC
        STQ     MQ
        SXA     XR1,1
        SXA     XR2,2
        SXA     XR4,4
SAVE    ENDM
RESET   MACRO   T,A
        IFF     1,/CRS/T,5
        IFF     1,/CRS/A,2
        XR-T-A
        SKIP
        LXA     XR-T,T
        SKIP
        CLA     AC
        LDQ     MQ
        LXA     XR1,1
        LXA     XR2,2
        LXA     XR4,4
RESET   ENDM
****** MACRO TO SIMULATE WHENEVER TYPE OF CONDITIONAL
*       WHNVR   X,TEST,Y,TRUE,FALSE
*       X       LOCATION TO BE COMPARED WITH Y.  IF AC THE C(AC) WILL BE
*               IF X IS MQ THE C(MQ) WILL BE USED.
*       TEST    A BOOLEAN RELATION, .G.,.GE.,.E.,.LE.,.L.,.NE.
*       Y       THE SECOND OPERAND
*       TRUE    LOCATION TO WHICH CONTROL IS TO BE TRANSFERRED IF
*               RELATION IS TRUE
*       FALSE   LOCATION TO WHICH CONTROL IS TRANSFERRED IF RELATION
*               IS FALSE.  IF -FALSE- IS MISSING CONTROL TRANSFERS TO
*               NEXT OPERATION AFTER CONDITIONAL
WHNVR   MACRO   X,TEST,Y,TRUE,FALSE
        IFF     0,X,AC
        CLA     X
        IFF     1,X,MQ
        XCA
        CAS     Y
        IFF     1,TEST,.G.,7
        IFF     1,TEST,.GE.,6
        IFF     1,TEST,.NE.,5
        IFF     1,/CRS/FALSE,2
        TRA     FALSE
        SKIP    1
```

```
          TRA     *+3
          SKIP    1
          TRA     TRUE
          IFF     1,TEST,.GE.,7
          IFF     1,TEST,.E.,6
          IFF     1,TEST,.LE.,5
          IFF     1,/CRS/FALSE,2
          TRA     FALSE
          SKIP    1
          TRA     *+2
          SKIP    1
          TRA     TRUE
          IFF     1,TEST,.LE.,7
          IFF     1,TEST,.L.,6
          IFF     1,TEST,.NE.,5
          IFF     1,/CRS/FALSE,2
          TRA     FALSE
          SKIP    1
          TRA     *+1
          SKIP    1
          TRA     TRUE
WHNVR     END
****** IFP      MACRO TO CONVERT INTEGER C(AC) TO FLOATING POINT
IFP       MACRO
          ORA     =K233K9
          FAD     =K233K9
          END
****** FPI      MACRO TO CONVERT FLOATING POINT C(AC) TO INTEGER
FPI       MACRO
          UFA     =K233K9
          FRA     =K233K9
          LLS     0
          END
****** MACRO TO SIMULATE INTEGER THRU LOOP
*         THRU    LOOP,T,IO,DI,IMAX
*         LOOP    DUMMY OPCODE (DO NOT USE OPS OR PSEUDO-OPS)
*                 USED TO TERMINATE LOOP
*         T       TAG INDICATING INDEX REGISTER TO BE USED (1,2, OR 4)
*         IO      INITIAL VALUE OF INTEGER COUNTER
*         DI      INCREMENT TO BE USED ON COUNTER
*         IMAX    MAXIMUM VALUE OF COUNTER ALLOWED
*         WHEN    /H/X*/B/606060606060,.E.,0,5
*         DETERMINES WHETHER X IS A NUMBER OR A SYMBOL
*         IF X IS A NUMBER, EXPANSION CONTINUES WITH THE CARD LABELED S
*         FOR S A SYMBOL OR THE S+1ST CARD FOLLOWING IF S IS A NUMBER
*         IF T IS A SYMBOL, THEN A FLOATING POINT LOOP IS CONSTRUCTED
THRU      MACRO   LOOP,T,IO,DI,IMAX,XRT,CHECK,FLOAT
          WHEN    /H/T*/B/606060606060,.NE.,0,FLOAT
          SXA     XRT,T
          WHEN    /H/IMAX*/B/606060606060,.E.,0,2
          LXA     IMAX,T
          SXD     CHECK,T
          WHEN    /H/DI*/B/606060606060,.E.,0,2
          LXA     DI,T
          SXD     XRT-1,T
          WHEN    /H/IO*/B/606060606060,.E.,0,2
```

```
         LXA     I0,T
         SKIP    1
         AXT     I0,T
CHECK    TXH     XRT,T,IMAX
LOOP     MACRO
         TXI     CHECK,T,DI
XRT      AXT     **,T
LOOP     ENDM
         SKIP
FLOAT    CLA     I0
CHECK    STO     T
         FSB     IMAX
         TMI     *+2
         TRA     XRT+1
LOOP     MACRO
         CLA     T
         FAD     DI
XRT      TRA     CHECK
LOOP     ENDM
THRU     ENDM
****** MACRO TO OBTAIN UP TO FOUR VALUES FROM THE P,F,W0,W1 TABLES
*        RDTAB   ((A,P)(B,F)(C,W0)(D(W1))X,T,MODE
*        A,B,C,D ARE THE LOCATIONS WHERE THE VALUES ARE TO BE STORED
*        X IS THE COMMON VALUE OF THE ARGUMENT
*        T IS THE INDEX REGISTER TO BE USED (1,2,4)
*        IF MODE IS LINEAR A LINEAR INTERPOLATION WILL BE CARRIED OUT
*        OTHERWISE THE VALUE RETURNED WILL BE THE TABULAR VALUE CORRESPOND
*        TO THE NEAREST 100TH PART OF THE ARGUMENT
RDTAB    MACRO   VALTAB,ARG,T,MODE,ZOUT,OUT,LAST
         SAVE    T
         CLA     ARG
         SSP
         WHNVR   AC,.G.,=5.,ZOUT+1
         XCA
         FMP     =100.
         IFF     0,MODE,LINEAR
         FAD     =.5
         FRN
         FPI
         PAX     ,T
         IFF     0,MODE,LINEAR,9
         IFP
         FDP     =100.
         XCA
         SSM
         FAM     ARG
         STO     TEMP4
         SSM
         FAD     =1.
         STO     TEMP5
         IRP     VALTAB
         IFF     1,MODE,LINEAR,2
         NINTRP  VALTAB,T
         SKIP    1
         LINTRP  VALTAB,T
         IRP
```

```
ZOUT    TRA     OUT
        IRP     VALTAB
        SPCVAL  VALTAB,ARG
        IRP
OUT     EQU     *
        IRP     VALTAB
        SETP    VALTAB,LAST,ARG
        IRP
LAST    RESET   T
RDTAB   END
****** MACRO TO PICK OUT SPECIAL VALUES WHEN .ABS.X .G.5.
SPCVAL  MACRO   VAL,TAB,ARG,T
        IFF     0,TAB,F,2
        STZ     VAL
        SKIP
        IFF     0,TAB,P,3
        CLA     =1.
        STO     VAL
        SKIP
        IFF     0,TAB,W0,6
        IFF     1,/CRS/T,2
        CLA     ARG,T
        SKIP    1
        CLA     ARG
        STO     VAL
        SKIP
        IFF     1,TAB,W1
        STZ     VAL
SPCVAL  END
****** MACRO TO SET THE VALUE OF P TO 1-P IF X.L.5.
SETP    MACRO   VAL,TAB,LAST,ARG,T
        IFF     0,TAB,P
        SKIP
        IFF     1,/CRS/T,2
        CLA     ARG,T
        SKIP    1
        CLA     ARG
        TPL     LAST
        CLS     VAL
        FAD     =1.
        STO     VAL
SETP    END
****** MACRO WHICH DOES NO INTERPOLATION
NINTRP  MACRO   VAL,TAB,T
        CLA     TAB,T
        STO     VAL
NINTRP  ENDM
****** MACRO WHICH DOES LINEAR INTERPOLATION
LINTRP  MACRO   VAL,TAB,T
        LDQ     TEMP4
        FMP     TAB-1,T
        STO     VAL
        LDQ     TEMP5
        FMP     TAB,T
        FAD     VAL
        STO     VAL
```

```
LINTRP ENDM
****** MACRO TO ACHIEVE AN ARBITRARY NUMBER OF STZ INSTRUCTIONS
STZERO MACRO   X
       IRP     X
       STZ     X
       IRP
STZERO ENDM
****** MACRO TO SET ARBITRARY NUMBER OF SWITCHES
SWITCH MACRO   P,MODE
       IRP     P
       CLA     MODE-P
       STO     SW+P
       IRP
SWITCH ENDM
****** MACRO TO STORE INDEX T IN AN ARBITRARY NUMBER OF ADDRESSES
SXADD  MACRO   LOCS,T
       IRP     LOCS
       SXA     LOCS,T
       IRP
SXADD  ENDM
****** MACRO TO STORE INDEX T IN AN ARBITRARY NUMBER OF DECREMENTS
SXDEC  MACRO   LOCS,T
       IRP     LOCS
       SXD     LOCS,T
       IRP
SXDEC  ENDM
****** PROGRAM COMMON ASSIGNMENT
P      PGMCOM  500
F      PGMCOM  500
W0     PGMCOM  500
W1     PGMCOM  500
T      PGMCOM  5000
BINP   PGMCOM  7K/30000
DOSE   PGMCOM  10
CDF    PGMCOM  10
R      PGMCOM  10
RF     PGMCOM  10
LOGN   PGMCOM  10
X      PGMCOM  10
M      PGMCOM  30
S      PGMCOM  50
D      PGMCOM  4
EST    PGMCOM  4
TREST  EQU     D
SPACE  PGMCOM  3
       NOMAC
       PMC     OFF
       CALL    FTRAP
       SWITCH  (4,6,8,9,10,11,12)ON
       SWITCH  13,OFF
****** COMPUTATION OF MEAN VECTOR AND COVARIANCE MATRIX OF SPEARMAN-
****** KARBER ESTIMATORS AND THE PROBIT ESTIMATORS OVER THE RESTRICTED
****** SAMPLE SPACE CONSISTING OF THAT SUBSET IN WHICH THE PROBIT
****** ESTIMATORS HAVE DETERMINATE VALUES AND THE ESTIMATOR OF SIGMA IS
****** POSITIVE.  SAMPLE POINTS FOR WHICH THE PROBIT METHOD DOES NOT
****** CONVERGE WITHIN -ITMAX- ITERATIONS ARE ALSO EXCLUDED.
```

```
         NEWID   START
START    PRINT   =H1H1*   ,0
         RPDATA
         WHNVR   (SW13).NE.(ON13),GO
         CALL    SETEOF,EOF
         CALL    SETREC,K
GO       SWITCH  (2,3,5)ON
         PROCT   SW1,ON1,OFF1                    SWITCH 1 CONTROLS
         ENDCS                          ELIMINATION OF NEGATIVE SLOPE ESTIMATES
         PROCT   SW2,ON2,OFF2                    SWITCH 2 CONTROLS
         ENDCS                          EVALUATION OF MCODE (FIRST POINT ONLY)
         PROCT   SW3,ON3,OFF3                    SWITCH 3 CONTROLS
         ENDCS                          EVALUATION OF MSCODE (FIRST POINT ONLY)
         PROCT   SW4,ON4,OFF4                    SWITCH 4 CONTROLS
         ENDCS                          PRINTING OF TRANSFORMED ESTIMATES
         PROCT   SW5,ON5,OFF5                    SWITCH 5 CONTROLS
         ENDCS                          THE SETTINGS OF SWITCHES 2,3,5
         PROCT   SW6,ON6,OFF6                    SWITCH 6 CONTROLS
         ENDCS                          PRINTING OF INTERMEDIATE M L ESTIMATES
         PROCT   SW7,A7,B7,C7                    SWITCH 7 CONTROLS
         ENDCS                          FLOW AFTER PRINTING OF M L ESTIMATES
         PROCT   SW8,ON8,OFF8                    SWITCH 8 CONTROLS
         ENDCS                          PRINTING OF BINOMIAL TABLES
         PROCT   SW9,ON9,OFF9                    SWITCH 9 CONTROLS
         ENDCS                          PRINTING OF S K ESTIMATES
         PROCT   SW10,ON10,OFF10                 SWITCH 10 CONTROLS
         ENDCS                          PRINTING OF FINAL M L ESTIMATES
         PROCT   SW11,ON11,OFF11                 SWITCH 11 CONTROLS
         ENDCS                          PRINTING OF RESPONSE PATTERN
         PROCT   SW12,ON12,OFF12                 SWITCH 12 CONTROLS
         ENDCS                          PRINTING OF COMPLEMENTARY POINT COMMENT
         PROCT   SW13,ON13,OFF13                 SWITCH 13 CONTROLS
         ENDCS                          RECORDING OF ESTIMATES ON TAPE
******   CHECKS ON K AND N
         LXA     N,1
         TXH     BIGN,1,10
         LXA     K,2
         TXH     BIGK,2,10
******   COMPUTATION OF AUXILIARY QUANTITIES
         TXI     *+1,1,1
         TXI     *+1,2,1
         SXA     N+1,1
         SXA     K+1,2
         SXDEC   (BNCMP6,PCOMP1),1
         TXI     *+1,2,-2
         TXI     *+1,1,-2
         SXA     N-1,1
         SXA     K-1,2
         CLA     N
         IFP
         STO     NF
         FSB     =1.
         STO     NF-1
         FAD     =2.
         STO     NF+1
         CLA     K
```

```
          IFP
          STO       KF
          FSB       =1.
          STO       KF-1
          FAD       =2.
          STO       KF+1
          LDQ       N+1
          MPY       K
          MPY       PAR
          STQ       DIM
          CLA       =K30000
          TLQ       *+2
          TRA       BADIM
          CLS       PAR
          ALS       4
          ADD       =XT
          PAX       ,4
          SXA       DESIST+6,4
          SXD       DESIST+2,4
          LAC       K,1
          TXI       *+1,1,DOSE
          SXD       BNCMP4,1
          TXI       *+1,1,CDF-DOSE
          SXD       BNCMP5,1
          TXI       *+1,1,R-CDF
          SXD       CNTNU1,1
          SXD       ITEXIT+2,1
          TXI       *+1,1,X-R
          SXD       PSD,1
          CLA       K
          ADD       K+1
          XCA
          MPY       N
          STO       2KNPN
          LDQ       K
          MPY       N
          STO       KN
          LDQ       NF
          FMP       NF
          FDP       =12.
          STO       SHEP
          LDQ       N
          MPY       K-1
          XCA
          IFP
          STO       TEMP
          CLA       Z
          FDP       TEMP
          FMP       =2.
          STO       HDN
*******   GET NKZ CODE AND STORE IN FORMAT TABLES
          CLA       N
          ALS       24
          STO       TEMP
          CLA       K
          ALS       12
```

```
         ORS     TEMP
         CLA     Z
         FPI
         ORA     TEMP
         STO     T
         STO     DECKID
         ORA     =HZ00000
         SLW     TABLES+1
         THRU    LOOP1,I,1,1,K
         PXA     ,1
         ALS     1
         SUB     K+1
         IFP
         FDP     KF-1
         FMP     Z
         STO     X,1
         LOOP1
         PRINT   STDOSE
PSD      IOP     X-1,,**
         ENDIO
         CALL    ZERO,T=5000,...,T-1
******   COMPUTE DOSES, PROBABILITIES OF RESPONSE, AND BINOMIAL TABLES
         NEWID   BNCMP
BNCMP    AXT     0,2
         THRU    LOOP1,1,1,1,NM
         CLA     M,1
         STO     M
         PRINT   MFMT,M,0
         THRU    LOOP2,1,1,1,NS
         LDQ     S,1
         STQ     S
         FMP     Z
         STO     TEMP
         CHS
         FAD     M
         STO     DOSE-1
         PRINT   SFMT,S,0
         CLA     TEMP
         ADD     =K1K9
         FDP     KF-1
         STQ     H
         SAVE    2,1
******   COMPUTE DOSES AND PROBABILITIES OF RESPONSE
         THRU    LOOP3,1,1,1,K
         CLA     DOSE,1
         FAD     H
         STO     DOSE-1,1
         RDTAB   T(CDF,PT)(DOSE,1)4,LINEAR
         CLA     CDF
         STO     CDF,1
         CHS
         FAD     =1.
         STO     Q
         CALL    LOG10,CDF,CDFO
         STO     TEMP1
         CALL    LOG10,Q,QQ
```

```
          STO       TEMP2
          XCA
          FMP       NF
          STO       TEMP
******    COMPUTE BINOMIAL TABLES
          LXA       N,4
BNCMP1    THRU      LOOP4,1,0,1,N
          SAVE      4,1
          CALL      EXP3,=10.,TEMP,BNCMP2-1
          WHNVR     AC,.G.,=1.E-37,BNCMP2
          ZAC
BNCMP2    STO       BINP,2
          RESET     4,1
          CLA       TEMP
          FAD       TEMP1
          FSB       TEMP2
          FAD       LOGN,4
          FSB       LOGN-1,1
          STO       TEMP
          TIX       *+1,4,1
          TXI       *+1,2,1
BNCMP3    LOOP4
          LOOP3
******    PRINT OUT DOSES
          PRINT     DOSES
BNCMP4    IOP       DOSE-1,,**
          ENDIO
******    PRINT OUT PROBABILITIES OF RESPONSE
          PRINT     PROBS
BNCMP5    IOP       CDF-1,,**
          ENDIO
******    PRINT OUT BINOMIAL TABLES
SW8       PRINT     BNTAB0,1,0
          SAVE      2,2
          THRU      LOOP3,1,0,1,N
          RESET     2,1
          SAVE      1
          SXD       *+1,1
          TXI       *+1,2,XR1
          PRINT     BNTAB1,XR1
          THRU      LOOP4,1,1,1,K
          IOP       BINP,2
BNCMP6    TXI       *+1,2,**      C(N+1)ADD
          LOOP4
          ENDIO
          LOOP3
          RESET     2,2
ESW8      LOOP2
          LOOP1
******    INITIALIZE GENERATOR
          NEWID     INIT
          TRA       SETCRN
******    PRINT OUT RESPONSE PATTERN
          NEWID     CNTNUE
CNTNUE    SWITCH    1,ON
SW11      PRINT     NDEAD
```

```
CNTNU1  IOP     R-1,,**
        ENDIO
******  SPEARMAN-KARBER ESTIMATION
        NEWID   SKEST
SKEST   CLS     S0
        ALS     1
        ADD     KN
        IFP
        FDP     =2.
        FMP     HDN
        STO     M
        STO     EST-1
        CLS     S1
        ALS     1
        XCA
        MPY     N
        STQ     TEMP
        CLA     2KNPN
        SUB     S0
        XCA
        MPY     S0
        XCA
        ADD     TEMP
        IFP
        FSB     SHEP
        STO     TEMP
        CLA     S11
        IFP
        FDP     NF-1
        XCA
        FAD     TEMP
        STO     S
        CALL    SQRT,S
        XCA
        FMP     HDN
        STO     S
        STO     EST-2
SW9     PRINT   SKFMT,M,S,J
        MIDDLE
******  MAXIMUM LIKELIHOOD ESTIMATION
        NEWID   MLEST
MLEST   STZ     IT
        CLA     =1.
        FDP     S
        STQ     B
        FMP     M
        CHS
        STO     A
MLEST1  STZERO  (L1,L2,L11,L12,L22)
        THRU    LOOP1,1,1,1,K
        LDQ     X,1
        FMP     B
        FAD     A
        STO     X
        RDTAB   ((TEMP,P)(TEMP1,W)(TEMP2,W1))X,2
        LDQ     TEMP
```

```
          FMP       NF
          CHS
          FAD       RF,1
          XCA
          FMP       TEMP1
          STO       TEMP1
          FAD       L1
          STO       L1
          LDQ       TEMP1
          FMP       X,1
          FAD       L2
          STO       L2
          LDQ       NF
          FMP       TEMP2
          STO       TEMP2
          FAD       L11
          STO       L11
          LDQ       TEMP2
          FMP       X,1
          STO       TEMP1
          FAD       L12
          STO       L12
          LDQ       TEMP1
          FMP       X,1
          FAD       L22
          STO       L22
          LOOP1
          CLA       L1
          SSP
          SUB       DELTA
          TPL       MLEST2
          CLA       L2
          SSP
          SUB       DELTA
          TPL       MLEST2
          SWITCH    7,A
          TRA       MLEST5
MLEST2    ZET       L12
          TRA       MLEST3
          CLA       L1
          FDP       L11
          XCA
          STO       TEMP3
          FAD       A
          STO       A
          CLA       L2
          FDP       L22
          XCA
          STO       TEMP4
          FAD       B
          STO       B
          TRA       MLEST6
MLEST3    CLA       L11
          FDP       L12
          STO       TEMP
          FMP       L22
```

```
          FSB     L12
          STO     TEMP1
          LDQ     TEMP
          FMP     L2
          FSB     L1
          FDP     TEMP1
          XCA
          STO     TEMP4
          FAD     B
          STO     B
          CLA     L22
          FDP     L12
          FMP     L1
          FSB     L2
          FDP     TEMP1
          XCA
          STO     TEMP3
          FAD     A
          STO     A
MLEST6    CLA     TEMP3
          SSP
          CAS     EPSA
          TRA     MLEST4
          TRA     *+1
          CLA     TEMP4
          SSP
          CAS     EPSB
          TRA     MLEST4
          TRA     *+1
          SWITCH  7,A
          TRA     MLEST5
MLEST4    WHNVR   (IT).GE.(ITMAX)ITEXIT
          ADD     =1
          STO     IT
SW6       TRA     *+1
          SWITCH  7,B
          TRA     MLEST5
ITEXIT    PRINT   NOEAD
          TOP     A-1,,**
          ENDIO
          SWITCH  7,C
MLEST5    CLA     =1.
          FDP     B
          STQ     S
          STO     EST-4
          FMP     A
          CHS
          STO     M
          STO     EST-3
SW10      PRINT   MLFMT,IT,L1,L11,M,L2,L12,L22,S,J
SW7       TRA     SW13
SW13      TRA     *+1
          DESIST
          SAVE
          CALL    RECORD,K
          RESET
```

```
          RESUME
          CLA     S
          TMI     SW1
****** LOOP ON PARAMETER POINTS
          NEWID   LOOPM
LOOPM     AXT     0,2
          STZ     TSS
          THRU    LOOP1,1,1,1,NM
          CLA     M,1
          STO     M
SW2       PXA     ,1
          XCA
          MPY     =1000
          STQ     MCODE
LOOPS     THRU    LOOP2,1,1,1,NS
          CLA     S,1
          STO     S
SW3       PXA     ,1
          ADD     MCODE
          STO     MSCODE
          LXA     TSS,4
          STO     T-1,4
****** COMPUTE PROBABILITY OF SAMPLE POINT
          NEWID   PCOMP
PCOMP     LDQ     =1.
          STQ     TREST
          THRU    LOOP3,1,1,1,K
          SAVE    2,1
          CLA     R,1
          ALS     18
          STD     *+1
          TXI     *+1,2,0
          LDQ     TREST
          FMP     BINP,2
          STO     TREST
          RESET   2,1
PCOMP1    TXI     *+1,2,**        C(N+1)ADD
          LOOP3
PTEST     NHITVR  MQ,,L,,PMIN,,PZERO
****** TRANSFORM ESTIMATES
          NEWID   TRXFRM
TRXFRM    LDQ     EST-1
          FMP     S
          FAD     M
          STO     TREST-1
          LDQ     EST-2
          FMP     S
          STO     TREST-2
          LDQ     EST-3
          FMP     S
          FAD     M
          STO     TREST-3
          LDQ     EST-4
          FMP     S
          STO     TREST-4
SW4       PRINT   TRESTS,TREST,...,TREST-4,0
```

```
****** UPDATE COVARIANCE MATRIX
       NEWID   COVM
COVM   LXA     TSS,4
       CLA     T-2,4
       STO     TEMP
       FAD     TREST
       STO     T-2,4
       CLA     TREST
       FDP     T-2,4
       STO     TEMP1
       CLA     TEMP
       FDP     T-2,4
       STO     TEMP
       THRU    LOOP3,1,1,1,4
       SAVE    1
       CLA     TREST,1
       FSB     T-2,5
       STO     TEMP2
       XCA
       FMP     TEMP1
       STO     D,1
       FAD     T-2,5
       STO     T-2,5
       CLA     TSS,1
       PAX     ,1
       THRU    LOOP4,2,1,1,XR1
       LDQ     D,2
       FMP     TEMP2
       FAD     T-1,5
       XCA
       FMP     TEMP
       STO     T-1,5
       TXI     *+1,1,1
       LOOP4
       RESET   1
       LOOP3
PZERO  CLA     TSS
       ADD     =16
       STO     TSS
       LOOP2
       LOOP1
SW5    TRA     *+1
       SWITCH  (2,3,5)OFF
       TRA     GEN
****** SAMPLE SPACE EXHAUSTED
       NEWID   DESIST
DESIST PRINT   TABLES
       TOP     T-1,,**
       ENDIO
       CALL    PCPCH,DECKID
       PLK     **,,1
       PRINT   ENDT,T,1
       CLS     =1
       STO     K
       CALL    RECORD,K
       TRA     START
```

```
****** SETUP FOR INCLUSION OF COMPLEMENTARY POINT
       NEWID   RCOMP
SW1    TRA     *+1
RCOMP  SWITCH  1,OFF
       THRU    LOOP1,1,1,1,K
       CLS     R,I
       ADD     N
       STO     R,1
       IFP
       STO     RF,1
       LOOP1
       CLS     S0
       ADD     KN
       STO     S0
       LDQ     KN
       MPY     K+1
       XCA
       ARS     1
       SUB     S1
       STO     S1
SW12   PRINT   COMPLP,0
       TRA     SW11
****** SAMPLE SPACE GENERATOR      SETUP ENTRY
       NEWID   SETGEN
SETGEN STZ     NPGEN
       CALL    EXP1,N+1,K
       SUB     =1
       ARS     1
       STO     RMAX
       CLA     N
       STO     R
****** SAMPLE SPACE GENERATOR      NORMAL ENTRY
       NEWID   GEN
GEN    STZERO  (S0,S1,S11)
       CLA     R
       ADD     =1
       STO     R
       WHNVR   AC,.G.,RMAX,NUPAGE
       STZ     OP1
       STZ     1P0
       SAVE    2
       LXA     K,2
       LDQ     R
GEN0   ZAC
       DVP     N+1
       STO     R,2
       STO     TEMP
       ADD     S0
       STO     S0
       PXA     ,2
       XCA
       MPY     R,2
       XCA
       ADD     S1
       STO     S1
       CLS     R,2
```

```
        ADD     N
        XCA
        MPY     R,2
        XCA
        ADD     S11
        STO     S11
        CLA     R,2
        IFP
        STO     RF,2
        LDQ     R,2
        CLA     OP1
        CAS     =1
        TRA     GEN3
        TRA     GEN2
GEN1    XCA
        CAS     N
        CALL    ERROR
        TRA     *+3
        LDQ     =1
        STQ     OP1
        XCA
        TRA     GEN3
GEN2    XCA
        TZE     *+3
        LDQ     =2
        STQ     OP1
        XCA
GEN3    CLA     IPO
        CAS     =1
        TRA     GEN5
        TRA     GEN4
        XCA
        TZE     *+3
        LDQ     =1
        STQ     IPO
        XCA
        TRA     GEN5
GEN4    XCA
        CAS     N
        CALL    ERROR
        TRA     GEN5-1
        LDQ     =2
        STO     IPO
        XCA
GEN5    LDQ     TEMP
        TIX     GEN0,2,1
        RESET   2
        CLA     =1
        CAS     OP1
        TRA     GEN
        TRA     GEN
        CAS     IPO
        TRA     GEN
        TRA     GEN
        LDQ     K+1
        MPY     SO
```

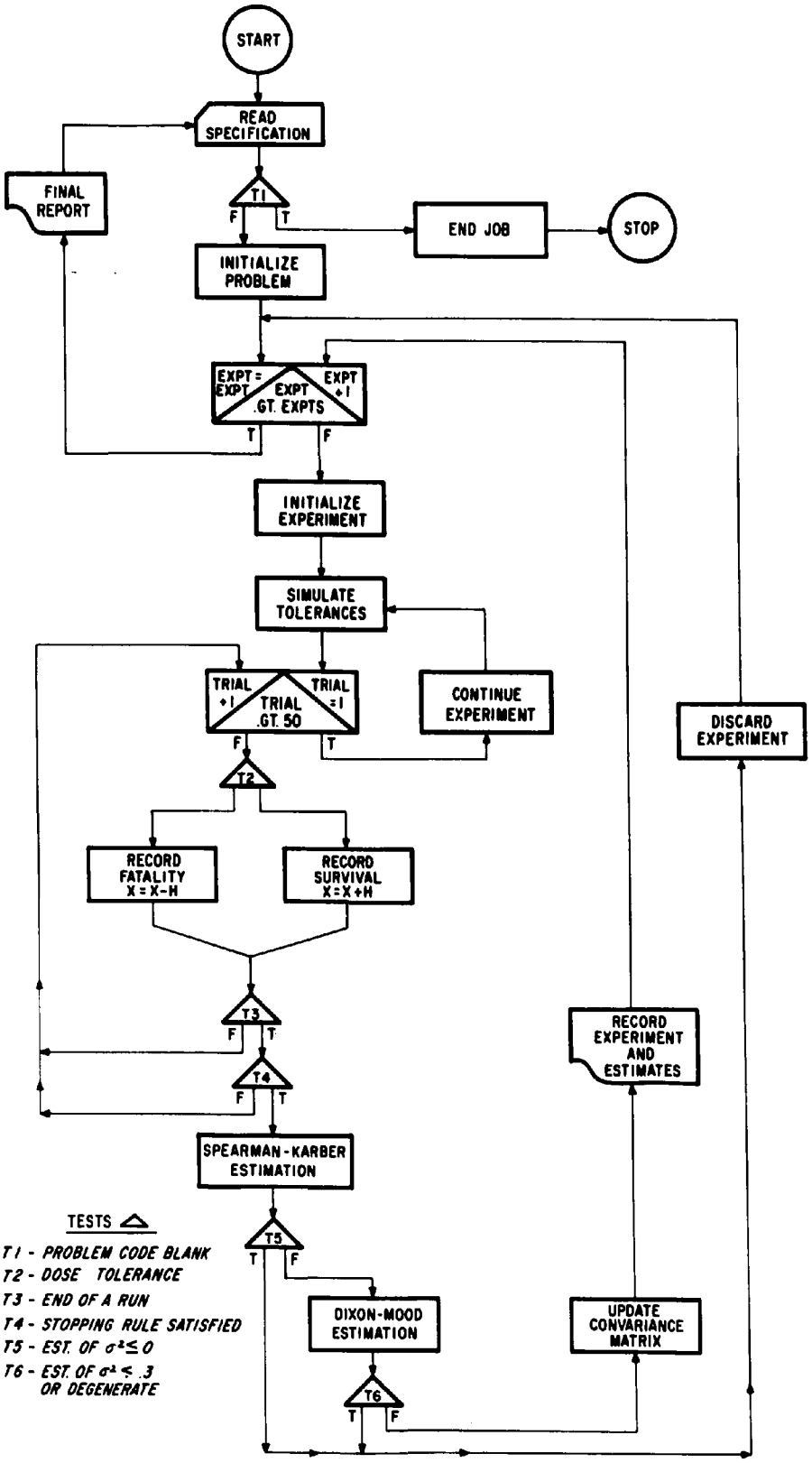
```
          STQ     TEMP
          CLA     S1
          ALS     I
          SUB     TEMP
          TZE     GEN
          TMI     RCOMP
          CLA     NPGEN
          ADD     =1
          STO     NPGEN
          TRA     CNTNUE
****** SPECIAL COMPUTATION OF BINOMIAL TABLE IF P OR Q IS ZERO
          NEWID   CDFC
CDF0      CLA     =1.
          STO     BINP,2
          THRU    LOOP4,1,1,1,N
          TXI     *+1,2,1
          STZ     BINP,2
          LOOP4
          TXI     BNCMP3+2,2,1
Q0        THRU    LOOP4,1,0,1,N-1
          STZ     BINP,2
          TXI     *+1,2,1
          LOOP4
          CLA     =1.
          STO     BINP,2
          TXI     BNCMP3+2,2,1
****** ERROR COMMENTS
          NEWID   ERRORS
BIGN      PRINT   NCOMNT,N,0
          TRA     START
BIGK      PRINT   KCOMNT,K,0
          TRA     START
BADIM     PRINT   DIMCMNT,DIM,0
          TRA     START
ZNEG      PRINT   NGCMNT,0
          CALL    ERROR
NUPAGE    PRINT   =H1H1*   ,0
          TRA     DESIST
EOF       CLS     =2
          STO     R
          CALL    RECORD,K
****** SWITCHES
          NEWID   SWITCH
ON1       TRA     SW1+1
OFF1      TRA     ZNEG
ON2       PXA     ,1
OFF2      TRA     LOOPS
ON3       PXA     ,1
OFF3      TRA     PCOMP
ON4       CALL10  .PRINT
OFF4      TRA     COMM
ON5       TRA     SW5+1
OFF5      TRA     GEN
ON6       TRA     SW6+1
OFF6      TRA     MLEST1
A7        TRA     SW13
```

```
B7      TRA     MLEST1
C7      TRA     GEN
ON8     CALLIO  *PRINT
OFF8    TRA     ESW8
ON9     CALLIO  *PRINT
OFF9    TRA     MLEST
ON10    CALLIO  *PRINT
OFF10   TRA     SW7
ON11    CALLIO  *PRINT
OFF11   TRA     SKEST
ON12    CALLIO  *PRINT
OFF12   TRA     CNTNUE
ON13    TRA     SW13+1
OFF13   TRA     LOOPM
****** VARIABLE STORAGE
        NEWID   STORAGE
DUMMY   BRAS    50
        BRLIST  TEMP,TEMP1,TEMP2,TEMP3,TEMP4,TEMP5
        DEC     12
        DEC     9
        DEC     7
        DEC     6
TSS     BZE
        ASSIGN  KN,FDN
        ZERO    ,N,,,NF,,,K,,,KF,,
        ASSIGN  S0,S1,S11
        ASSIGN  RMAX,NPGET,JP1,IPJ
        ZERO    ILC
        ZERO    AC,MQ,XR1,XR2,XR4,TIME
        ASSIGN  A,S
        ASSIGN  L1,L2,L11,L12,L22,IT
        ASSIGN  H,Q,Z
        ASSIGN  NP,NS,DIM,PAR
        ZERO    MCODE
        ZERO    MSCODE
        ASSIGN  SHEP
        ASSIGN  2KNPN
        BZE
DECRID  BZE
        BZE     0
DELTA   DEC     1.E-5
EPSA    DEC     .001
EPSB    DEC     .001
ITMAX   DEC     3
PMIN    DEC     1.E-37
BIGIT   BCI     *,H-***** TOO MANY ITERATIONS *****-*
BNTAB0  BCI     *,T12,H-BINOMIAL PROBABILITIES WITH N = -I2*
BNTAB1  BCI     *,T20,I5,T30,10F10.7*
COMPLP  BCI     *,T12,H-COMPLEMENTARY POINT USED-*
DMCMNT  BCI     *,H-***** INSUFFICIENT STORAGE FOR PROBLEM *****-I10*
DOSES   BCI     *,T12,H-DOSES-T30,10G10.5*
ENDT    BCI     *,H-***** END OF PROBLEM -C8*
KCOMNT  BCI     *,H-***** K IS TOO LARGE *****-,I5*
MEMT    BCI     *,T12,H-ERROR IN INITIAL ESTIMATE OF MEAN-T59,G10.5*
MLEMT   BCI     *,T12,H-MAXIMUM LIKELIHOOD ESTIMATION-/T12,H-IT-S7,3HL- ,
MLEMT   BTC     S7,3HL--,S17,H-ESTIMATES-/T12,I2,S2,2G10.5,S10,G10.5/
```

```
MLFMT   ETC     T12,S4,4G10.5*
NCOMNT  BCI     *,H-***** N IS TOO LARGE *****-,I5*
NDFAD   BCI     *,T12,H-RESPONSE PATTERN-10I3*
NGCMNT  BCI     *,H-***** TWO NEGATIVE SCALE PARAMETER ESTIMATES *****-*
PROBS   BCI     *,T12,H-PROBABILITIES-T30,10F10.7*
SFMT    BCI     *,T12,H-ERROR IN INITIAL ESTIMATE OF STANDARD DEVIATION-
SFMT    ETC     G10.5*
SKFMT   BCI     *,T12,H-SPEARMAN KARBER ESTIMATION-/T12,H-M-G10.5,S5,H-S-
SKFMT   ETC     G10.5*
STDOSE  BCI     *,T12,H-STANDARD DOSES-T30,10G10.5*
TABLES  BCI     *,10H NKZ00000      ,S5,H-MS -I6,S5,H-PROBABILITY -F10.7/
TABLES  ETC     T30,3HSKN,T42,3HSKS,T54,3HMLM,T66,3HMLS/
TABLES  ETC     T12,H-MEAN VECTOR -T25,4F12.7/1H0,T25,F12.7/
TABLES  ETC     T12,H-COVARIANCE - T25,2F12.7/T12,H-MATRIX-T25,3F12.7/
TABLES  ETC     T25,4F12.7/1H6*S
TRESTS  BCI     *,T12,H-TRANSFORMED ESTIMATES-F10.7,4G10.5*
PATCH   BSS     500
LENGTH  END
```

EXHIBIT B

UP AND DOWN SIMULATOR FOR COMPARISON OF
SPEARMAN-KARBER AND DIXON-MOOD ESTIMATORS



```
$IBFTC UPDN    DECK,M94,XR7,FULIST
C      UP AND DOWN SIMULATOR FORTRAN IV VERSION 11/10/65
C      ESTIMATION BY SPEARMAN-KARBER AND DIXON-MOOD METHODS
       DIMENSION E(26),V(4,4),SKT(26,50),DMT(26,50),DOSE(50),EST(6)
       DIMENSION LABEL(50)
       DIMENSION NULL(3)
       DIMENSION Z(50),PIC(100,50),N(150),R(50)
       INTEGER EXPT,EXPTS,RUN,RUNS,TRIAL,TRIALS,RULE,TAPE,RS1,RS2,SKT,DMT
       INTEGER R
       INTEGER COUNT
       INTEGER ST,ST2
       DATA BCD0/6H0      /,BCDX/6HX      /,BLANK/6H       /
       DATA (LABEL(J),J=1,50)/8*6H      ,6H-2.   ,7*6H      ,6H-1.   ,
      X7*6H      ,6H 0.   ,7*6H      ,6H 1.   ,7*6H      ,6H 2.   ,
      X6*6H      ,6HTOTAL /
       LOGICAL TEST,STOP,CHECK
       LOGICAL NOTEST
       EQUIVALENCE (EST(6),P)
       EQUIVALENCE (E(5),V(1)),(E(21),EST(1)),(N(51),R(1))
       EQUIVALENCE (N(101),NF),(N(102),NFK),(N(103),NFKK)
       EQUIVALENCE (N(104),IST),(N(105),NSK),(N(106),NSKK)
       EQUIVALENCE (N(107),MIN),(N(108),K),(N(109),MAX)
       EQUIVALENCE (N(110),MINS),(N(111),MAXF)
       EQUIVALENCE (N(112),EXPT),(N(113),EXPTS),(N(114),RUN)
       EQUIVALENCE (N(115),RUNS)
       EQUIVALENCE (N(116),TRIAL),(N(117),TRIALS),(N(118),RULE)
       EQUIVALENCE (N(119),IOS)
C      STOPPING RULE
       STOP(N)=((N.EQ.1).AND.(RUN.GE.RUNS)).OR.
      1  ((N.EQ.2).AND.(TRIAL.GE.TRIALST).OR.
      2  ((N.EQ.3).AND.(RUN.GE.2).AND.(MINS.LT.MAXF))
C      CHECK LIMITS OF K
       CHECK(K)=(K.LT.1).OR.(K.GT.50)
 1000  READ 1, PROBLM,EXPTS,XO,H,RULE,RUNS,TRIALS,TAPE,RS1,RS2
       IF (PROBLM.NE.BLANK) GO TO 1001
         IF (NOTEST) REWIND TAPE
         CALL EXIT
 1001  TEST=TAPE.EQ.6
       NOTEST = .NOT.TEST
       PRINT 2, PROBLM,EXPTS,XO,H,RULE,RS1,RS2
       IF (TEST) GO TO 1002
         PUNCH 2, PROBLM,EXPTS,XO,H,RULE,RS1,RS2
         WRITE (TAPE,2) PROBLM,EXPTS,XO,H,RULE,RS1,RS2
 1002  GO TO (1010,1020,1030), RULE
 1010    PRINT 3, RUNS
         IF (TEST) GO TO 1040
           PUNCH 3, RUNS
           WRITE (TAPE,3) RUNS
           GO TO 1040
 1020    PRINT 4, TRIALS
         IF (TEST) GO TO 1040
           PUNCH 4, TRIALS
           WRITE (TAPE,4) TRIALS
           GO TO 1040
 1030    PRINT 5
         IF (TEST) GO TO 1040
```

```
            PUNCH 5
            WRITE (TAPE,5)
C       INITIALIZATION SECTION
1040    CALL ZERO (E,20,SKT,1300,DMT,1300,NULL,3)
        ST=0
        STZ=0
        IDS=MIN0(50,MAX0(1,IFIX(X0/H)+25))
        SHEP = H*H/12.
        HALFH = .5*H
        WT1 = 0.
        EXPT = 1
        DO 1050 I=1,50
1050      DOSE(I)=X0+FLOAT(I-IDS)*H
C       LOOP ON EXPERIMENT NUMBER   (EXPT)
1100    DO 2000 EXPT=EXPT,EXPTS
          CALL ZERO (N,109)
          COUNT=0
          X=X0
          RUN=0
          I1=1
          K=IDS
          MIN=K
          MAX=5
          MINS=50
          MAXF=1
C       OBTAIN NORMAL TOLERANCES
1150      CALL NORMA (Z,50,RS1,R=2)
          CALL SPRAY (BLANK,PIC,5000)
C       LOOP ON TRIAL NUMBER    (TRIAL)
          DO 1500 TRIAL=1,50
            IF (X-Z(TRIAL)) 1200,1200,1300
C       NON-LETHAL DOSE
1200          PIC(TRIAL,K)=BCDO
              N(K)=N(K)+1
              NF=NF+1
              NFK=NFK+K
              NFKK=NFKK+K*K
              X=X+H
              I2=2
              MIN=MIN0(MIN,K)
              K=K+1
              IF (CHECK(K)) GO TO 1520
              GO TO (1500,1500,1250), I1
1250          MINS=MIN0(MINS,K)
              GO TO 1400
C       LETHAL DOSE
1300          R(K)=R(K)+1
              PIC(TRIAL,K)=BCDX
              NS=NS+1
              NSK=NSK+K
              NSKK=NSKK+K*K
              X=X-H
              I2=3
              MAX=MAX0(MAX,K)
              K=K-1
              IF (CHECK(K)) GO TO 1520
```

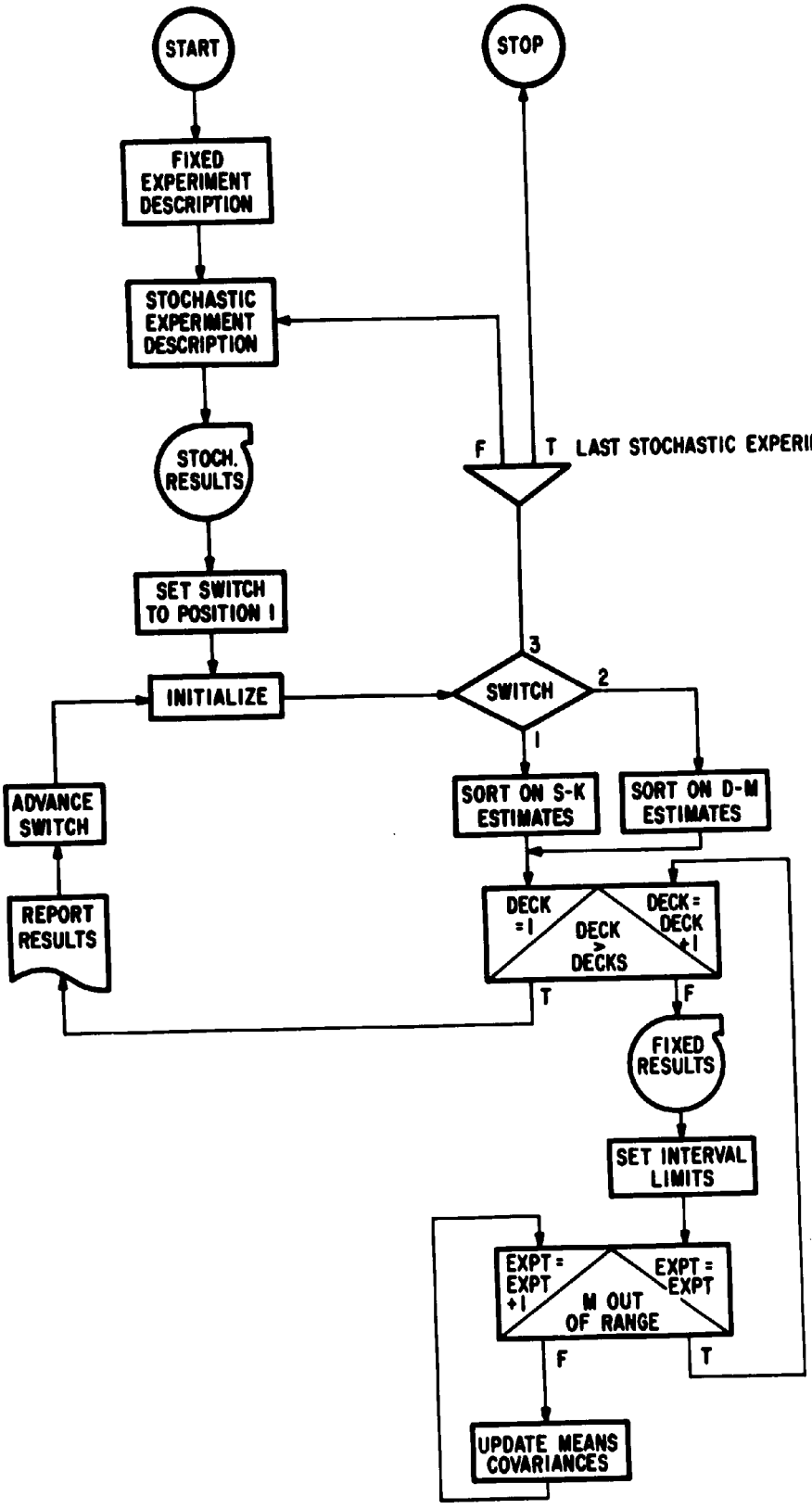
```
            GO TO (1500,1350,1500), I1
1350        MAXF=MAX0(MAXF,K)
C       END OF A RUN
1400        RUN=RUN+1
            IF (STOP(RULE)) GO TO 1600
1500        I1=I2
C       MORE THAN 50 TRIALS REQUIRED    SUSPECT STOPPING RULE ERROR
1510      PRINT 6,EXPT,RULE
            WRITE (TAPE,20) EXPT
            WRITE (TAPE,12) (DOSE(J),(PIC(I,J),I=1,100),J=MIN,MAX)
            COUNT=COUNT+1
            GO TO 1150
C       K OUTSIDE LIMITS      SUSPECT ERRONEOUS CHANGE OF DOSES
1520      PRINT 7, EXPT,TRIAL,K
            IF (NOTEST) WRITE (TAPE,7) EXPT,TRIAL,K
            PRINT 12, (DOSE(J),(PIC(I,J),I=1,100),J=MIN,MAX)
            GO TO 1000
C       SPEARMAN-KARBER ESTIMATE OF SIGMA**2 LE ZERO
1530      WRITE (TAPE,8)
            NULL(1)=NULL(1)+1
            GO TO 1550
C       ITERATIVE ESTIMATION REQUIRED
1540      IF (MINS.GE.MAXF) GO TO 1550
            WRITE (TAPE,17)
            NULL(3)=NULL(3)+1
            GO TO 1560
C       DIXON-MOOD ESTIMATE OF SIGMA DEGENERATE
1550      WRITE (TAPE,9)
            NULL(2)=NULL(2)+1
1560      WRITE (TAPE,12) (DOSE(J),(PIC(I,J),I=1,100),J=I1,I2)
            GO TO 1100
C       STOPPING RULE SATISFIED     PROCEED TO ESTIMATE
C       SPEARMAN-KARBER ESTIMATION
1600      CALL ZERO (EST,6)
            WRITE (TAPE,13) EXPT
            L=MAX0(1,MIN0(MIN,(MIN+MAX)/2-5))
            I1=L
            I2=MIN0(50,MAX0(MAX,L+10))
            CALL USEBUF
            PRINT 101
            CALL USEBUF
            READ 11, (PIC(I,L),I=81,100)
            DO 1610 I=MIN,MAX
              P1=FLOAT(R(I))/FLOAT(N(I)+R(I))
              D=P1-P
              P=P1
              XSTAR=DOSE(I)-HALFH
              EST(1)=EST(1)+XSTAR*D
              EST(2)=EST(2)+XSTAR*XSTAR*D
1610          EST(5)=EST(5)+P*(1.-P)/FLOAT(N(I)+R(I)-1)
            EST(2)=EST(2)-EST(1)*EST(1)+EST(5)
            IF (EST(2).LE.0.) GO TO 1530
            EST(2)=SQRT(EST(2)+.5*EP)
            J=MIN0(49,MAX0(1,IFIX((EST(1)+3.1875)/.125)))
            I=MIN0(24,MAX0(1,IFIX((EST(2)+.1875)/.125)))
            SKT(I,J)=SKT(I,J)+1
```

```
      SKT(I,50)=SKT(I,50)+1
      SKT(25,J)=SKT(25,J)+1
      L=L+1
      CALL USEBUF
      PRINT 102, EST(1),EST(2)
      CALL USEBUF
      READ 11, (PIC(I,L),I=61,100)
C     DIXON-MOOD ESTIMATION
      IF (NS-NF) 1620,1620,1630
1620    EST(3)=FLOAT(NSK)/FLOAT(NS)-.5
        EST(4)=FLOAT(NS*NSKK-NSK*NSK)/FLOAT(NS*NS)
        GO TO 1640
1630    EST(3)=FLOAT(NFK)/FLOAT(NF)+.5
        EST(4)=FLOAT(NF*NFKK-NFK*NFK)/FLOAT(NF*NF)
1640  IF (EST(4).LT.0.3) GO TO 1540
      EST(3)=(EST(3)-25.)*H
      EST(4)=1.62**2*(EST(4)+.029)
1645  I=MIN0(24,MAX0(1,IFIX((EST(4)+.1875)/.125)))
      J=MIN0(49,MAX0(1,IFIX((EST(3)+3.1875)/.125)))
      DMT(I,J)=DMT(I,J)+1
      DMT(I,50)=DMT(I,50)+1
      DMT(25,J)=DMT(25,J)+1
      L=L+1
      CALL USEBUF
      PRINT 103,EST(3),EST(4)
      CALL USEBUF
      READ 11, (PIC(I,L),I=61,100)
      TRIAL=50*COUNT+TRIAL
      PUNCH 22, EXPT,TRIAL,(EST(I),I=1,4),PROBLM
      ST=ST+TRIAL
      ST2=ST2+TRIAL*TRIAL
C     UPDATE COVARIANCE MATRIX
1650  WT2=WT1
      WT1=WT1+1.
      L=L+2
      CALL USEBUF
      PRINT 104
      CALL USEBUF
      READ 11, (PIC(I,L),I=51,100)
      DO 1800 I=1,4
        L=L+1
        D=EST(I)-E(I)
        EST(I)=D/WT1
        E(I)=E(I)-EST(I)
        DO 1700 J=1,I
1700      V(J,I)=(V(J,I)-D*EST(J))*WT2/WT1
        CALL USEBUF
        PRINT 105,E(I),(V(J,I),J=1,I)
        CALL USEBUF
        K=(I+1)*10+50
1800    READ 11, (PIC(J,L),J=51,K)
        L=L+1
        CALL USEBUF
        PRINT 18, RS,NSK
        CALL USEBUF
        READ 11, (PIC(J,L),J=51,100)
```

```
2000    WRITE (TAPE,12) (DOSE(J),(PIC(I,J),I=1,100),J=11,12)
      PRINT 14, (E(I),(V(J,I),J=1,I),I=1,4)
      L=NULL(1)+NULL(2)+NULL(3)
      PRINT 19,L,NULL(1),NULL(2),NULL(3)
      TM=FLOAT(ST)/FLOAT(EXPTS)
      TV=FLOAT(EXPTS*ST2-ST*ST)/FLOAT(EXPTS*(EXPTS-1))
      PRINT 21, TM,TV
      CALL CONVRT(SKT,1300)
      PRINT 15, (LABEL(J),(SKT(I,J),I=1,25),J=1,50)
      PRINT 23
      CALL CONVRT(DMT,1300)
      PRINT 16, (LABEL(J),(DMT(I,J),I=1,25),J=1,50)
      PRINT 23
      IF (NOTEST) END FILE TAPE
      GO TO 1000
1     FORMAT (A6,4X,I5,F5.0,F5.3,4I5,2015)
2     FORMAT (1H1,A6,I4,25H EXPERIMENTS STARTING AT ,F3.1,11H WITH STEP
     X,F5.3,16H, STOPPING RULE ,I1/15H RANDOM STARTS ,2015)
3     FORMAT (24H MAXIMUM NUMBER OF RUNS ,I3)
4     FORMAT (26H MAXIMUM NUMBER OF TRIALS I3)
5     FORMAT (19HMAXIMUM NON-LETHAL DOSE OF MINIMUM LETHAL DOSE    )
6     FORMAT (12H0EXPERIMENT ,I3,6H RULE ,I1,29H UNSATISFIED AFTER 50 TR
     XIALS )
7     FORMAT (15H < BEYOND LIMITS/12H EXPERIMENT ,I3,7H TRIAL ,I3,3H < ,
     XI2)
8     FORMAT (39H NON-POSITIVE S-K ESTIMATE OF SIGMA**2      )
9     FORMAT (34H DEGENERATE D-H ESTIMATE OF SIGMA          )
101   FORMAT (10X,10HESTIMATES ,5X,5HMU    ,5X,5HSIGMA    )
102   FORMAT (5X,15HSPEARMAN-KARBER ,2F10.5      )
103   FORMAT (5X,15HDIXON-400D      ,2F10.5      )
104   FORMAT (10H     MEANS ,10X,20H COVARIANCE MATRIX   ,10X)
105   FORMAT (5F10.5)
11    FORMAT (80A1)
12    FORMAT (F10.3,100A1)
13    FORMAT (1H4,10X,16HEXPERIMENT NUMBER    ,I3)
14    FORMAT (35H0MEAN VECTOR AND COVARIANCE MATRIX                    /
     X2X,F10.5,10X,F10.5/2X,F10.5,10X,2F10.5/2X,F10.5,10X,3F10.5/2X,F10.
     X5,10X,4F10.5)
15    FORMAT (45H1FREQUENCY TABLE FOR SPEARMAN-KARBER ESTIMATES    /
     X(5X,A6,5X,25A3))
16    FORMAT (42H1FREQUENCY TABLE FOR DIXON-400D ESTIMATE)     /
     X(5X,A6,5X,25A3))
17    FORMAT (35H ITERATIVE D-H ESTIMATION REQUIRED      )
18    FORMAT (20H RANDOM STARTS      ,2015)
19    FORMAT (42H0NUMBER OF EXPERIMENTS DISCARDED                ,I5/
     142H NON-POSITIVE S-K ESTIMATES OF SIGMA**2                 ,I5/
     242H DEGENERATE  D-H ESTIMATES OF SIGMA                     ,I5/
     342H ITERATIVE D-H ESTIMATION REQUIRED                      ,I5)
20    FORMAT (19H EXPERIMENT NUMBER     ,I3,11H CONTINUED       )
21    FORMAT (30H0NUMBER OF TRIALS PER EXPT          /
     X30H MEAN                                    ,F10.2/
     X30H VARIANCE                                ,F10.2)
23    FORMAT (4X,9H1,  ,2H2,  ,2H3,  ,2H4,  ,2H5,  ,2H6,  ,2H7,  ,2H8,  ,
     X2H9,  ,3H10,  ,3H11,  ,3H12,  ,3H13,  ,3H14,  ,3H15,  ,3H16,  ,3H17,
     X,3H18,  ,3H19,  ,3H20,  ,3H21,  ,3H22,  ,3H23,  ,3H24,  ,3H25)
22    FORMAT (2I5,  4F10.5,  4X,5)
      END
```

EXHIBIT C

EVALUATION OF MIXED EXPERIMENT BY
AVERAGING FIXED EXPERIMENT RESULTS
OVER RESULTS OF UP AND DOWN SIMULATIONS



```
$IBFTC MIXED   FULIST,M94,XR7,DD
C      MIXED EXPERIMENT EVALUATION
       DIMENSION INDEX(1000),X(15),E(15),EE(4),VE(10),EV(10)
       DIMENSION STOCH(4,100),FIXED(16,200),NM(6),NS(6),S(6),FPROB(12)
       DIMENSION RULE(12),SLIMIT(30)
       INTEGER SWITCH
       INTEGER STAPE,FTAPE(6),DECK,DECKS,EXPT,EXPTS,ORDER(2),RANK(1000)
       REAL M(6),MLIMIT(30)
       EQUIVALENCE (ORDER(1),ISS),(ORDER(2),IMS),(E,EP),(E(2),EE)
       EQUIVALENCE (E(6),EV)
       READ 1,FPROB,DECKS,HM,HS,
      A  (NM(I),M(I),NS(I),S(I),FTAPE(I),I=1,DECKS)
 1000  READ 2, EXPTS,DOSE,HDOSE,STAPE,RULE
       IF (EXPTS.EQ.0) STOP
       IF (STAPE.EQ.0) STAPE = 5
       PRINT 16,EXPTS,DOSE,HDOSE,RULE,FPROB
       PUNCH 16, EXPTS,DOSE,HDOSE,RULE,FPROB
    16 FORMAT (I3,37H UP AND DOWN EXPERIMENTS STARTING AT ,F2.0,16HWITH S
      ATEP SIZE ,F4.2,18H AND STOPPING RULE /12A6/55HMIXED WITH FIXED EXP
      SERIMENT CENTERED AT MU AND WITH RANGE 2 SIGMA /12A6)
       READ (STAPE,3) ((STOCH(I,J),I=1,4),J=1,EXPTS)
       SWITCH = 1
 2000  CALL ZERO (E,15,VE,10,NOUT,1)
       GO TO (3000,4000,1000), SWITCH
 3000  PRINT 11
       PUNCH 17
    17 FORMAT (54HSPEARMAN-KARBER ESTIMATES USED TO SET STIMULUS LEVELS )
       ORDER(1)=2
       ORDER(2)=1
       GO TO 5000
 4000  PRINT 12
       PUNCH 18
    18 FORMAT (54HDIXON-MOOD ESTIMATES USED TO SET STIMULUS LEVELS      )
       ORDER(1)=4
       ORDER(2)=3
 5000  CALL SORT(STOCH,INDEX,RANK,4,EXPTS,ORDER,2,2)
       EXPT=1
       DO 8000 DECK=1,DECKS
         NTAPE=FTAPE(DECK)
         N1=NM(DECK)
         N2=NS(DECK)
         N=N1*N2
         IF (N.GT.200) CALL EXIT
       READ (NTAPE) ((FIXED(I,J),I=1,16),J=1,N)
       IF (NTAPE.NE.FTAPE(DECK+1).OR.DECK.EQ.DECKS) REWIND NTAPE
         MLIMIT(1)=M(DECK)-HM*.5
         DO 5100 I=1,N1
 5100      MLIMIT(I+1)=MLIMIT(I)+HM
       SLIMIT(1)=S(DECK)-HS*.5
         DO 5200 I=1,N2
 5200      SLIMIT(I+1)=SLIMIT(I)+HS
         DO 7000 EXPT=EXPT,EXPTS
           I=INDEX(EXPT)
           STOCHM=ABS(STOCH(IMS,I))
           DO 5300 IMF=1,N1
```

```
5300        IF (STOCHM.LT.MLIMIT(IMF+1)) GO TO 5400
          GO TO 8000
5400      STOCHS=STOCH(ISS,I)
          DO 5500 ISF=1,N2
5500        IF (STOCHS.LT.SLIMIT(ISF+1)) GO TO 5600
          NOUT=NOUT+1
          GO TO 7000
5600      J=(IMF-1)*N2+ISF
          DO 5700 K=1,15
5700        X(K)=FIXED(K+1,J)
          IF (STOCH(IMS,I).GE.0.) GO TO 5800
            X(2)=-X(2)
            X(4)=-X(4)
5800      DO 5900 J=1,15
5900        E(J)=E(J)+X(J)
          L=0
          DO 6000 J=2,5
            DO 6000 K=2,J
              L=L+1
6000          VE(L)=VE(L)+X(J)*X(K)
7000      CONTINUE
8000    CONTINUE
        PRINT 13, NOUT
        PUNCH 13,NOUT
        FN=EXPTS-NOUT
        DO 9000 I=1,15
          E(I)=E(I)/FN
9000    IF (I.LE.10) VE(I)=VE(I)/FN
        K=0
        DO 10000 I=2,5
          DO 10000 J=2,I
            K=K+1
10000       EV(K)=EV(K)+VE(K)-E(J)*E(I)
        PRINT 14,E
        PUNCH 15, E
        SWITCH = SWITCH + 1
        GO TO 2000
     1 FORMAT (12A6/I2,8X,2F10.5/(I5,F10.5,I3,F10.5,I5))
     2 FORMAT (I5,2F10.5,I3/12A6)
     3 FORMAT (10X,4F15.7)
     4 FORMAT ((8(3X,O12)))
    10 FORMAT (12HIRESULTS OF ,I4,37H UP AND DOWN EXPERIMENTS STARTING AT
      A ,F10.5,14H WITH SPACING ,F10.5/
      B60H TERMINATED AFTER THE FIRST RUN SUCH THAT
      C/1X,12A6/
      D60H FOLLOWED BY A FIXED EXPERIMENT IN WHICH
      E/60H THE CENTER DOSE AND RANGE ARE DETERMINED BY THE
      F/60H UP AND DOWN EXPERIMENT.  THE FIXED EXPERIMENT IS
      G/1X,12A6)
    11  FORMAT (/
      A60H SPEARMAN-KARBER ESTIMATION USED IN UP AND DOWN EXPERIMENT
      B)
    12 FORMAT (/
      A60H DIXON-MOOD ESTIMATION USED IN UP AND DOWN EXPERIMENT
      B)
    13 FORMAT (/
```

```
      A60H NUMBER OF UP AND DOWN EXPERIMENTS YIELDING ESTIMATES
      B/60H OUTSIDE RANGE OF TABULATION OF FIXED EXPERIMENT RESULTS
      C,I5)
   14 FORMAT (/
      A60H PROBABILITY OF NON-DEGENERATE RESULTS FROM SECOND STAGE
      B/60H FIXED EXPERIMENT
      C/F15.7/30HOMEAN VECTOR                    /10X,4F15.7/
      D30HOCOVARIANCE MATRIX                     /10X,F15.7/10X,2F15.7/10X,3F15.
      E7/10X,4F15.7)
   15 FORMAT (5F15.7/,15X,F15.7/,15X,2F15.7/,15X,3F15.7/15X,4F15.7/)
      END
```

EXHIBIT D

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SPH 3073

USE OF GRAFIX PROGRAM

Grafix allows the user to describe and prepare graphs on the computer by means of commands designed to be easily remembered and understood as well as flexible.

Every command begins with one of the following verbs.
DEFINE, PLOT, PRINT, ERASE, REWIND, REPEAT, REMARK, DUMP, FINISH
The possible qualifiers of these verbs are either objects or phrases and are illustrated with explanations below. Words and numbers are separated by commas and/or blanks as in English. A '$' in column 80 of any command card indicates that the command is continued on the next card.

DEFINE NAMES X, Y, Z, ALPHA, BETA, MU, SIGMA

This command informs grafix that the variable and/or parameter names are as specified. All references to variables or parameters must use these names until the names are redefined. Names must be alpha-numeric sequences of characters which cannot be confused with numeric values or keywords. Since all character strings are truncated to six characters names must be distinct in the first six characters. Since words and numbers are delimited by commas and/or blanks such symbols are illegal in names.

```
       (AXES)   (HORIZONTAL)
DEFINE-(    )-,-(          )-FROM 0. TO 5., LABEL
       (AXES)   (VERTICAL  )
```

This command specifies that the limits on the vertical or horizontal axes are to extend from 0. to 5. and that the specified axis is to be labeled with the contents of the next record. For horizontal labels 80 characters are used, for vertical labels only the first 50 of an 80 character record is used.

DEFINE TITLE

This command indicates that the next record is to be used as a title or legend to be printed above the graph. If more than one line is desired, an integer no greater than 5 may be used to indicate the number of title lines following

```
       (STRATA     )
DEFINE-(CONTOURS   )- 1. 2. 5. 10.
       (TOLERANCES)

       (STRATA     )
DEFINE-(CONTOURS   )-  FROM 1. TO 10. BY .5
       (TOLERANCES)
```

These commands have two forms as shown above. The former allows up to 20 contours, strata, or tolerances to be specified, and the latter defines a sequence of up to 20 regularly spaced values. The words 'CONTOURS' and

'STRATA' refer to values of functions and dependent variables respectively. 'TOLERANCES' refers to deviations from the corresponding contour or stratum such that all values of the function or variable within the specified tolerance of the desired controur will be plotted with the appropriate symbol. If fewer tolerance values than strata or contours are specified, the sequence of tolerances will be extended by repetition of the last value specified. A tolerance of zero has special meaning in the case of contour plotting of a function. It indicates that as fine a line as possible is desired on the final graph.

DEFINE SYMBOLS + * X Y

This command specifies a sequence of up to 20 plotting symbols. Since digits cannot be distinguished from integers, to indicate that a digit is to be used for a plotting symbol, the digit should be followed immediately by the character 'A' as shown below.

DEFINE SYMBOLS 1A 2A 3A 4A 5A 6A 7A

DEFINE VALUES X 0. Y .5 ALPHA 200. BETA 1.

This command causes the variables or parameters named to assume the values which follow their respective names.

DEFINE FILE TESTDATA, TAPE 7, SKIP 1,0, CASES 50, EOF ENDFILE, FORMAT

This command specifies that the file named 'TESTDATA'is found on tape 7, and that it is the second file on that tape. The file is made up of 50 cases, and is terminated with the word 'ENDFILE' in columns 1 through 7 and that the format for the file is found on the next record. If more than 1 format record is required, an integer no greater than 5 may follow 'FORMAT' to indicate the number of format records following. If the number of cases is not specified, the data pass will continue until either a system end of file or the user defined end of file is found or an error condition is encountered while reading. Up to 5 files may be active simultaneously, thereafter, the first, second, etc. files are deleted as new files are defined.

DEFINE GROUP MALES, BY-(FUNCTION 3 / SEX)-.EQ 0.

This command indicates that membership in the group 'MALES' is specified by the equivalence of the specified function or variable and the constant indicated. Up to 20 groups may be defined simultaneously.

DEFINE SOURCE AS-(CARDS / TAPE 9)

This command indicates that successive commands are to be found on the indicated input medium until the next occurrence of a 'DEFINE SOURCE' command.

```
                (FUNCTION 1)              (ALPHA      )
PLOT CURVE OF-(             )-  .VS.  -(              )
                (BETA       )             (FUNCTION 2)
```

This command causes the preparation of the specified curve with the first mentioned quantity plotted on the vertical axis and the latter on the horizontal axis. If this command is modified by the phrase

VARY Z FROM 0. TO 1. BY .25

a loop will be constructed which varies the parameter specified through the indicated values, plotting the designated curve for each value of the parameter with successive symbols taken from the symbol sequence which is repeated when it is exhausted. Such parameter loops may be nested up to 20 deep, thus allowing the user to plot many curves for various values of the parameters on the same graph. Caution must be exercised that an excessive number of curves is not requested since confusion will result and the graphs will be incomprehensible.

PLOT CONTOURS OF FUNCTION 1, Y .VS. X

This command causes the preparation of a contour map of function 1 in the plane of variables Y and X. The previously mentioned 'VARY' phrase may be used to restrict the range of the variables to only a portion of the region defined by the axes limits.

```
                (FUNCTION 1)              (FUNCTION 2)
PLOT SCATTER OF-(           )-  .VS.  -(              )-FROM FILE TESTDATA FOR GROUP
                (AGE        )             (HEIGHT     )            MALES
```

This command causes a pass of the data file names 'TESTDATA' and the plotting of the designated quantities for all cases satisfying the membership criterion for the group 'MALES'. If no group is mentioned, all cases are plotted. If no file name is given, the most recently mentioned file is used. All outliners are reported as well as the number of cases found in the specified group.

PLOT STRATA OF WEIGHT, AGE .VS. HEIGHT

This produces a scatter plot as above except that the plotting symbol is varied according to the value of the dependent variable 'WEIGHT' as defined by the 'DEFINE STRATA' command. Group selection and file use are determined as in the 'PLOT SCATTER' command.

PLOT HISTOGRAM OF AGE

This command causes the preparation of a histogram of the variable mentioned for the specified group (if any) and the file in use.

The 'PRINT', 'ERASE', and 'REWIND' commands each have two uses. They may be used to set modes of operation and/or to cause the indicated action. The normal mode is 'AUTOMATICALLY' which means

> For 'PRINT' a graph is printed as soon as prepared.
> For 'ERASE' a graph is erased as soon as printed.
> For 'REWIND' a tape is rewound as soon as the data pass is terminated.

If the commands 'PRINT', 'ERASE', or 'REWIND' are qualified by the phrase 'ON COMMAND', the indicated action must then be requested by the occurrence of the corresponding unqualified command or the resetting of the mode via 'PRINT AUTOMATICALLY', etc.

If the unqualified 'REWIND' is followed by 'TAPE' and an integer, the specified (FORTRAN logical) tape is rewound immediately.

The 'REPEAT' command qualified by up to 20 'VARY' phrases causes the next command to be repeated once for each value of the parameters varied. In order to link several commands into one, the conjunction 'AND' is used. The following sequence illustrates this usage.

```
PRINT ON COMMAND
REPEAT, VARY X FROM 1. TO 3. BY 1.
DEFINE SYMBOL * AND PLOT CURVE OF FUNCTION 1 .VS. Y AND DEFINE SYMBOL $
+ AND   PLOT CURVE ON FUNCTION 2 .VS. Y AND PRINT
```

This sequence produces three graphs each with function 1 versus Y plotted with asterisks and function 2 versus Y plotted with plus signs.

The 'REMARK' command is printed and ignored. If it is inside a 'REPEAT' loop, the next command is repeated instead of the 'REMARK'.

The 'DUMP' command causes the printing of important quantities in the program. It should rarely be needed.

The 'FINISH' command signals the end of commands and causes the termination of the program execution.