VARIABILITY IN TIMING OF OVULATION AND MENSTRUATION

[An Experimentation in Modeling]

by

Alan W. Nordheim

Bioengineering

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Approved by:

Dr. Peter J. H. Sharpe

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I. ABSTRACT

The length of the menstrual and ovulatory cycle in women is notoriously variable. The frequency distribution of menstrual intervals for women and girls are both positively skewed. Researchers studying the rhythm or similar methods of birth control typically model the system as being symmetric, which introduces an error into the model (a drastic one for the woman who may fall into the area ignored).

This research was an attempt to break down the female reproductive system into its controlling components, and mathematically describe the distribution of menstrual intervals. The modeling of these components was based on the work of Sharp et. al. (1977).

It is shown in this analysis that the distribution of human menstrual intervals can be based upon the following two assumptions.

1) The interval length is dependant on the normally distributed development rate of the follicle/corpus luteum. From this, the positive skew in menstrual intervals follows mathematically.

2) The actual distribution of menstrual intervals can be described by a combination of development rates each representing a subgroup of the population by "cycle age" (number of cycles since menarche-first menstruation).

The distribution model developed agrees with the observed data for normal pubertal girls and for normal women.

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V. INTRODUCTION

Objectives: The goal of this research was the development of a general mathematical model capable of describing the distribution of human menstrual intervals.

The desirability of accurately modeling the human menstrual cycle becomes evident when the following facts are considered:

1) The variability of menstrual intervals exists even for single individuals of a population.

2) This variability is commonly assummed to be symmetrically distributed [Potter (1961)] as shown in Figure 1.

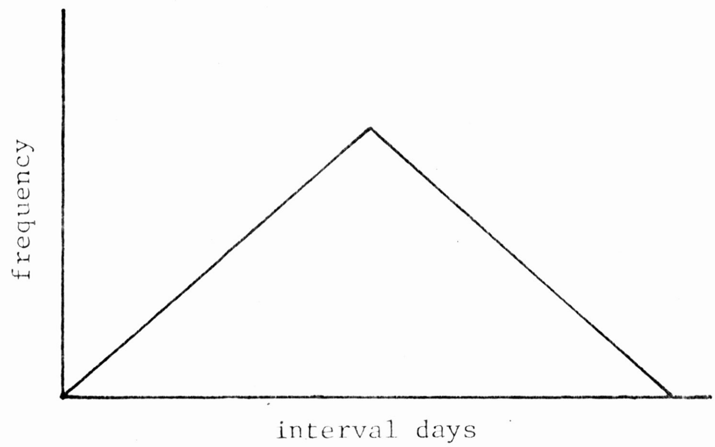
3) The actual distribution of intervals is positively skewed as shown in Figure 2 and 3.

Literature Review: A survey of the relevant literature reveals two basic approaches being taken in this field. The first approach is the traditional biological one, in which every available parameter of a system is measured and recorded. From this data, empirical relationships concerning the system are drawn [Speroff (1971)].

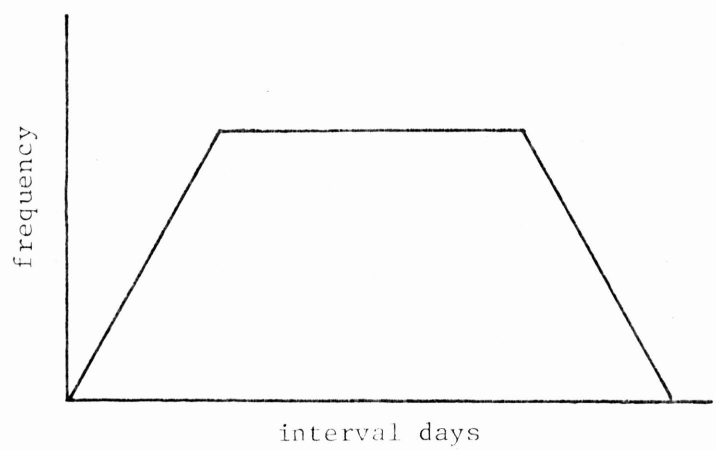
The second approach is the one in which there is some form of modeling taking place. This approach can be further broken down into 3 subclasses:

1) The first subclass is where statistical analysis is done on accumulations of data and predictions are made to aid in conception and contraception techniques [Tietze (1971)], or to aid in other studies in obstetrics and gynecology [Engle (1934) and Arey (1939)].

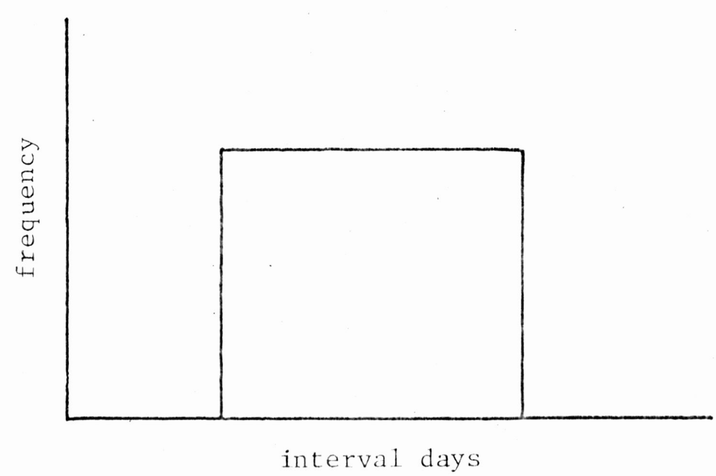
2) In the second subclass attempts are made to formulate mathematical models based on the work done in subclass #1. These models have been limited to crude symmetric approximations [Potter (1961)].



A. Triangular distribution



B. Trapezodial distribution



C. Rectangular distribution

Figure 1 Typical approaches to modeling menstrual intervals.

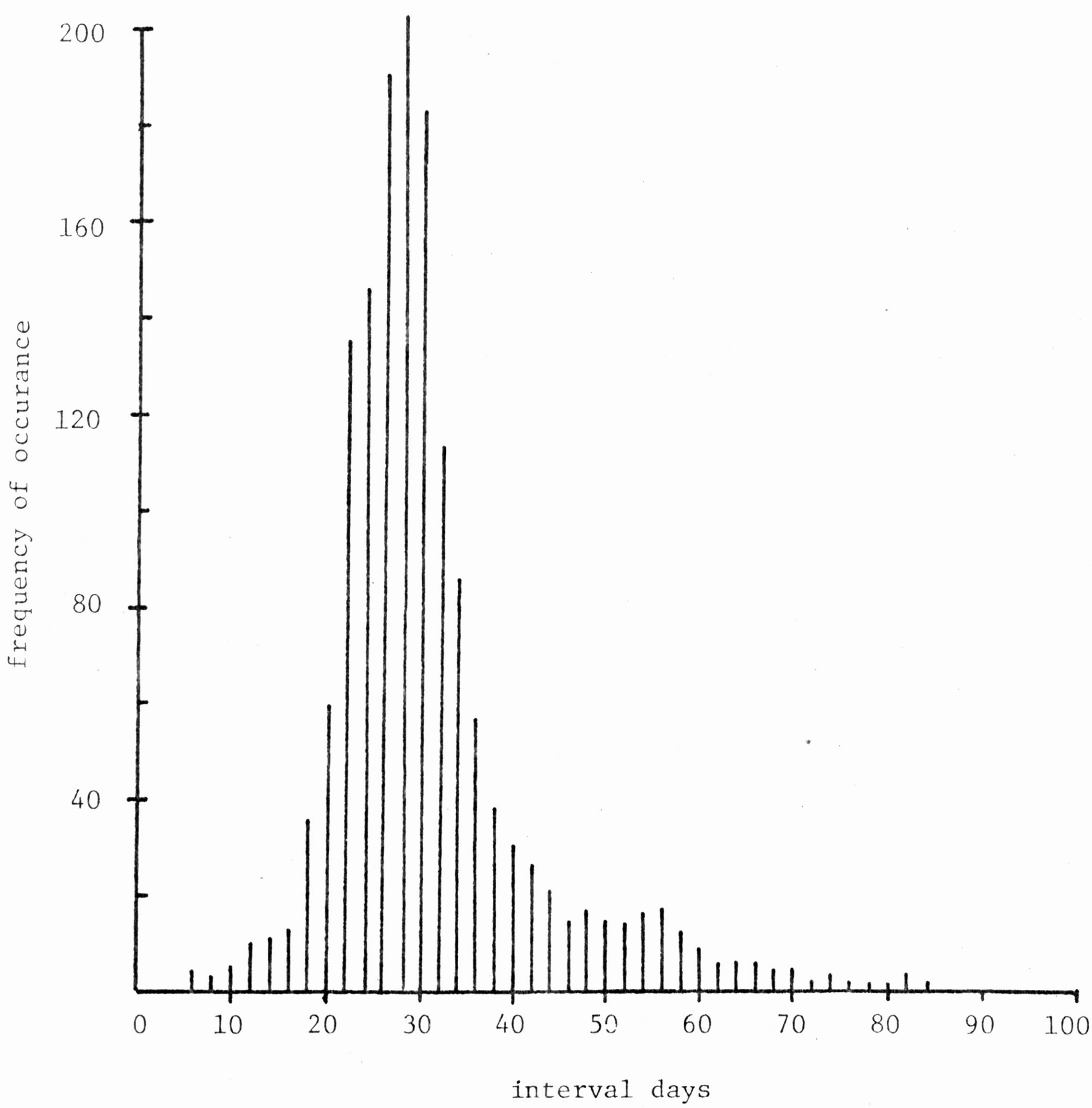


Figure 2. Frequency distribution of menstrual intervals for girls.

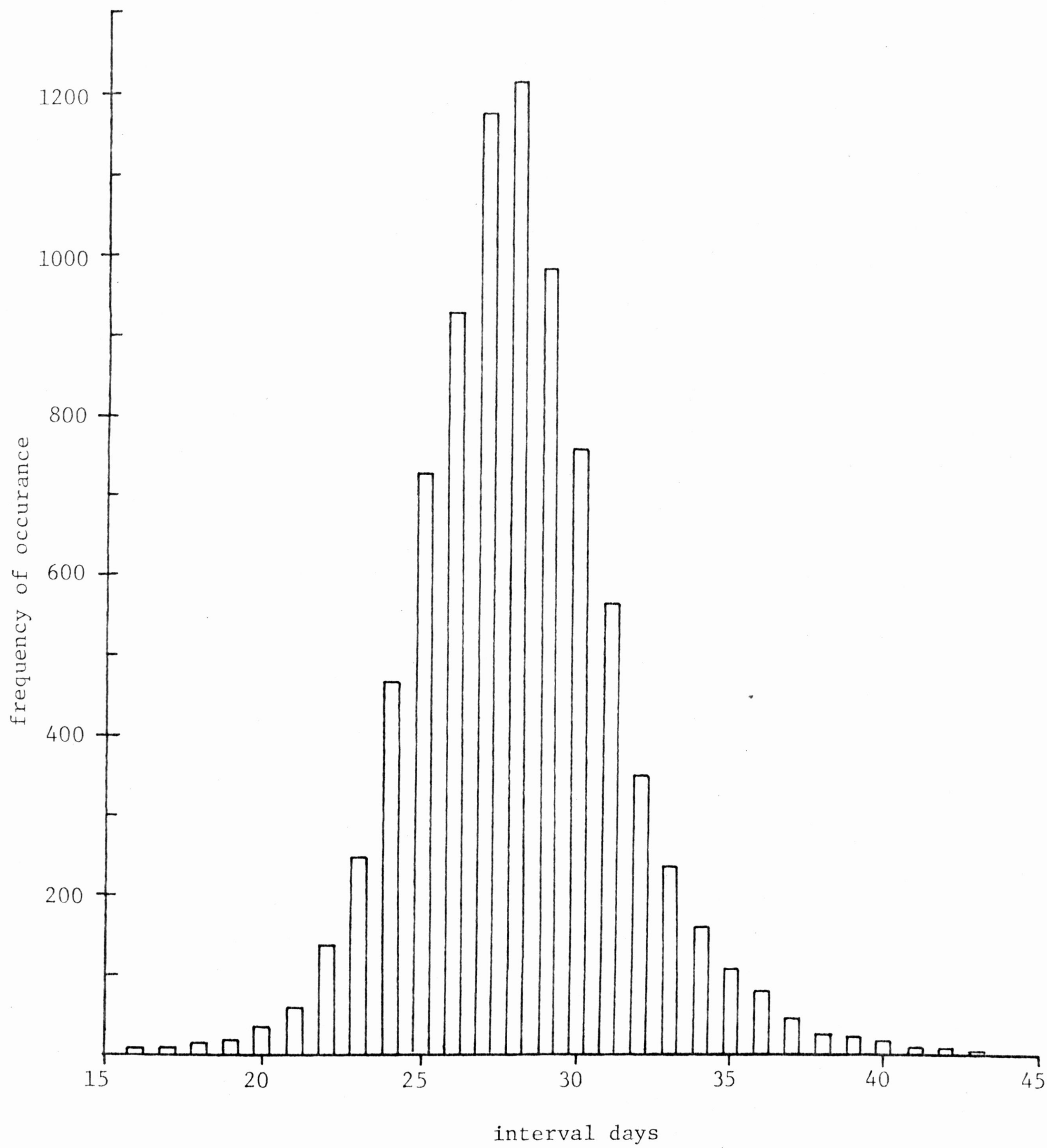


Figure 3. Frequency distribution of menstrual intervals for women.

3) In the third class, models are developed which are based on the underlying physiology of the system. Shack (1971) developed a mathematical model of the human menstrual cycle based on the hormonal interactions between the hypothalamus, pituitary, and ovaries. This model predicts the hormonal concentration levels in the body during the menstrual interval. It assumes a fixed neutral interval.

Nature of Research: The general approach used was developed by Sharpe et. al. (1977) for the prediction of insect development times (intervals) based on insect development rates.

Under constant temperature conditions, development times (menstrual interval) can be calculated from the reciprocal of the development rate. The following equation from Sharpe et. al. (1977) describes the relationship between the probability density function (p.d.f.-development rate) and the p.d.f. f_2 (development times-intervals).

$$f_2(y) = \frac{1}{y^2} f_1(\frac{1}{y}) \tag{1}$$

By assuming that the development rate of the menstrual cycle is normally distributed and by using this transform, one can obtain a positively skewed distribution of menstrual intervals. For the normal rate distribution

$$f_n = \frac{1}{\sigma\sqrt{2\pi}} e^{-1/2(\frac{x-u}{\sigma})^2} \tag{2}$$

one obtains the following transformed interval distribution

$$f_n(y) = \frac{1}{y^2\sigma\sqrt{2\pi}} e^{-1/2(\frac{1/y-u}{\sigma})^2} \tag{3}$$

this transformation is shown in Figure 4.

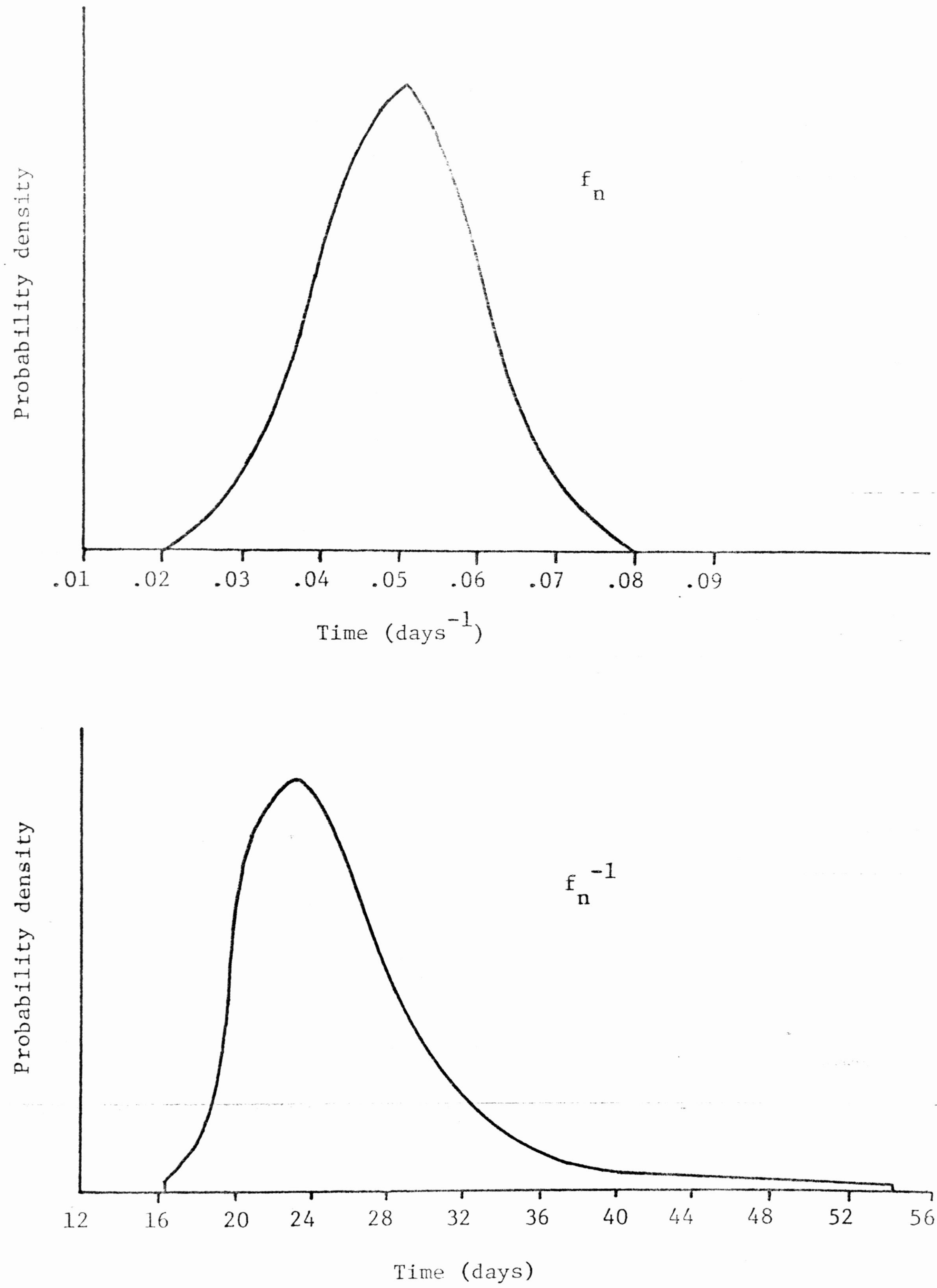


Figure 4. Transformation of development rate to development time.

VI. MODEL DEVELOPMENT

Before a system can be modeled, the system must be thoroughly understood. Excellent discussions of the endocrinology and physiology of the menstrual cycle are given in the book by Speroff (1971), Odell and Moyer (1971), Austin (1972), Curry (1974), and Gamong (1975). In this paper we will only consider the controlling components of the cycle.

The Reproductive System: Menstruation is defined as the cyclic structural changes the endometrium (mucosa lining of the uterus) undergoes in the periodic preparation for fertilization of the ovum and pregnancy.

In this research we were not interested in the complex hormonal interactions of the hypothalamus, pituitary, and of the ovaries (ovum, follicle, and corpus luteum) except to the extent of the over all controlling mechanism of the cycle. The menstrual cycle can be compared to a large self regulating machine, each component controlling and regulating the next component. The whole system needs only some general feed back loops to keep it running smoothly, this control system is diagramed in Figure 5.

By examining the system, one finds that the cycle begins with the initialization of follicle growth by a surge of FSH (follicle stimulating hormone). As the follicle begins to mature, it begins to produce estradiol. About the 12th day of the cylce the estradiol level increases rapidly (due to the growth of the follicle). On the 14th day there is surge of FSH and LH (luteinizing hormone) which causes ovulation on the following day. The ruptured follicle then forms the corpus luteum which produces estrogen and progesterone. When no fertilization occurs, the corpus luteum will begin to decay. The plasma concentrations of estrogen and progesterone will then drop dramatically and bring on the menses. When the levels of

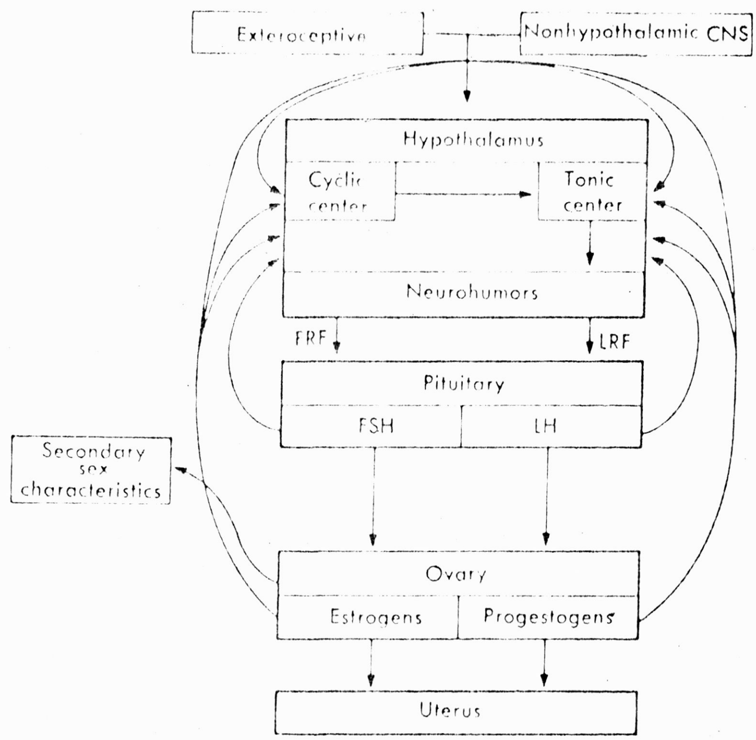


Figure 5. Dynamic Relationship of the ovary to the whole woman.

estrogen and progesterone drop sufficiently low, a new surge of FSH is then triggered, and the cycle begins again. The plasma hormone levels during the cycle are shown in Figure 6.

Assumptions: The fact that the controlling levels of estradiol and progesterone in Figure 6 corresponds to the growth rate of the follicle (and to the growth rate of the corpus luteum) suggests that the mechanism of the cycle is the growth rate of the follicle/corpus luteum. It is assumed that the development rate of the follicle/corpus luteum is normally distributed (a typical characteristic for many biological systems), and can be described by equation (1). Therefore, the menstrual interval can be modeled by the transform of equation (1), which is given by equation (2).

Data Analysis: Two sets of data were utilized in this analysis; one for normal pubertal girls [Engle (1934), see Figure 2] and the other for healthy normal adult women (mostly student nurses, see Figure 3, Arey (1939)).

One characteristic of the data was brought out by Engle (1934): The variability of menstrual cycles decreases as the menstrual life increases, or as shown in Figure 7, the standard deviation decreases steadily with the increased number of menstruations since menarche. This observation indicated that a single normal transformation would be insufficient to fit the true distribution; this was confirmed in our analysis early in the research.

The fact that the standard deviation changes with "cycle age" leads to the assumption that a distribution of data for girls of different menarche ages, could be modeled by a combination of distributions, each with a different mean and standard deviation corresponding the the "cycle age" of that sub-distribution.

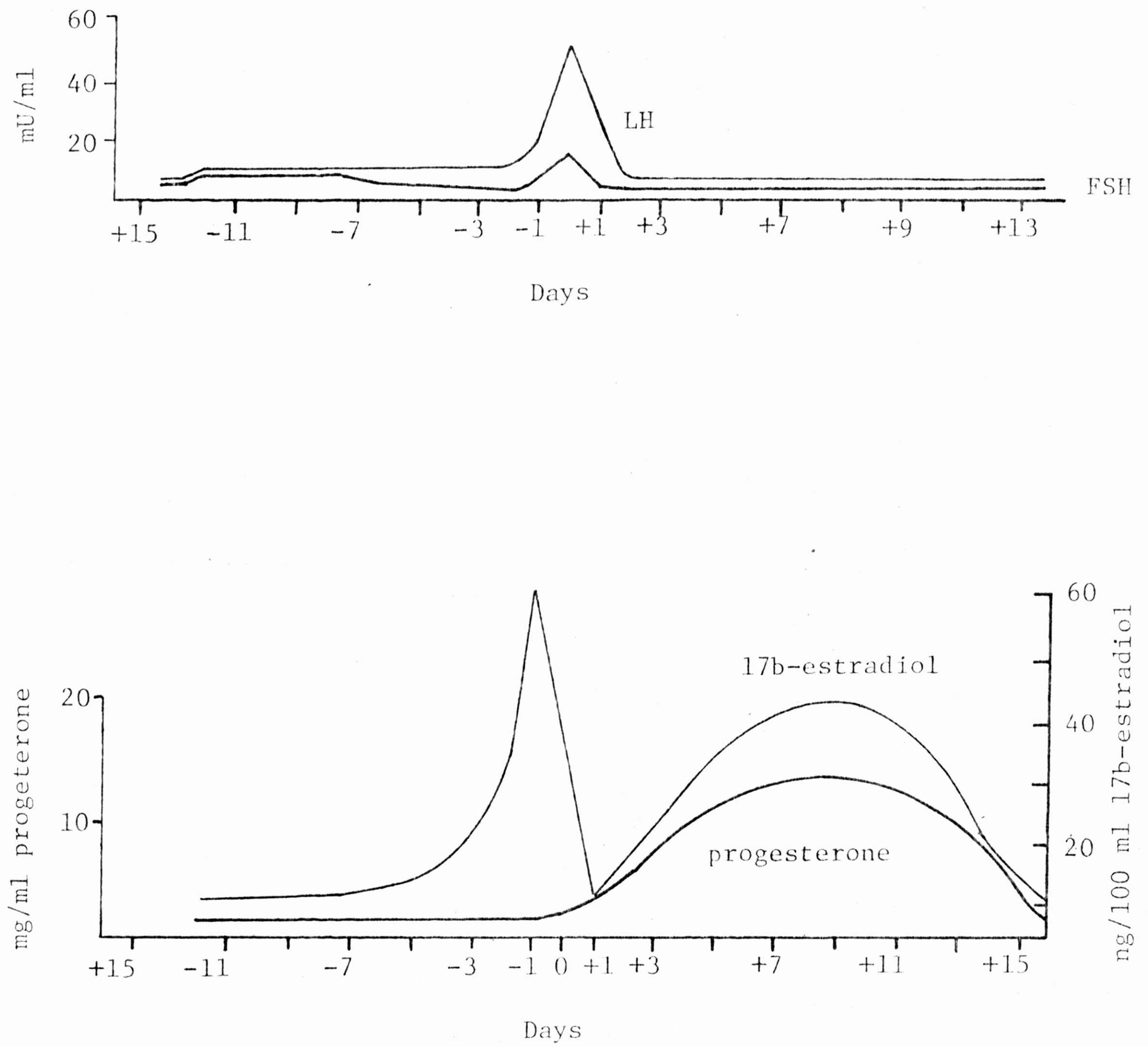


Figure 6. Changes in plasma hormone levels during normal menstrual cycle.

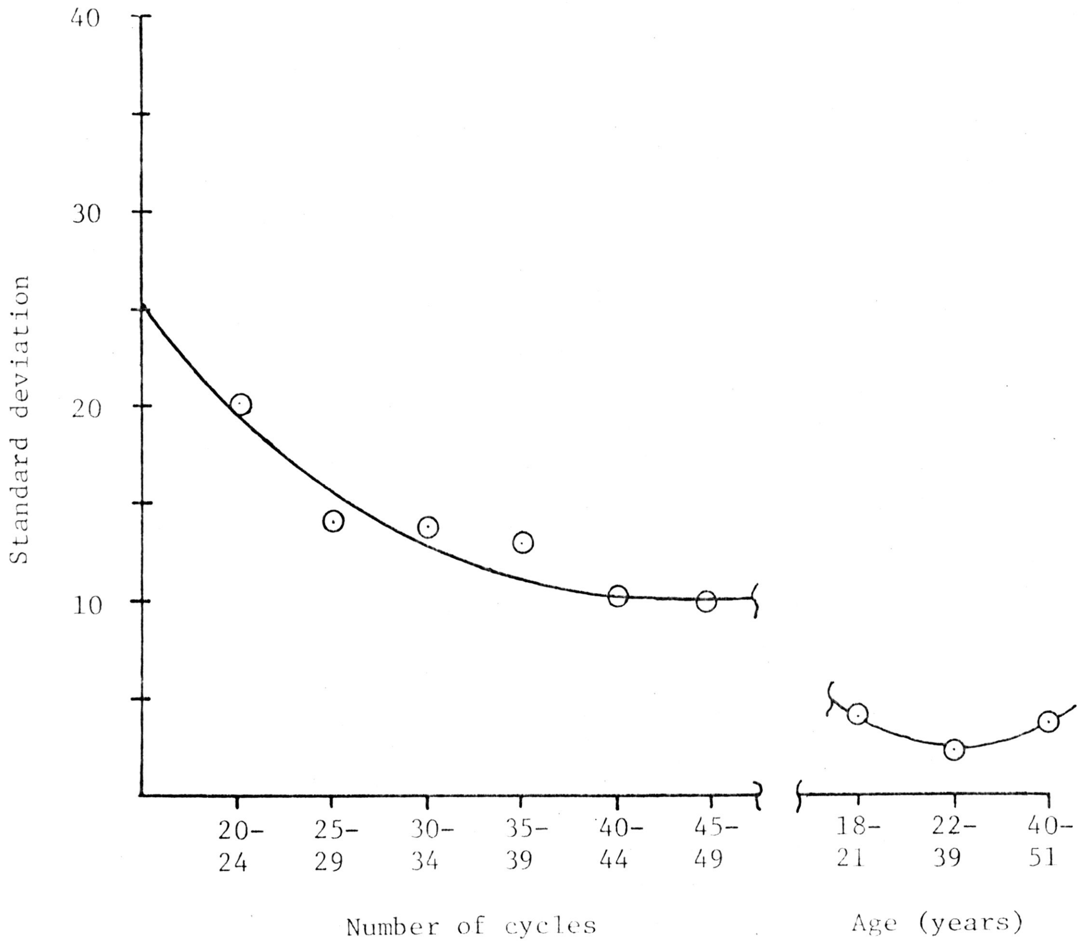


Figure 7. Trend toward menstrual regularity as a function of menstrual experience.

Due to the wide variation in means and standard deviations found in the data for pubertal girls (Figure 7), the distribution for girls needs to be modeled separately from the distribution for women.

To model the distribution of menstrual intervals for girls, the population was broken down into five groups. Each group was modeled by a transformed normal distribution. The parameters of these component models (mean and standard deviations) were estimated based on the "cycle ages" as shown in Figure 7. These groups are shown in Figure 8 and in Table 1. The groups were then weighted by the number of observations in each group, and combined to yield the distribution which is compared in Figure 9 to the observed data.

To model the distribution of menstrual intervals for normal women, the data population was only broken down into 3 groups. Again, each group was modeled by a transformed normal distribution, with it's parameters estimated by using the different standard deviations predicted by their "cycle ages". Figure 10 and Table 2 show these groups, while Figure 11 compares the combined model with the observed data.

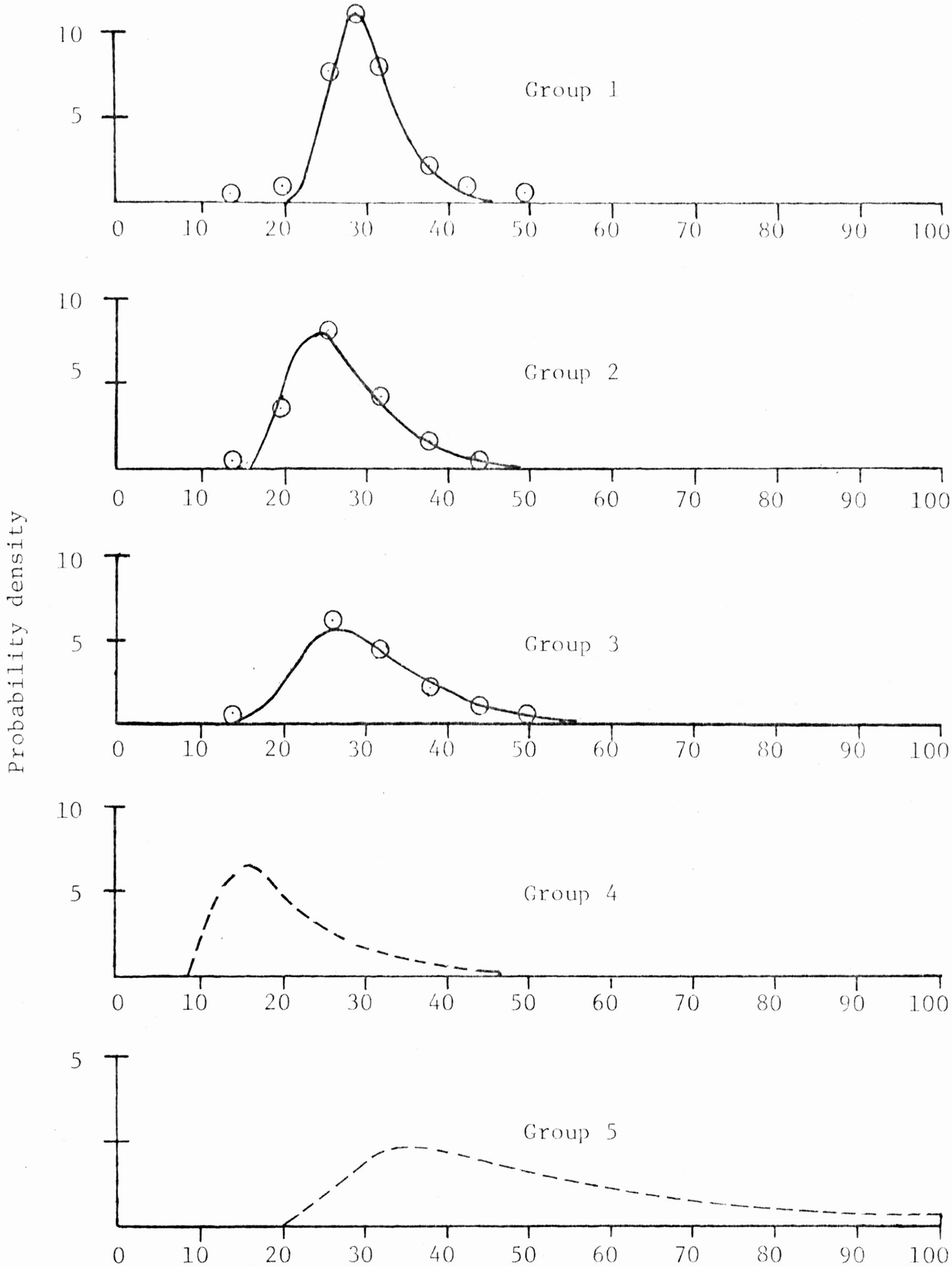


Figure 8. Groups for model of menstrual distribution for girls.

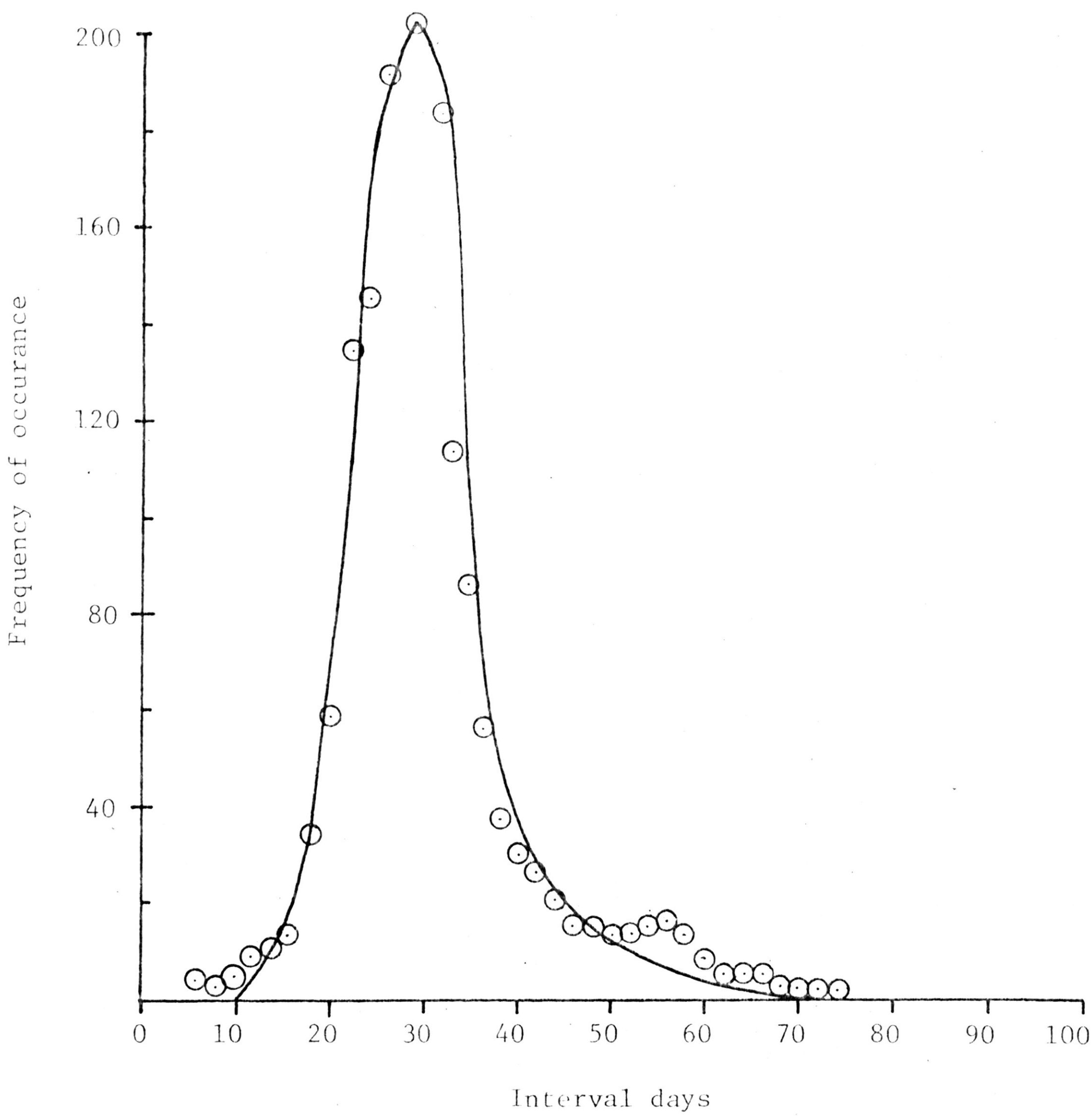


Figure 9. Comparison of combined transformations with data for pubertal girls.

Group	Number of observations	Mean (day^{-1})	Standard deviation (day^{-1})
1	1268	.0333	.009
2	850	.0385	.008
3	731	.0333	.004
4	157	.0500	.020
5	134	.0200	.010

Table 1

Population breakdown for pubertal girls

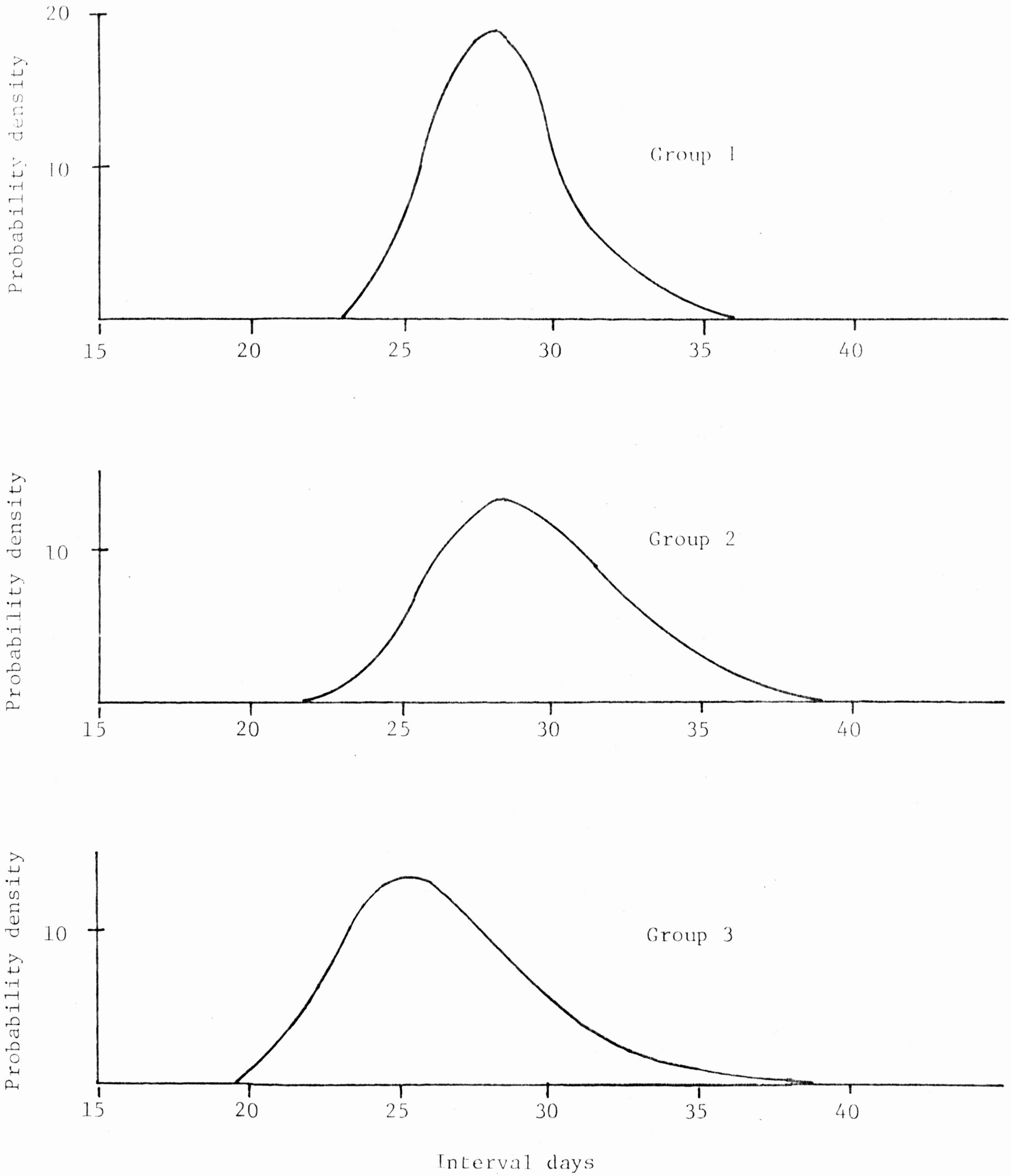


Figure 10. Groups for model of menstrual distribution for women.

Group	Number of observations	Mean (day^{-1})	Standard deviation (day^{-1})
1	2843	.0384	.0045
2	2843	.0344	.0037
3	2843	.0357	.0027

Table 2

Population breakdown for normal women

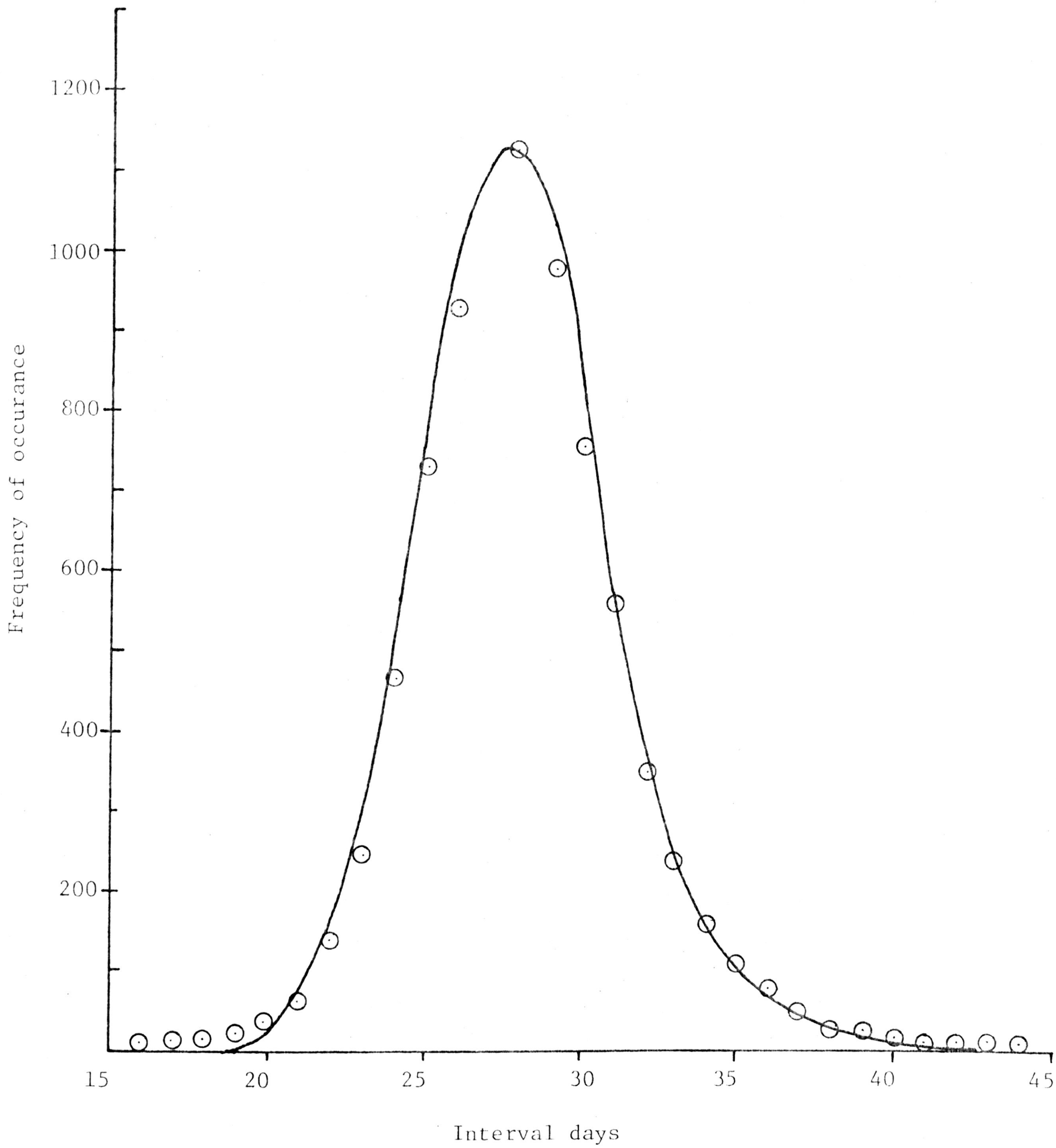


Figure 11. Comparison of combined transformations with data for normal women.

VII. CONCLUSIONS

1) The extremes in variability found in menstrual distributions can be accounted for by combining groups of distributions each representing a fraction of the population at different "cycle ages". These "cycle ages" have decreasing means and standard deviations as the number of cycles an individual experiences increases.
2) By analyzing the physiology of the human menstrual interval, it was assumed that the controlling follicle/corpus luteum development rate is normally distributed for similar cycle ages.
3) The skew in the distribution of menstrual intervals follows naturally from the transformation of development rate to development intervals.
4) It is felt that this type of approach is valuable, for now the system can start to be analyzed and controlled.

ACKNOWLEDGEMENTS

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