A MATHEMATICAL MODEL OF THE HUMAN MENSTRUAL CYCLE

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ABSTRACT A mathematical model for the hormonal interactions of the human menstrual cycle is presented. The feedback effects of estrogen on the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are considered, including a mechanism describing the midcycle LH peak. Computer simulation with this model yields results which are periodic and in good agreement with physiological data.

INTRODUCTION

There have been many attempts in recent years to construct mathematical models of such diverse physiological phenomena as the regulation of body temperature, the chemical control of breathing, endocrinology, and cardiology (see Riggs [1970] for a survey and bibliography of some of this work). The value of such mathematical models of complex physiological systems has been discussed previously by Yates et al. (1968) and others (Mesarović, 1968; Schwartz, 1969). It is clear from previous efforts in modeling different physiological systems that models help to organize information about a complex system, suggest the areas where additional knowledge is needed, and clarify the inadequacy of a proposed mechanism.

In this paper we present a mathematical model of the ovarian-pituitary relationships during the menstrual cycle of the human female. Excellent discussions of the endocrinology of the menstrual cycle are given in the book by Sawin (1969) and in the review paper by Henzl and Segre (1970). The bibliography of the latter paper gives many references to recent experimental measurements of hormone levels. Experimental data needed for modeling continues to become available because of new techniques of measurement, in particular, radioimmunoassay. Particularly valuable are the papers by Ross et al. (1970), Jaffe and Midgely (1969), and Vande Wiele et al. (1970).

One of the earliest attempts to construct a model for the cycle was made by Lamport (1940) who based his model on the well-known "push-pull" theory of estrogen-gonadotrophin interaction. His model, however, did not show the well-known cyclic variations in estrogen levels. By including the growing follicle explicitly

TABLE I *a*

VARIABLE LIST

Symbol	Description
EST	Plasma estradiol level (pg/ml)
FSH	Plasma level of FSH (ng LER 907/ml)
LH	Plasma level of LH (ng LER 907/ml)
PROG	Plasma level of progesterone (ng/ml)
FSL	Follicle maturity
PSLH	Pituitary storage of LH
PFSH	Pituitary storage of FSH

as one of the variables Thompson et al. (1969) obtained a model which did exhibit sustained oscillations; however, this model is a highly simplified one that includes only the interactions between estrogen, FSH, and the growing follicle.

A general description of the interrelationships between the ovary and anterior pituitary in mammals and their cyclic nature in terms of a systems approach was first given by Schwartz (1968). A more detailed model specifically concerned with the estrous cycle of the rat and the usefulness of systems theory in endocrine modeling is presented in Schwartz (1969). A computer simulation of the estrous cycle of the rat with respect to the blood levels of estrogen and LH and the timing of ovulation is contained in Schwartz and Waltz (1970).

A complete explanation of the human menstrual cycle must include the interactions of the hypothalamus, the anterior pituitary, and the ovary. A general overview of the central nervous system–pituitary–ovarian interrelations in women is shown in schematic form in Fig. 5.1 of Odell and Moyer (1971). While the formulation of such a general model is possible (Schwartz, 1968)[1], much additional experimental information is necessary before such a complete model can yield quantitative results.

An attempt to formulate a model of the anterior pituitary–ovarian interrelationship which includes the interactions between the gonadotrophins, LH and FSH; the steroids, estrogen, and androgen; and the growing follicle has been presented by Vande Wiele et al. (1970). (This paper also contains an excellent discussion of the physiological mechanisms regulating the menstrual cycle.) The model in their paper includes only the preovulatory phase of the cycle. It has been extended to include the complete cycle (R. L. Vande Wiele, private communication), and some results obtained from the complete model are presented in Speroff and Vande Wiele (1971), but no details of the formulation of the model are given.

Our primary variables are similar to those of Vande Wiele et al. (1970), but we have made different assumptions and descriptions of the form of functions describing steroid feedback, the release of LH and FSH from the pituitary during the midcycle surge, the transformation of the follicle, and the mechanism of ovulation. We have restricted our model to include only the variables shown in Table I *a*. (The model

[1] Schwartz, N. B. December, 1970. Seminar at Massachusetts Institute of Technology.

TABLE I *b*

VARIABLE LIST USED IN VANDE WIELE ET AL. (1970)

Plasma FSH	Measure of largest follicle $(MF)_1$
Plasma LH	Measure of smallest follicle $(MF)_2$
Plasma estradiol	Hypophysial LH content
Plasma androgens, AND	Plasma LH level due to surge mechanism
Plasma progesterone (not used)	

contains other variables and parameters, but these only describe the interactions of these primary variables; a complete list may be found in Table II.) The variables used by Vande Wiele et al. (1970) are shown in Table I *b*. A further discussion of the differences in the models will be presented subsequently. It is hoped that these different descriptions and assumptions will further stimulate attempts to understand actual hormone interactions.

DISCUSSION

The interactions between the hormones, follicle, and corpus luteum are described in terms of a set of first-order differential equations describing the rates of secretion for the various hormones, the growth rate of the follicle, etc., and logic functions. The timing of ovulation and the midcycle surge of gonadotrophins and the transformation of the follicle into the corpus luteum are determined by decision functions. The use of decision functions is an admission of an inadequate understanding of these phenomena, but perhaps the structure of these functions will suggest experimental work which will clarify the mechanisms of these complex events.

Our formulation using differential equations for the levels of different hormones (see Tables I and II for a listing of the variables and parameters) differs from that of Vande Wiele et al. (1970). Similarly, while they also use decision functions to control ovulation, the midcycle surge of gonadotrophins, and the transformation of the follicle into corpus luteum, the structure of the functions used in our model is different; further experimental work is needed to delineate the importance of these differences. Table III presents a summary of the formulation in Vande Wiele et al. (1970) for the preovulatory portion of the cycle.

In the following discussion the variables LH, FSH, etc., will represent plasma concentrations, and the time rates dLH/dt, dFSH/dt, etc., will represent the rates at which the various hormones enter into the bloodstream. Thus the synthesis-regulatory interaction of the pituitary and hypothalamus are only modeled very indirectly.

In what follows we first discuss the equations for the levels of gonadotrophins, then the equations governing the rate of maturation of the follicle and steroid levels, and finally the important decision functions used in the model. A description of the over-all dynamic relations and the organization of the model is shown in Fig. 9.

The rate at which the gonadotrophins are secreted depends upon the plasma steroid levels in a very complicated way. At moderate levels there is a negative feedback which depresses gonadotrophin secretion. Higher levels of estrogen, however,

TABLE II

VARIABLES AND PARAMETERS IN THE MODEL

Variables	
PSLH	Pituitary storage of LH
PSFSH	Pituitary storage of FSH
EST	Plasma level of estrogen
PROG	Plasma level of progesterone
SLH	Surge LH
SFSH	Surge FSH
PFSH	Plasma FSH level normally produced by pituitary
FSH	*Total* plasma FSH level
LH	*Total* plasma LH level
ICP	Index variable which "switches on" corpus luteum
LHS	Index variable which checks on whether an LH surge has occurred on a mature follicle
FSR	Measure of the *regressing* follicle
Parameters	
PS1	Maximum level of LH stored in the pituitary
RLH	Rate LH is stored
RFSH	Rate FSH is stored
TEST	Estrogen level which triggers LH surge
TPRG	Progesterone level which damps LH surge
PS2	Level of LH stored in the pituitary necessary to initiate a surge
SURGE	The cutoff level of LH which stops the surge
$(FSH)_T$	Tonic level of gonadotrophin secretion
$(LH)_T$	" " " " "

TABLE III

FORMAT OF EQUATIONS AND DECISION FUNCTIONS USED IN VANDE WIELE ET AL. (1970*)

Equations

$$\text{FSH} = a_1 e^{-\alpha_1(\text{EST})} + a_2 e^{-\alpha_2(\text{EST})} + a_3$$

$$\text{LH} = \tfrac{1}{2}a_1 e^{-\alpha_1(\text{EST})} + \tfrac{1}{2}a_2 e^{-\alpha_2(\text{EST})} + \tfrac{1}{2}a_3 + (\text{SURGE LH})$$

$$\text{EST} = \text{EST}_T + (\text{follicle size function})_1 \cdot \text{FSH}$$

$$\text{AND} = \text{adrenal androgen} + (\text{follicle size function})_2 \cdot \text{FSH}$$

$$\frac{d(MF)}{dt}\alpha = a_3(\text{FSH})\,(\text{LH}) + a_4(\text{EST}) - a_5^{(\alpha)}(\text{AND})\,[(MF_\alpha)^2 - a_6(MF_\alpha)^2];\ \alpha = 1, 2$$

Decision function for transition into corpus luteum; controlled by ovulatory transition state and ovulatory index (unused).

Decision function for LH surge; controlled by EST, pituitary content of L H, ovulatory transition index.

* See Table I *b*.

trigger a large surge in FSH and LH. We have incorporated these observations into our model by assuming that negative feedback is still present, but that a dominant surge term is superimposed on this. The equations governing the plasma levels of FSH and LH are:

$$\frac{d}{dt}(FSH) = FSH_T - CL_1 FSH - EST1 - PROD1 + \frac{d}{dt}(SFSH); \quad (1)$$

where

FSH_T = tonic level of production of FSH;

CL_1 = clearance rate of FSH from the body;

EST1 = negative feedback effect of estrogen (EST) on FSH levels, $E_1 - E_2 \exp(-\epsilon_1 EST) - E_3(-\epsilon_2 EST)$;

PROD1 = negative feedback effect of progesterone (PROG) on FSH levels, $= P_1 - P_2 \exp(-\rho_1 PROG)$;

$\frac{d}{dt}(SFSH)$ = surge contribution to FSH level which will be discussed in more detail later;

and

$$\frac{dLH}{dt} = LH_T - CL_2 LH - EST2 - PROD2 + \frac{d}{dt}(SLH); \quad (2)$$

where

LH_T = tonic level of production of LH;

CL_2 = clearance rate of LH from the body;

EST2 = negative feedback effect of estrogen on LH levels, $= E_4 - E_5 \exp[-\epsilon_3 EST] - E_6 \exp[-\epsilon_4 EST]$;

PROD2 = negative feedback effect of progesterone on LH levels, $= P_3 - P_4 \exp[-\rho_2 PROG]$;

$\frac{d}{dt}(SLH)$ = surge contribution to LH levels which will be discussed in more detail later.

The particular form of a function such as EST1 which describes the negative feedback effect of estrogen on the plasma level of FSH has been chosen to correspond to what seems physically reasonable. Undoubtedly other forms of the functions for the amount of feedback will suggest themselves as plausible.

The rate at which the follicle matures ($dFSL/dt$) depends on the plasma levels of FSH, LH, and also on the intraovarian levels of estrogen, androgen, and perhaps progesterone. The most important of these factors are FSH and LH, and in this model we will only consider the effects of these two hormones. The rate is some complicated nonlinear function of FSH and LH which schematically is probably of the form shown in Fig. 1.

Our model simulates this growth rate by a piecewise nonlinear curve.

$$\frac{d}{dt}(FSL) = 0 \text{ if } FSH < FSHC;$$

$$= F(1 - \exp[-f \cdot FSH \cdot LH]) \text{ if } FSH > FSHC, \quad (3)$$

where FSHC = level of FSH at which follicle growth begins.

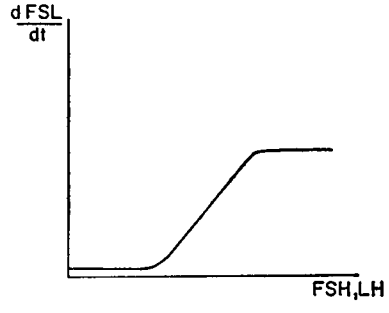

FIGURE 1

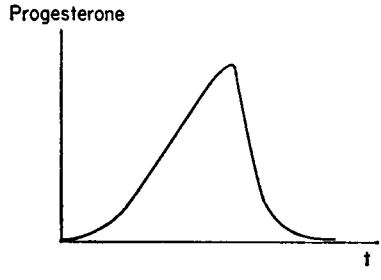

FIGURE 2

FIGURE 1 Rate of follicle maturation as a function of FSH and LH levels.
FIGURE 2 Progesterone output of the corpus luteum.

Modeling or simulating the transformation of the follicle into a corpus luteum is a difficult task. Indeed it is probably most dependent on intraovarian hormone levels, and cannot be accurately described in terms of plasma hormone levels. Similarly the factors affecting the maintenance and eventual regression of the corpus luteum are little understood. The idea that the corpus luteum is independent of pituitary control has been widely held, but seems to be contradicted by some recent experimental evidence (Vande Wiele et al., 1970). Nevertheless, the mechanisms of interaction are still poorly understood.

Our program simulates the functioning of the corpus luteum by a decision function which "turns on" the corpus luteum. It secretes progesterone for approximately 12 days and then the progesterone output quickly drops. In the model this progesterone output is simulated by a "black box" which produces a progesterone output curve that duplicates experimental measurements. The corpus luteum is also assumed to produce estrogen simultaneously with the progesterone.

Experimental evidence indicates that the progesterone output is similar to that shown in Fig. 2. A flow chart of the routine used in the model to simulate this output is shown in Fig. 3.

The equations governing the plasma levels of estrogen and progesterone depend on the maturity of the follicle and the contribution of the corpus luteum:

$$\frac{d}{dt}(\text{PROG}) = \text{PROG}_T - \text{CL}_s\text{PROG} + \text{CPL}, \tag{4}$$

where

PROG_T = production of progesterone by the adrenal cortex;

CL_s = clearance rate of progesterone from the body;

CPL = production of progesterone by the corpus luteum.

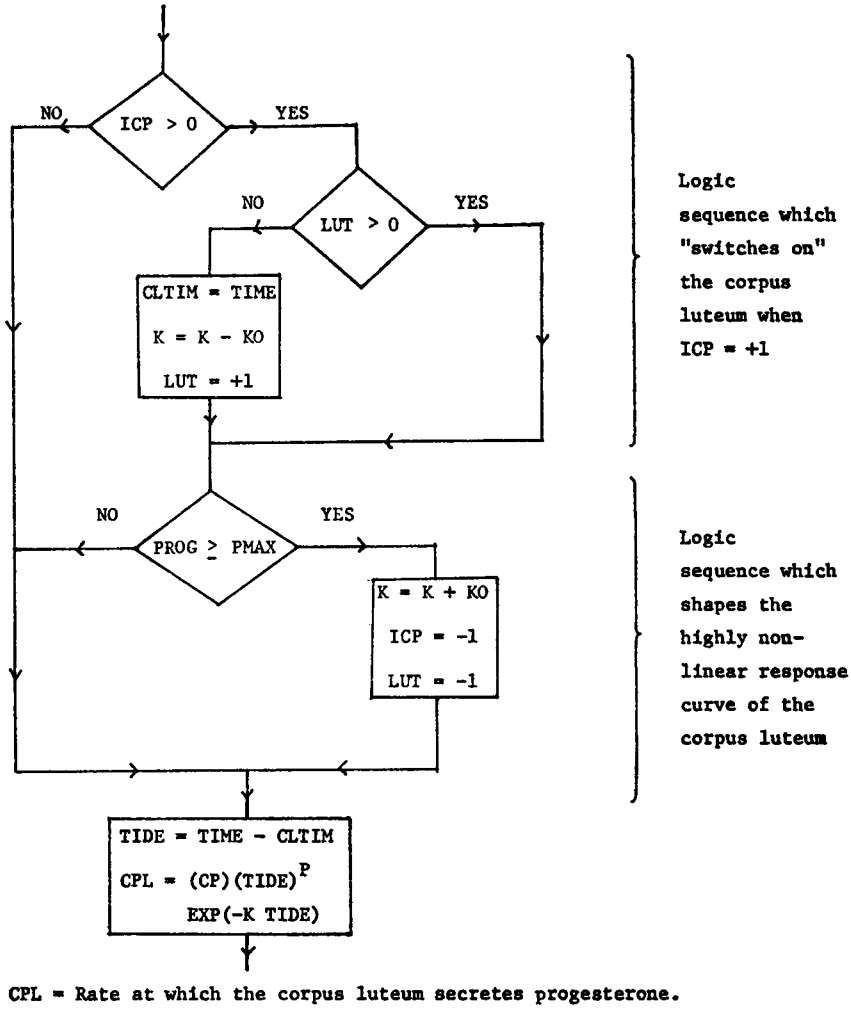

FIGURE 3 Flow chart for simulation of the corpus luteum progesterone production.

and

$$\frac{d}{dt}(EST) = EST_T - CL_4 EST + FLEST + E(CPL), \qquad (5)$$

where

EST_T = production of estrogen by the adrenal cortex;
CL_4 = clearance rate of estrogen from the body;
FLEST = contribution of the follicle to estrogen production
$= FSC_1[(FSL)^4 + F_L(FSR)^4] - FSC_2[<FSL)^8 + F_L(FSR)^8]$
(FSR measures the contribution of a regressing follicle);
E = parameter describing the estrogen production of the corpus luteum.

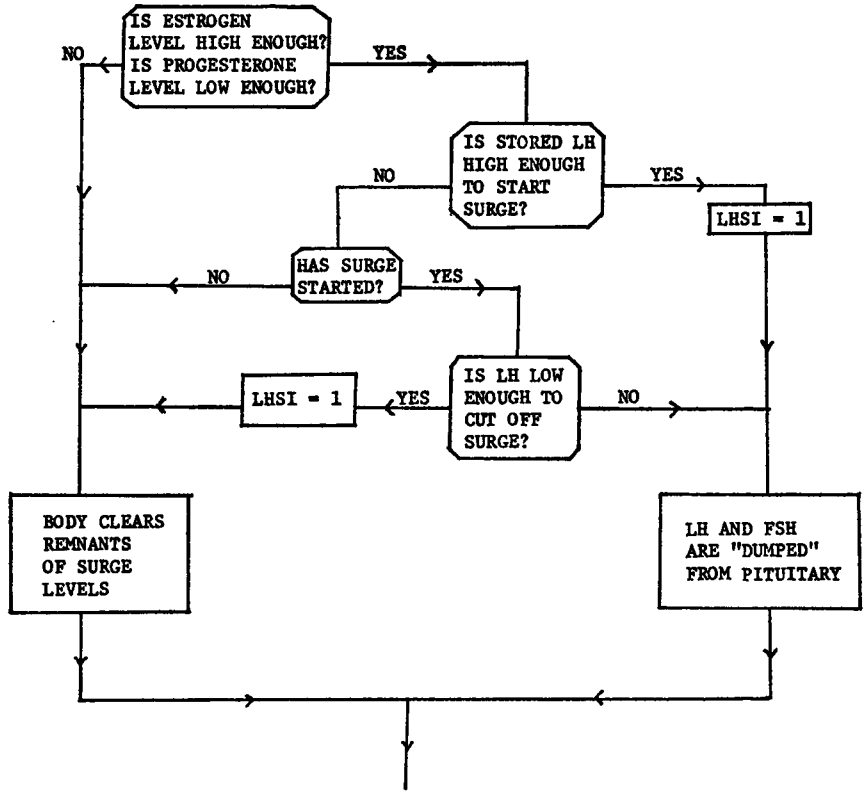

FIGURE 4 Decision function for the LH surge.

When levels of estrogen become sufficiently high, estrogen no longer has a negative feedback effect on gonadotrophins but instead stimulates a powerful surge of LH and FSH. In addition to the estrogen reaching a critical level our model also requires the estrogen:progesterone ratio to be within certain limits in order for the LH surge to occur. The surge itself is modeled as a "dumping" of LH and FSH by the pituitary. FSH and LH are assumed to be stored in the pituitary. When the surge is triggered, the pituitary begins to release FSH and LH; the surge continues as long as the critical estrogen-progesterone levels are maintained and sufficient FSH and LH are stored in the pituitary. The organization of the logic used in deciding whether a surge will occur is shown in Fig. 4. A flow chart which describes the implementation of this logic on the computer is given in Fig. 5.

The dynamic storage levels of the gonadotrophins have been modeled very simply. The pituitary was assumed to have constant rates of gonadotrophin synthesis (RFSH, RLH). Synthesis terminates when the pituitary has stored a maximum amount of gonadotrophin (PSI). A flow chart of the portion of the program describing this storage is shown in Fig. 6.

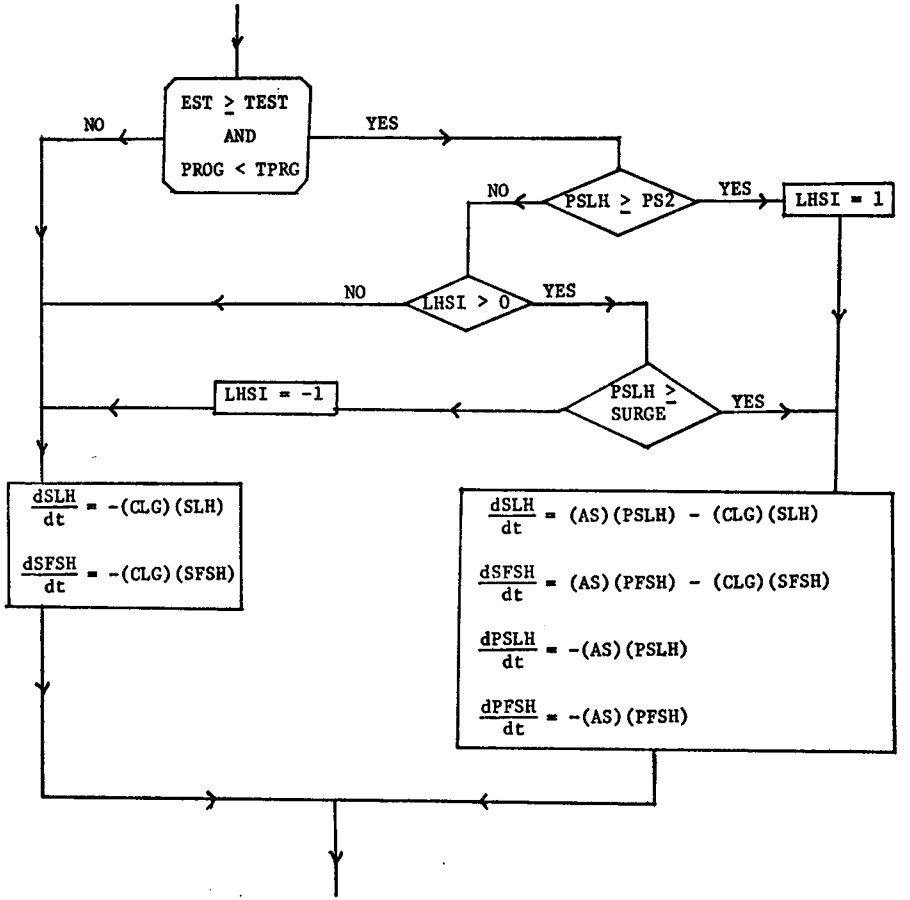

FIGURE 5

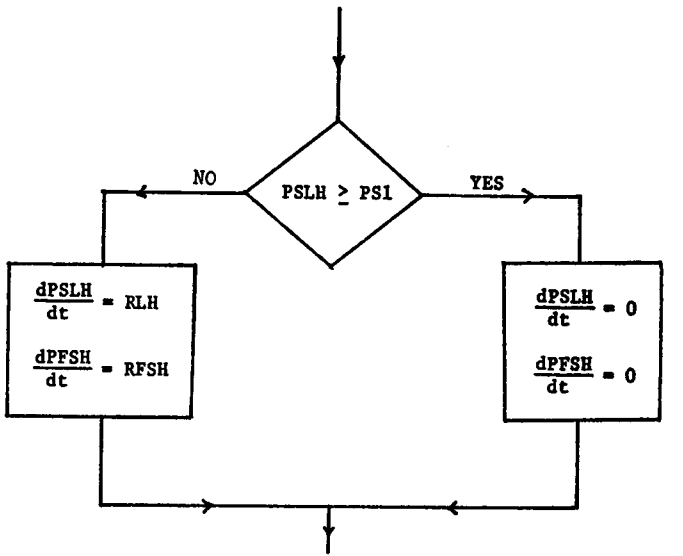

FIGURE 6

FIGURE 5 Flow chart for simulation of the LH surge.
FIGURE 6 Flow chart for simulation of pituitary synthesis of LH and FSH.

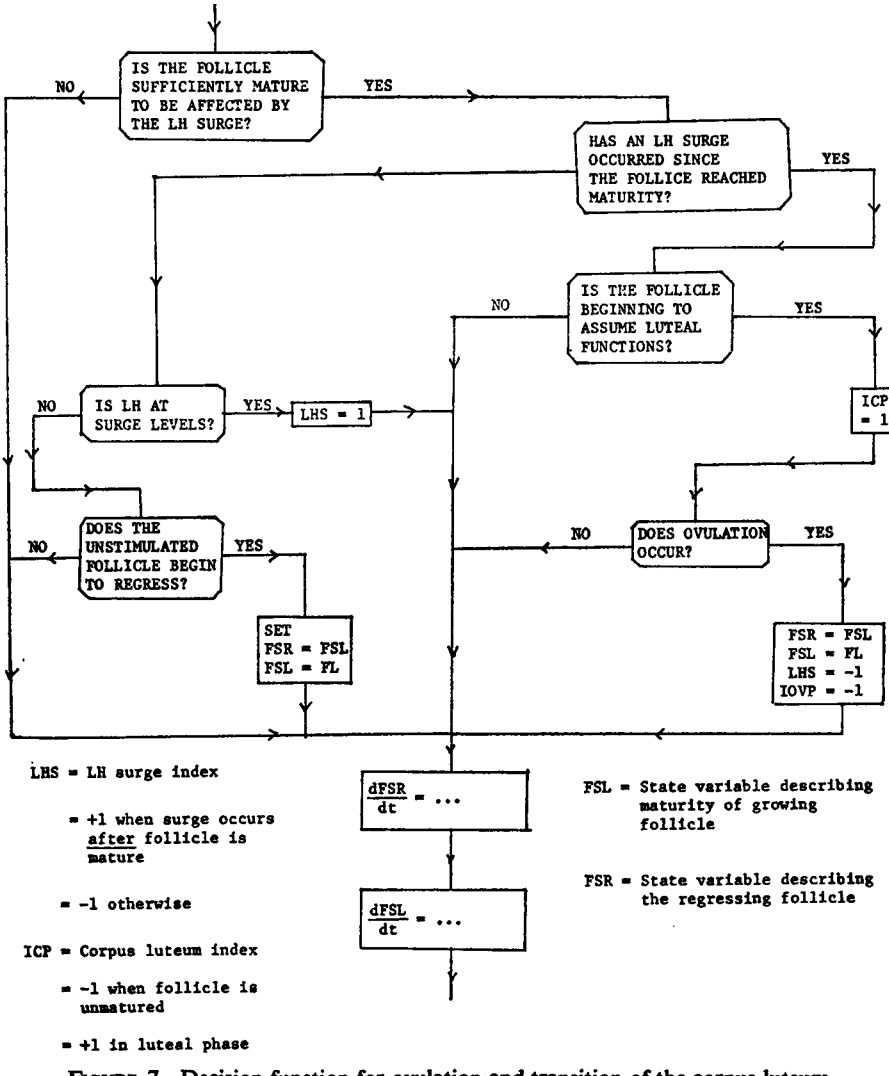

FIGURE 7 Decision function for ovulation and transition of the corpus luteum.

The most crucial logic section of the model decides when ovulation will occur and when the follicle will begin to assume a luteal function. The mechanisms of ovulation and luteal transformation are still poorly understood, but we assume that a realistic model must include the following features:

(*a*) Although relatively low levels of FSH and LH will stimulate the follicle and cause it to develop, ovulation will not occur unless an LH surge occurs as the follicle approaches full maturity.

(*b*) If an LH surge does not occur, the growing follicle simply regresses without transformation into a functioning corpus luteum.

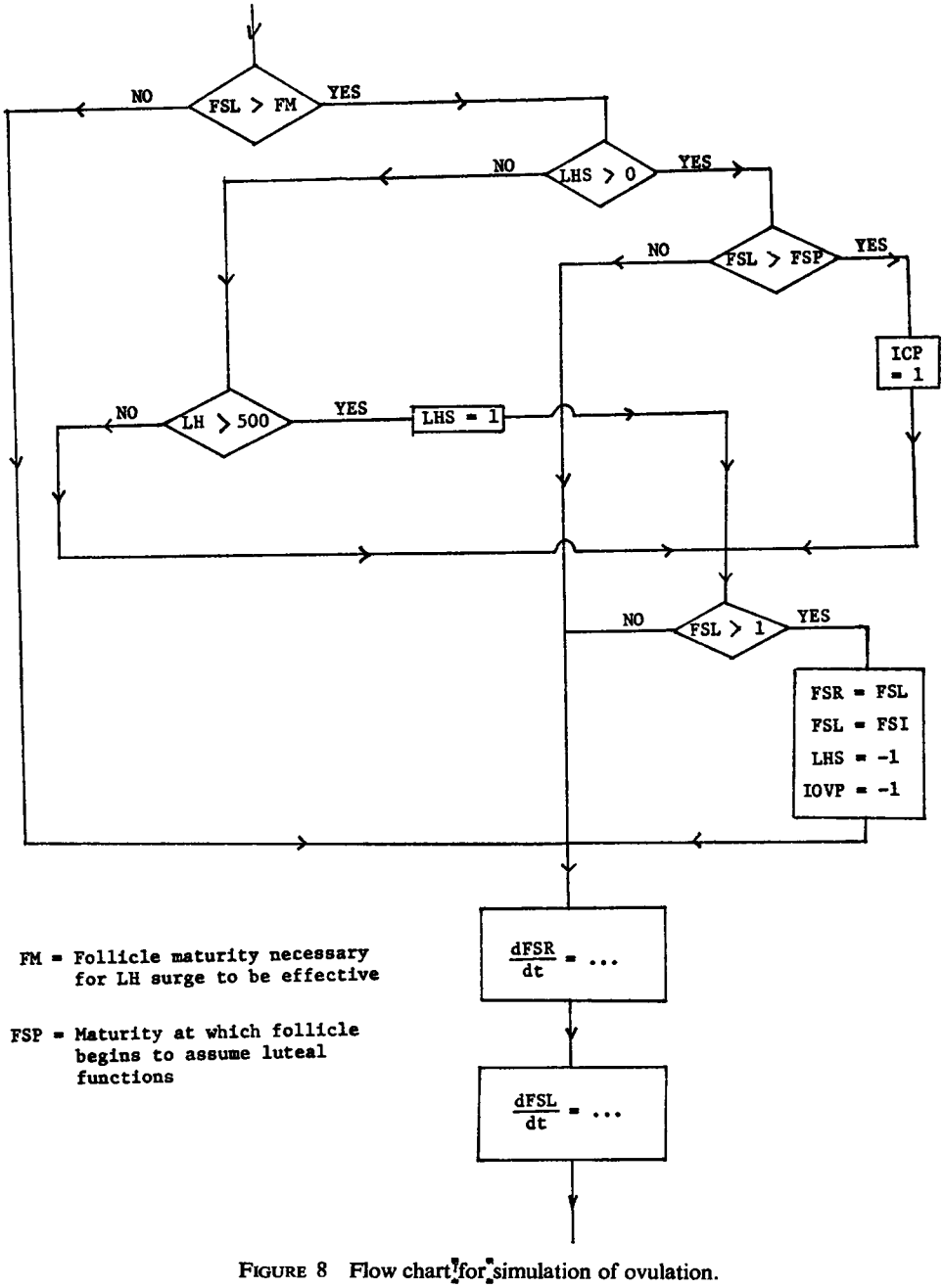

FIGURE 8 Flow chart for simulation of ovulation.

(*c*) The follicle begins to assume some luteal function, i.e., it begins to produce progesterone before ovulation.

A decision function for ovulation and transformation into the corpus luteum which satisfies these conditions is shown in Fig. 7. A flow chart for the computer simulation of ovulation is shown in Fig. 8.

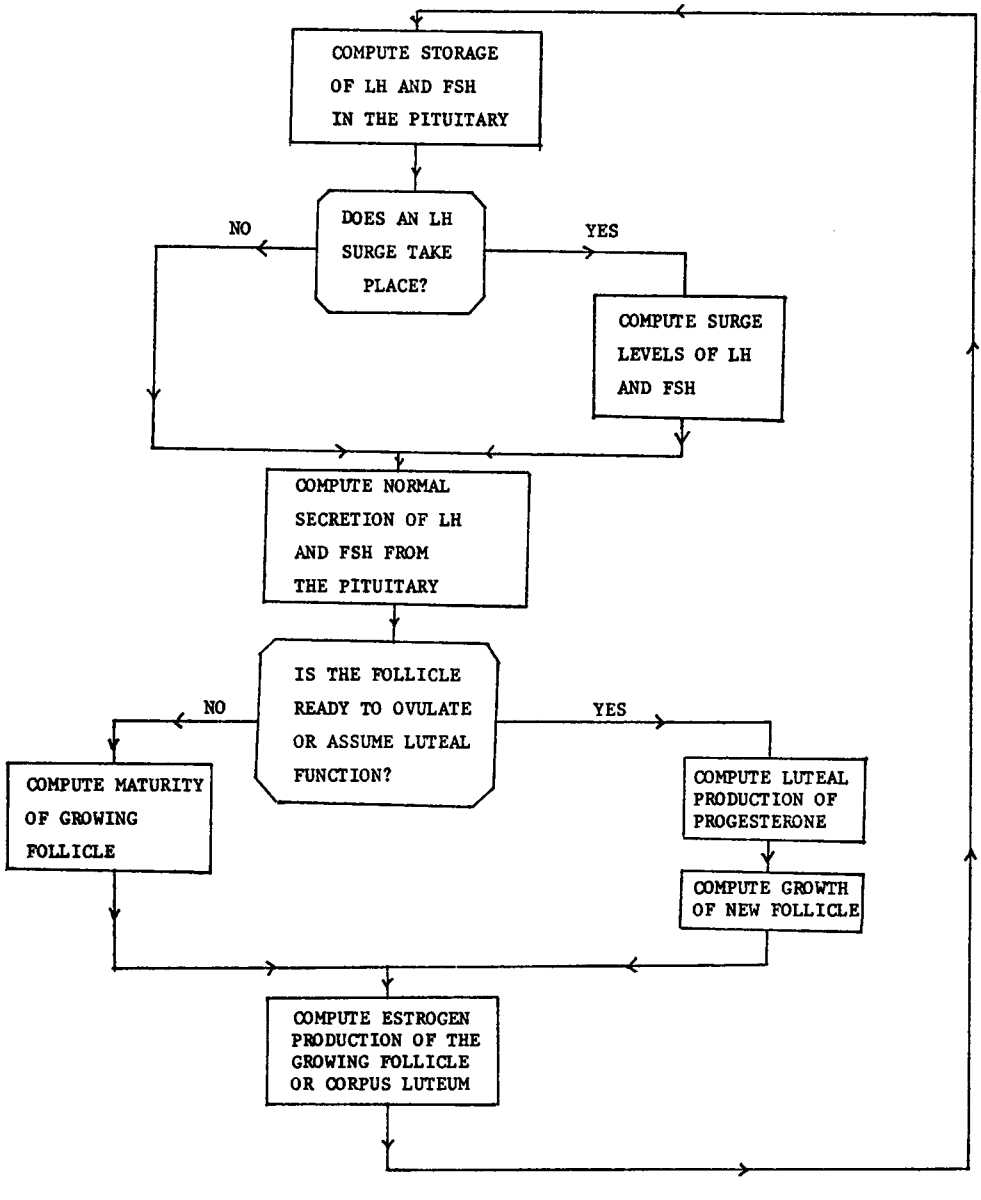

FIGURE 9 Outline of stimulation of the cycle.

Our mathematical model, the over-all organization of which is shown in Fig. 9, consists of equations 1–5 and the decision functions represented in Figs. 3–8. To solve the system of equations subject to the constraints imposed by the decision functions is obviously an impossible task analytically, but it is easy to do numerically on a computer. Because of the complicated decision functions necessary to describe the LH surge, ovulation, and the functioning of the corpus luteum, the program has been written in FORTRAN rather than a special purpose "systems" language like CSMP used in Schwartz and Waltz (1970). The values of the parameters in our equations were estimated from data in the literature and are found in Table II. The results of a typical run are shown in Fig. 10.

Our model simulates the normal cycle reasonably well. The model is presently being tested by perturbing the normal cycle through exogenous addition of estrogen

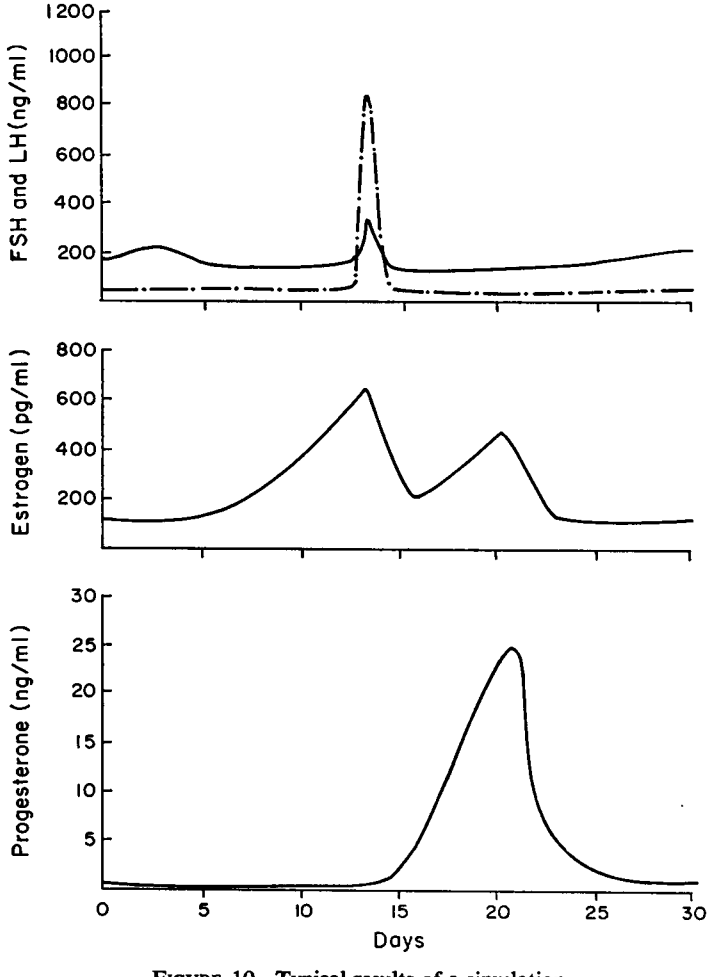

FIGURE 10 Typical results of a simulation.

and progesterone, i.e., we are simulating the effect of the "pill"; however, experimental measurements of hormone levels in women using the pill are just becoming available (Jaffe and Midgely, 1969), and it is difficult to estimate the accuracy of our simulation. We plan to revise the model as more data become available.

CONCLUSIONS

A mathematical model of the menstrual cycle which includes the interactions between FSH, LH, estrogen, progesterone, and the growing follicle has been presented. The model simulates the hormone levels during the normal cycle reasonably accurately.

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