

THE CONTROL OF FERTILITY

Gregory Pincus

THE CONTROL OF FERTILITY

Gregory Pincus

THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY
SHREWSBURY, MASSACHUSETTS

1965



ACADEMIC PRESS New York and London

COPYRIGHT © 1965, BY ACADEMIC PRESS INC.

ALL RIGHTS RESERVED.

**NO PART OF THIS BOOK MAY BE REPRODUCED IN ANY FORM,
BY PHOTOSTAT, MICROFILM, OR ANY OTHER MEANS, WITHOUT
WRITTEN PERMISSION FROM THE PUBLISHERS.**

ACADEMIC PRESS INC.

111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS INC. (LONDON) LTD
Berkeley Square House, London W.1

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 65-18442

PRINTED IN THE UNITED STATES OF AMERICA

Preface

The manuscript of this book was written and rewritten over a period of more than two years. During that period a break came in the apparent dam to publication on reproductive physiology and particularly its subdivisions concerned with reproductive behavior, conception, and contraception. The success of the oral contraceptives and the availability of many steroids of the types found effective have stimulated not only their experimental study but also numerous investigations in the general area of fertility control. What seemed at first to be a relatively uncomplicated task grew to rather formidable dimensions. To the experienced scientific writer this is evident from the need for over 1400 citations of experimental investigation. Even this does not tell the whole story, for in order to assess and select only the publications most pertinent to the subject matter of this book I have examined more than twice this number. Nevertheless, I have doubtless failed to cite a number of significant studies; certainly as the book is being processed and even as the faithful student reads it, accounts of new and relevant investigations are appearing. Nonetheless, I am confident that I have presented in this book the basic facts relative to the processes controlling fertility in higher animals. Moreover, I have attempted throughout to indicate the hiatuses in our knowledge, the questions demanding answers, and the probable needed directions of further research. To the inquiring mind this is perhaps not difficult, but the designation of meaningful areas for study requires also the familiarity of experience.

Indeed, it is because of a tolerably lengthy and fairly consistent experience that I have undertaken the writing of this book. As I

have mentioned in the text much of the subject matter is taken directly from my work and that of my colleagues. Without the collaboration and stimulation of these colleagues even my most sanguine efforts would have been meager indeed. Their efforts are acknowledged following this preface.

A number of the donors mentioned in the acknowledgment have made possible a feature of our work not described in the text of this book. This is the travel to meetings and conferences and to laboratories, clinics, and other institutions concerned with aspects of the multifaceted discipline of reproductive physiology. As a result we have conferred and lectured in many countries of the world, seen at first hand the research needs and possibilities in almost every European, Asiatic, Central, and South American country. We have faced the hard fact of overpopulation in country after country, learned of the bleak demographic future, assessed the prospects for the practice of efficient fertility control. This has been a saddening and a heartening experience; saddening because of the sight of continuing poverty and misery, heartening because of the dedicated colleagues and workers seeking to overcome the handicap of excess fertility and to promote healthy reproductive function. Among these we have made many friends, found devoted students.

Perhaps most stimulating has been the recognition among these workers throughout the world of the need and merit of objective scientific study of all aspects of fertility and sterility. The ready acceptance of validated statistics, of experimentally substantiated facts, has encouraged our belief in the internationalism of scientific inquiry. Birth control and the allied areas of sexual physiology and sexual behavior have long been battlegrounds of opinion-voicers. They have suffered from clashes among differing culture patterns, theologies, moralities, even politics. These struggles still continue, but they are being more and more delimited by the findings of science. Objective appraisal is surely but slowly replacing heated partisanship.

It is the operation of the scientific process in the area of fertility control that this book attempts to portray. That process is neither the acme of efficiency nor the "Final Solver of All Problems." As is evident to all who read, it works by fits and starts, it leads to errors

that must be painfully reviewed and critically rejected, it often dwells lengthily on minutiae, overstresses conditional findings, and for long periods fails to illumine factual obscurities. Nonetheless, it gets ahead, haltingly perhaps, but inevitably. The mystery and wonder of conception becomes describable in terms of gametes and their movements, in terms of fertilization reactions and the operation of replication mechanisms, in terms of oviduct chemistry and hormonal regulation. In each of these is also mystery and wonder, for there is still more to discover than we now know. But in the blazing or flickering light of what we do know a priori judgments and willful prejudices fade. And our considered and tested knowledge offers a firm basis for what we can and should do.

GREGORY PINCUS

Shrewsbury, Massachusetts
May, 1965

Acknowledgments

The list of my colleagues is a long one, beginning with my first research students at Harvard University, Drs. E. V. Enzmann and N. T. Werthessen, and continuing over a period of about thirty-five years to the present day. Reference to the work of most of these devoted research workers is made in the text, but I should like here to single out those who have long and consistently participated in my researches in reproductive physiology. Among them is Dr. M. C. Chang whose brilliant and illuminating animal experimentation is the product of an original mind which continues to stimulate all who talk and work with him, including myself. In this area of animal experimentation I have been particularly indebted for many years to the meticulous efforts of Miss Ann Merrill and Mr. T. Hopkins. In recent years Drs. E. S. E. Hafez, L. Fridhandler, E. B. Romanoff, M. X. Zarrow, T. Miyake, Y. Ogawa, N. Purshottam, B. Tamaoki, D. Layne, A. Erickson, Y. Kurogochi, A. Kulangara, G. Bialy, K. Arai, K. Yoshinaga, and U. K. Banik have contributed devoted and critical effort to investigations ranging from hormone assay and metabolism to pituitary-gonad relationships, to ovum and uterine biochemistry.

In the realm of advanced clinical investigation Dr. C. R. Garcia has been the skillful, knowledgeable, scientific physician dedicated to his patients as well as to the objectives of a far-ranging research effort. Working with him in our joint studies of human fertility control have been Drs. John Rock, E. Rice-Wray, M. Paniagua, A. Pendleton, F. Laraque, R. Nicolas, N. Borno, V. Pean, J. Shepard, E. E. Wallach, E. Klaiber, A. Parthenis, H. Rocamora, and J. Curet. The special studies in human subjects of the metabolism and bio-

chemistry of hormones concerned with reproduction have occupied the skilled and thorough efforts of Mrs. L. P. Romanoff and her associates, of Drs. J. F. Tait, C. J. Meyer, D. S. Layne, and T. Golab.

To all of these workers in the scientific vineyard and to their assistants and associates we express not only gratitude for devotion and unremitting effort but admiration for their enormous patient competence in ofttime difficult and always demanding research.

In addition to those associated immediately with my experimental studies there are many without whose efforts and cooperation neither this book nor the work which my colleagues and I have conducted would have been possible. Foremost among them is Elizabeth Pincus, my patient and beloved wife who has always been by my side through trying times, and who has sacrificed much to the forwarding of an effort in which she has had consistent faith. And to Dr. A. L. Raymond I am indebted not only for a staunch friendship but for the constant availability of his extraordinary critical acumen and scientific scepticism. Among his many colleagues at G. D. Searle and Company I have enjoyed particularly the chemical perspicacity of Drs. F. Colton, B. Riegel, and R. Burtner, the biological inventiveness and insight of Drs. F. J. Saunders, V. A. Drill, R. L. Elton, and R. A. Edgren, and the clinical knowledge of Drs. I. C. Winter, W. J. Crosson, W. Stewart, and G. R. Venning. Many other workers in the field of pharmaceuticals have been helpful with materials and advice. Their contributions have been acknowledged in our cited publications. So many men and women have aided us in our work that it would be difficult to name them all; they include workers at the Asociacion pro Bienestar de los Familias in San Juan, Puerto Rico, social workers, nurses, and secretaries in Humacao, Puerto Rico, in Port-au-Prince, Haiti, at the Free Hospital for Women in Brookline, Massachusetts, and at the Worcester Foundation in Shrewsbury, Massachusetts. To my faithful and hardworking amanuenses, the Misses P. Purtell and J. Sanford I am especially indebted.

Finally I should here state my debt to those organizations and individuals that have made possible my work by grants-in-aid of research. Outstanding is G. D. Searle and Company and its officers who had the courage to assist my pioneer efforts when practically all other pharmaceutical companies had "cold feet." Other com-

Contents

PREFACE	vii
ACKNOWLEDGMENTS	xi

I

Introduction

1. BACKGROUNDS

Text	3
References	9

2. THE REPRODUCTIVE PROCESSES AND THEIR VULNERABILITIES IN MAMMALS

Processes in the Male	10
Processes in the Female	16
References	24

II

Animal Studies

3. SPERMATOGENESIS AND SEMEN

Pituitary and Gonadotropin Inhibition	29
Direct Effects on Testis Tissue	36
Semen and Seminal Fluid	51
References	53

4. OVULATION

The Hypothalamopituitary Axis	57
Steroidal Ovulation Inhibitors	59
Antigonadotropin Assay	67
Antigonadotropins and the Hypothalamus	71
Inhibition of Exogenous Gonadotropin	75
Miscellaneous Antigondotropic Agents	79
References	82

5. FERTILIZATION

Text	88
References	99

6. FREE OVUM DEVELOPMENT

Text	103
References	109

7. BLASTOCYST DEVELOPMENT AND IMPLANTATION

Ovarian Hormones and Implantation Processes	113
Extra-ovarian Influences on Implantation	117
The Lability of Implantation Processes	121
Estrogens and Anti-estrogens	123
Antiprogestins	128
Poisons and Antimetabolites	138
Intrauterine Trauma	140
Corpus Luteum Inhibition	141
Abortion	143
References	144

8. SOME BIOLOGICAL ACTIVITIES OF COMPOUNDS AFFECTING FERTILITY

Some Activities of Estrogens	151
Anti-estrogens	157
Estrogens and Androgens	160
The Activities of Gestagens	161
Effects on Fetuses	169
Hormones and Tumors	171
The Metabolism of Compounds Affecting Fertility	171
References	175

III

Clinical Studies

9. CONTROL OF FERTILITY IN MEN

Text	187
References	194

10. FERTILITY IN WOMEN—OVOGENESIS AND OVULATION

Fertility Potential in Women	197
Detection of Ovulation	199
The Stimulation of Ovulation	209
References	212

11. THE INHIBITION OF OVULATION

The Assay of Ovulation Inhibitors in Human Subjects	219
Contraception	226
References	232

12. SOME BIOLOGICAL PROPERTIES OF OVULATION INHIBITORS IN HUMAN SUBJECTS

Functions Associated with Reproductive Organs and Processes	237
Mammary Glands and Lactation	260
Pregnancy and Postpartum	263
Functions Associated with Other Endocrine Organs	266
Effects on Somatic Tissues and Functions	272
Weight Gain and Aspects of Organic Metabolism	275
Hematology	277
Skin and Related Tissues	282
Psychological Effects	283
References	287

13. SOME CONSEQUENCES OF THE APPLICATION OF FERTILITY CONTROL

The Effectiveness of Contraception	295
The Acceptability of Contraception	298
References	306

AUTHOR INDEX	309
------------------------	-----

SUBJECT INDEX	345
-------------------------	-----

I INTRODUCTION

CHAPTER 1

Backgrounds

This book is primarily concerned with investigations into aspects of reproduction conducted by the author and his colleagues. It is, first of all, an attempt to summarize a collection of data hitherto either partially or not at all presented. Secondly, we shall attempt to indicate those avenues which hold promise for future investigation. Finally, we shall attempt an assessment of the implications of our understandings and ignorances.

Our own work began with a curiosity about mammalian fertilization and ovum maintenance (1). The evolution of internal fertilization and gestation in the oviducts has led to the establishment of various mechanisms for the safeguarding of the gametes and the conceptus. Because of their relative inaccessibility and certain difficulties in their maintenance *in vitro*, mammalian ova have, until lately, been used only to a limited extent as subjects for experimental study. Nonetheless, out of these early inquiries several findings emerged: (a) rabbit ova in moderately large number may be obtained by stimulating ovaries to superovulation by the administration of certain gonadotropic preparations (2)—this may be accomplished in a number of species of laboratory and domestic animals (3-5); (b) such ova may be readily fertilized (cf. 6), recovered, and cultured *in vitro*; (c) the fertilization of mammalian ova *in vitro* is accomplished with difficulty (7), and this may be due in large measure to the need for capacitation of the sperm, which is accomplished by their residence in the oviducts for a number of hours (8, 9); (d) fertilized rabbit eggs will readily

cleave at apparently normal rates *in vitro* (1, 10), but those of other species, e.g., guinea pig (11), rat (12), sheep, and goat (13), show only a limited amount of cleavage or none under a variety of culture conditions; (e) rabbit blastocyst growth under optimal conditions *in vitro* does not attain the rate observed *in vivo* (14) and growth *in vivo* is sharply limited by the action of ovarian hormones, particularly progesterone (15, 16); (f) energy for blastocyst growth *in vitro* appears to be derived from the Meyerhof glycolytic system provided enzyme maintenance by sulfhydryl-containing compounds occurs (17), but probably special growth-promoting substances present in blood serum are additionally necessary.

In these probings into the range of mammalian egg activities extending from maturation and ovulation to implantation, several conclusions implied or stated have emerged as the basis for more recent investigations. First, the dependence of the ovarian follicle on pituitary gonadotropic hormones for stimulation to ovulation is emphasized. Second, fertilization is seen to be not merely a chance meeting of egg and sperm, but an event requiring maturation (capacitation) of sperm as well as eggs within the female reproductive tract. Third, the fertilized egg cleaves readily *in vivo* in the absence of ovarian hormones or even in the presence of an excess of estrogen (18), but unknown factors essential for normal cleavage are difficult to supply *in vitro*, at least for the eggs of certain species. Fourth, growth of the blastocyst in the uterus appears to depend upon a serum ultrafiltrate containing a variety of nutritional essentials and ordinarily made abundantly available as the result of progestational uterine states normally controlled by ovarian hormones, especially progesterone and possibly conditioned by some of its metabolites (19).

Each of these conclusions supports the possibility of control of fertility by manipulation of the ovum environment, and particularly its hormonal environment. Curiously, the cardinal basis for a large portion of the work forming the subject matter of this book was unapparent in these early researches. Thus we specifically found (and stated) that estrogen did not prevent ovulation in the rabbit (18), and, therefore, the important concept of a steroid feedback upon pituitary hormone production and/or release evaded us.

Actually, recent experimentation has indeed emphasized that many estrogens in otherwise "physiological" doses are poor or ineffective inhibitors of ovulation in the rabbit (20).

In 1937, Makepeace, Weinstein, and Friedman (21) noted the effectiveness of progesterone as an ovulation inhibitor in the rabbit, but the logical extension of this observation into a more intensive study of the nature of the progesterone action as well as the action of certain derivatives and putative metabolites were not reported by us until 1953 (22).

Why this "logical extension" occurred after a latent period of approximately 16 years is a question concerning which we have raised some speculation. Certainly, judging by publications, there was a period during which our own activities in this field fell to a minimum, both absolutely and relatively (Table 1). An examination

TABLE 1
PAPERS PUBLISHED BY THE AUTHOR AND NUMBERS LISTED BY AUSTIN (9) FOR
THE PERIOD 1934-1961

Period of publication	Total number of papers	Number concerned with reproduction and allied phenomena	Number in Austin's bibliography
1934-1937	29	18	35
1938-1941	35	22	34
1942-1945	26	12	18
1946-1949	27	5	70
1950-1953	54	10	119
1954-1957	60	21	150
1958-1961	41	27	132

of the bibliography of any book concerned with reproductive phenomena (e.g., 9) discloses similarly a minimum number of publications during the period 1942-1945, and a significant rise in output from 1950 on. In our own case, the special demands of "war" research accounted for a shift of interest to studies of adrenocortical function, particularly in relation to physical and mental stress, and this interest has continued to a greater or lesser degree. Indeed, World War II probably accounts for the lapse observed generally. In our case, the increase of activity as indicated by publications from 1950 on has been due to two overtly ascertainable factors:

(a) a visit from Mrs. Margaret Sanger in 1951 and (b) the emergence of the appreciation of the importance of the "population explosion."

At the time of her visit, Mrs. Sanger's interest in the world-wide dissemination of information on birth control was at high tide. Her experience as President of the International Planned Parenthood Federation had made her aware of the deficiencies of conventional contraceptive methods, particularly in underdeveloped areas of the world. Her hope, expressed to us, was that a relatively simple and fool-proof method might be developed through laboratory research. Drs. Chang and Pirie and I had already had some experience with hyaluronidase inhibitors in the rabbit (23) but we had found that such potent inhibitors could act only on direct contact with sperm and that there was no possibility of an effect by parenteral administration. Although some preliminary experiments by the late Dr. Abraham Stone had indicated that at least one of these inhibitors might be quite active as the component of an intravaginal preparation in the human, the limitations to its use still appeared to be rather formidable. Accordingly, Dr. Chang and I drew up a modest project proposal that received support under a grant from the Planned Parenthood Federation of America. Work under this grant resulted in the paper on the rabbits mentioned above (22) and in the finding that the compounds that we found to be potent as ovulation inhibitors in the rabbit were also quite active as anti-fertility agents in the rat (24).

The impetus to research, particularly on the physiology of reproduction, given by the recognition of the population explosion has been described a number of times (25, 26). Although the physiologist has generally been called upon to undertake research which might lead to easily effective and acceptable means of birth control, his role is indeed a much wider one. The modern-day investigator cannot be satisfied with the invention of a "cunning device." The present accumulated knowledge concerning reproductive processes indicates that the production of gametes, their transport and mating, their fusion, and the fate of the fertilized egg involves an intricate and delicately balanced set of sequential events. Interfering with this sequence at any of a large number of stages may have physiologic consequences that are not apparent on