



12-1972

Ovum Transport in Rabbits Injected with Prostaglandin E₁ or F_{2α}

James Vernon Ellinger

Follow this and additional works at: https://scholarworks.wmich.edu/masters_theses



Part of the Veterinary Anatomy Commons

Recommended Citation

Ellinger, James Vernon, "Ovum Transport in Rabbits Injected with Prostaglandin E₁ or F_{2α}" (1972).

Master's Theses. 2745.

https://scholarworks.wmich.edu/masters_theses/2745

This Masters Thesis-Open Access is brought to you for free and open access by the Graduate College at ScholarWorks at WMU. It has been accepted for inclusion in Master's Theses by an authorized administrator of ScholarWorks at WMU. For more information, please contact wmu-scholarworks@wmich.edu.



OVUM TRANSPORT
IN RABBITS INJECTED WITH
PROSTAGLANDIN E₁ OR F_{2α}

By
James Vernon Ellinger

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment
of the
Degree of Master of Arts

Western Michigan University
Kalamazoo, Michigan
December 1972

ACKNOWLEDGEMENTS

I wish to thank Professors Jean M. Lawrence and Leonard J. Beuving, Western Michigan University, for serving on my advisory committee; the advice and friendship that Dr. Beuving provided as committee chairman is greatly appreciated.

I am sincerely indebted to the Fertility Research Unit of The Upjohn Company, where all phases of this investigation were conducted. Without the assistance and encouragement of these people, this project could not have been completed. Special thanks is expressed to Ralph Crosby, Kristi Forbes, Mary Meissner and Jerome Norland.

I am deeply grateful to Dr. Ken Kirton and Dr. John Wilks, The Upjohn Company, for their guidance, constructive criticism, and most of all, their encouragement at times when it was needed most. Needless to say, I have been greatly influenced by these men and their approach to scientific investigation.

James Vernon Ellinger

INFORMATION TO USERS

This dissertation was produced from a microfilm copy of the original document. While the most advanced technological means to photograph and reproduce this document have been used, the quality is heavily dependent upon the quality of the original submitted.

The following explanation of techniques is provided to help you understand markings or patterns which may appear on this reproduction.

1. The sign or "target" for pages apparently lacking from the document photographed is "Missing Page(s)". If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting thru an image and duplicating adjacent pages to insure you complete continuity.
2. When an image on the film is obliterated with a large round black mark, it is an indication that the photographer suspected that the copy may have moved during exposure and thus cause a blurred image. You will find a good image of the page in the adjacent frame.
3. When a map, drawing or chart, etc., was part of the material being photographed the photographer followed a definite method in "sectioning" the material. It is customary to begin photoing at the upper left hand corner of a large sheet and to continue photoing from left to right in equal sections with a small overlap. If necessary, sectioning is continued again — beginning below the first row and continuing on until complete.
4. The majority of users indicate that the textual content is of greatest value, however, a somewhat higher quality reproduction could be made from "photographs" if essential to the understanding of the dissertation. Silver prints of "photographs" may be ordered at additional charge by writing the Order Department, giving the catalog number, title, author and specific pages you wish reproduced.

University Microfilms

300 North Zeeb Road
Ann Arbor, Michigan 48106
A Xerox Education Company

MASTERS THESIS

M-4246

ELLINGER, James Vernon
OVUM TRANSPORT IN RABBITS INJECTED WITH
PROSTAGLANDIN E_1 OR $F_{2\alpha}$

Western Michigan University, M.A., 1972
Physiology

University Microfilms, A XEROX Company, Ann Arbor, Michigan

THIS DISSERTATION HAS BEEN MICROFILMED EXACTLY AS RECEIVED.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

PLEASE NOTE:

Some pages may have

indistinct print.

Filmed as received.

University Microfilms, A Xerox Education Company

TABLE OF CONTENTS

I	INTRODUCTION	1
II	LITERATURE REVIEW	2
	Ovum Transport, General	2
	Effect of Ovarian Steroids on Ovum Transport	4
	Effect of Prostaglandins on Ovum Transport	7
	Oviduct Motility	7
	Methods of Measurement	7
	Effect of Ovarian Steroids on Oviduct Motility	8
	Effect of Prostaglandins on Oviduct Motility	9
	Effect of Adrenergic Stimulation on Oviduct Motility	11
III	MATERIALS AND METHODS	16
	Animals	16
	Measurement of Oviduct Motility	16
	Effect of Prostaglandins on Ovum Transport	18
	Outline of Experiments	18
IV	RESULTS	21
	Effect of Prostaglandins on Ovum Transport	21
	Oviduct Motility Studies	29
V	DISCUSSION	37
	Effect of Prostaglandins on Ovum Transport	37
	Effect of Prostaglandins on Oviduct Motility	39
	Possible Physiological Role for Prostaglandins in Oviduct	44

VI	SUMMARY	48
VII	PREPARATION OF OVIDUCT CANNULAS	49
VIII	BIBLIOGRAPHY	52

LIST OF TABLES

Table 1.	Outline of ovum transport experiments	20
Table 2.	Distribution of ova during passage through the oviduct of untreated rabbits	22
Table 3.	The effect of prostaglandin E_1 and $F_{2\alpha}$ on ovum transport (Experiment 2)	24
Table 4.	The location of ova 1 hr. after $PGF_{2\alpha}$ administration (Experiment 3)	25
Table 5.	The effect of repeated injections of PGE_1 on ovum transport (Experiment 4)	25
Table 6.	The effect of prostaglandins on ova in the cumulus cell mass (Experiment 5)	27
Table 7.	The effect of $PGF_{2\alpha}$ on ovum transport when admin- istered 9 hr. after ovulation (Experiment 6)	28
Table 8.	The effect of a reduced dose (2 mg) of $PGF_{2\alpha}$ on ovum transport (Experiment 7).	28

LIST OF FIGURES

Figure 1.	Diagrammatic representation of the rabbit oviduct	3
Figure 2.	Sketch of recording system used for measuring oviduct motility	17
Figure 3.	Experimental design for ovum transport studies	19
Figure 4.	Motility of the rabbit oviduct. <u>In vivo</u> control recordings from two different animals	31
Figure 5.	The response of the rabbit oviduct to $\text{PGF}_{2\alpha}$ and PGE_1 in vivo	32
Figure 6.	The response of the rabbit oviduct to intravenous administration of $\text{PGF}_{2\alpha}$	33
Figure 7.	The response of the rabbit oviduct to intravenous administration of PGE_1	34
Figure 8.	Effect of ovariectomy on tubal motility of the rabbit	35
Figure 9.	Oviduct recordings from an intact rabbit showing the response to an intravenous injection of $\text{PGF}_{2\alpha}$ before treatment with progesterone (Day 1) and during the progesterone effect (Day 2)	36
Figure 10.	Chronic Oviduct Cannula for measuring tubal motility in rabbits	51

INTRODUCTION

The mammalian oviduct plays a crucial role in the normal events of the reproductive cycle. In addition to providing a milieu for the fertilization and maintenance of gamete viability, the oviduct transports the egg and blastocyst to the uterus.

Transport of the ovum from the ovary to the uterus takes three or four days, regardless of the length of the oviduct (Hartman, 1962). Although the exact mechanism of transport is not known, it is generally felt that muscular activity of the oviduct plays an important role in ovum transport; both ovarian steroids and the sympathetic nervous system have been implicated in the regulation of oviduct motility. Because of the important role oviduct function plays in maintaining reproductive efficiency, clarification of the mechanisms regulating oviduct physiology is needed.

More recently, the prostaglandins have been postulated to have physiological significance in many reproductive processes; much of this interest is related to the ability of prostaglandins to modify smooth muscle contractility. Despite ample evidence in the literature citing a stimulatory effect of prostaglandins on oviduct motility, little work has been done to investigate possible effects of prostaglandins on ovum transport. The present study was undertaken to investigate possible effects of some prostaglandins on ovum transport in the rabbit.

LITERATURE REVIEW

An exhaustive review of the literature on the mechanism of ovum transport will not be reported here, but rather only those concepts pertinent to the understanding and discussion of the present investigation will be presented. Although ciliary action and oviductal secretion play a role in ovum transport, these processes will not be reviewed here. Discussion will center primarily on the role of oviduct muscular activity in the transport of ova, and the regulation of oviduct motility by various factors.

Ovum Transport, General

The mammalian oviduct consists of basically two segments, the ampulla and the isthmus (Fig. 1). Movement of ova through the first few millimeters of the ampulla is thought to be the result of ciliary action. Borell, Nilsson and Westman (1957) reported that the rate of ciliary movement in the rabbit oviduct at estrus is 1500 beats/min, and that this rate increases by about 20 per cent after ovulation. However, movement of ova through the lower ampulla and isthmus is thought to be the result of tubal muscular activity, due to the presence of both circular and longitudinal muscular layers and the scarcity of ciliated cells (Nilsson and Reinuis, 1969).

By flushing segments of the rabbit oviduct at various times after inducing ovulation with human chorionic gonadotropin (HCG), Greenwald (1961) studied the passage of ova through the oviduct over a three-day period. He found that by two hours after ovulation (12 hr. post-

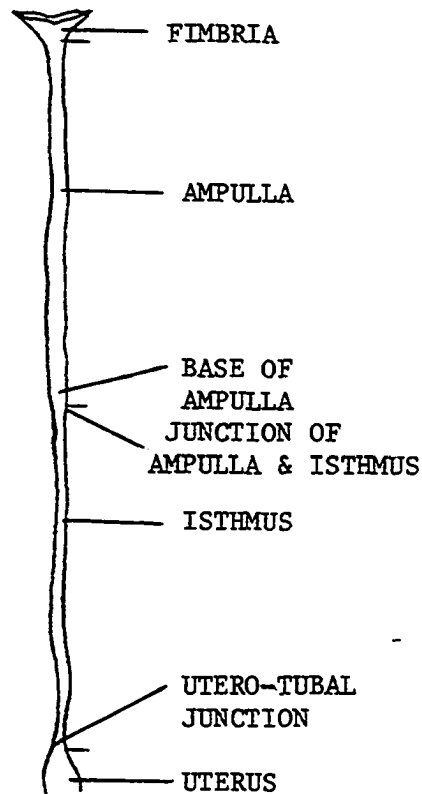


Figure 1. Diagrammatic representation of the rabbit oviduct.

HCG) most ova had already travelled half the length of the oviduct; Harper (1961) reported that eggs transferred with cumulus cells stained with Toluidine Blue, reached the base of the ampulla within six minutes. Upon arrival at the ampullar-isthmic junction, ova remain at the junction until at least 48 hr. after mating or HCG injection (Greenwald, 1961). Using donor and recipient rabbits, Chang (1950) demonstrated that this delay in ovum transport was necessary for successful implantation. He concluded that there was little chance for a transferred ovum or blastocyst to develop if it was 1 to 2 days out of sequence with the development of the corpus luteum. By 70 hr. after ovulation most ova have entered the isthmus; final passage of ova into the uterus is then completed within 2-5 hr. (Greenwald, 1961).

Effect of ovarian steroids on ovum transport

Early studies with ovarian steroids suggested that progesterone accelerates and estrogen inhibits ovum transport through the oviduct. The removal of corpora lutea (15-20 hr. after mating) in rabbits resulted in delayed ovum transport; ova were found in the oviducts at 108 and 180 hours after mating (Corner, 1928). Wislocki and Synder (1933) found that the induction of a second ovulation in rabbits at various stages of pregnancy resulted in the premature entry (60 hr. post-HCG treatment) of ova into the uterus. They postulated that the excess of corpora lutea had an inhibiting effect on oviduct motility resulting in accelerated ovum transport, presumably due to greater progesterone secretion. Burdick and Pincus (1935) found that daily injections of estrin (100-150 rat units per day) starting on the day of mating resulted in retention of ova in the oviducts of rabbits for

several days. They postulated that estrin caused constriction of the tubo-uterine junction resulting in delayed ovum transport.

Greenwald (1961) reported that a single 250 μ g injection of estradiol cyclopentylpropionate caused retention of ova in the oviduct for as long as 6 days, while 25 μ g of the same hormone accelerated the passage of ova through the rabbit oviduct. A single 5 mg injection of progesterone five hours after mating or HCG treatment hastened ovum transport. At 48 hr. post injection the distribution of ova was similar to that of control animals at 70 hr. post-HCG. Twenty-five mg of progesterone (same schedule) accelerated the passage of some ova into the uterus within 24 hr., while the concurrent administration of estrogen and progesterone resulted in tubal retention of ova at the ampullary-isthmic junction of the oviduct (Greenwald, 1961). Greenwald concluded from these studies that the presence or absence of estrogen was the controlling ovarian-hormone factor in ovum transport. However, Chang and Harper (1966) demonstrated that both retention of ova in the oviduct and acceleration of ova into the uterus occurred after a single dose (0.02-10 mg) of ethinyl estradiol administered 24 hr. after insemination. As the dose of ethinyl estradiol was increased (from 0.02 to 10 mg/rabbit) a greater number of ova were found in the uterus. However with smaller doses of ethinyl estradiol (0-0.5 mg) the mean percentage of eggs found in the ampulla increased from 2 to 25%. Chang and Harper (1966) concluded that estrogen promotes ovum transport at high doses, while small doses caused a partial occlusion of the isthmus resulting in "temporary tube-locking."

Oral administration of ethinyl estradiol (0.1 mg) to rabbits 2 hr. before and on the morning after transfer of ova to the ampulla

of these animals resulted in accelerated transport; 38% of the eggs reached the uterus 24 hr. after transfer (Chang, 1966a). However, Boling and Blandau (1971a) reported that in the presence of physiological concentrations of estrogens, oviduct smooth muscle is minimally active and that muscle activity increases as estrogen content of this tissue decreases. The mean transport time for supravitaly-stained donor eggs to pass through the ampullae of the oviducts in untreated castrate rabbits, and in castrate animals observed 1 to 3 hr. and 30 to 32 hr. after estrogen treatment was 15.2 ± 3.6 (S.D.) min., 12.0 ± 0.7 min. and 2.4 ± 1.6 min., respectively (Boling and Blandau, 1971b). Ovum transport through the ampullae of progesterone-treated rabbits was significantly faster than that seen in normal, unstimulated, estrous animals (Boling and Blandau, 1971a). Chang (1966b) found that progesterone administration before ovulation hastened the passage of ova through the oviduct, but had no effect when given after ovulation.

Contradictory opinion exists as to the role of steroids in both the regulation of oviduct motility and ovum transport. However, the recent work of Boling and Blandau (1971a) has shed new light on the problem; they suggest that an increase in the secretion of progestins and a decrease in the level of estrogens promote oviduct motility as well as acceleration of egg transport. Yet, it appears that, until quantitative analyses of both tissue and plasma steroids is obtained, a satisfactory explanation of the role of ovarian hormones on the oviduct will remain elusive (Boling and Blandau, 1971a).

Effect of prostaglandins on ovum transport

Despite the general feeling that oviduct smooth muscle plays a major role in ovum transport and the interest in prostaglandins as stimulators of smooth-muscle contractility, little work has been reported on the effects of prostaglandins on ovum transport. In work with rats, Nutting and Cammarata (1969) found that prostaglandin E₂ (PGE₂) had an inhibitory effect on ovum transport. Administration of PGF_{2α} to the hamster (Labhsetwar, 1972) and PGE₂ to the hamster and rabbit (Nutting, 1969) had no effect on ovum transport. However, more recently Chang and Hunt (1972) have reported that subcutaneous injection of PGF_{2α} (5 mg/kg) 24 hours after insemination caused the elimination of ova from the oviducts and uterus of rabbits; in 4 rabbits no ova (36 ovulation points) were recovered on day 2.

Oviduct Motility

Methods of measurement

Cineradiography, kymography, uterotubal insufflation and abdominal window observations have been employed by various investigators to study oviductal muscular activity (Boling, 1969). However in recent years most measurements of oviduct motility have been with intratubular cannulas which allows for chronic recording of tubal motility in vivo. Horton, Main and Thompson (1963) and Brundin (1965) introduced the use of an open-ended catheter method whereby a catheter is inserted through an incision in the uterine horn with the open catheter tip residing in the isthmus of the oviduct. Fluid is constantly perfused through the

catheter to avoid occlusion of the tip; changes in intraluminal pressure are used as an index of oviduct motility. Maia and Coutinho (1968) reported the use of a fluid-filled catheter with a ballooned end to measure oviduct motility in both the rabbit and human. Using this technique, DeMattos and Coutinho (1971) reported that oviduct contractions in the rabbit occurred at a rate of 5-10/min. with the amplitude of contractions ranging from 5 to 20 mm of mercury. Salomy and Harper (1971) modified the technique of Maia and Coutinho (1968) to measure motility in the nonpregnant, intact rabbit; they found the frequency of contractions to range from 1-14/min. with amplitude varying from 1 to 25 mm of mercury.

Effect of ovarian steroids on oviduct motility

It is generally felt that in mammals exogenous estrogenic substances increase oviduct motility while a decrease in the rate of contractions is noted after progesterone administration (summarized by Boling, 1969). Needless to say, the literature presenting these concepts contains many diverse hypotheses on the endocrine basis of ovum transport. Boling (1969) suggested that contradictory observations may be the result of inadequate techniques and unphysiological doses of administered hormones.

Oviduct motility has been recorded during the various phases of the menstrual cycle in both the monkey and the human. Neri et al. (1972) reported that in the rhesus monkey the amplitude of oviductal contractions was greater during the ovulatory phase than at any other time of the cycle. Maia and Coutinho (1970) reported the occurrence of both peristalsis and antiperistalsis in the human Fallopian tube

at midcycle; they postulated that the increase in antiperistalsis is probably the result of an overall increase in the frequency of tubal contractions determined by estrogen at this stage of the menstrual cycle. DeMattos and Coutinho (1971) reported that in the rabbit treatment with estrogen resulted in a marked reduction in the amplitude of contractions, and a general pattern of depressed tubal motility; progesterone was found to increase the amplitude and decrease the frequency of tubal contractions. It has been postulated that the stimulatory effect of progesterone on oviduct activity may play a role in ovum transport by counteracting the restraining action of estrogen on tubal activity (DeMattos and Coutinho, 1971). Boling and Blandau (1971a) reported that while oviduct activity increases as tissue estrogen content decreases, they also suggest that an increase in the secretion of progestins might be partly responsible for the increase in oviduct muscle activity.

Effect of prostaglandins on oviduct motility

Ingelman-Sundberg et al. (1971) demonstrated that PGE_1 caused a strong increase in the tonus of the longitudinal musculature in the isthmus of the human oviduct in vitro whereas it relaxed the circular musculature; PGE_1 had a relaxing effect on both types of muscle in the ampulla.

Prostaglandin E_1 (PGE_1) at doses of 0.5 $\mu\text{g}/\text{kg}$ or more intravenously (i.v.) reduced tubal tone, and both the size and frequency of contractions in rabbits anesthetized with urethane; intravaginal administration of higher doses of PGE_1 produced a similar inhibition of tubal tone and peristalsis (Horton, Main and Thompson, 1965).

This observation was confirmed by Brundin (1968). In comparing the actions of PGE_1 and $\text{PGF}_{2\alpha}$ on smooth muscle, Horton and Main (1965) found that the rabbit oviduct in vivo is relaxed by PGE_1 , while $\text{PGF}_{2\alpha}$ caused contractions. Similarly, Spilman and Harper (1972) reported that spontaneous oviduct motility in the unanesthetized rabbit is suppressed following an i.v. injection of PGE_1 or PGE_2 at doses of 25 or 50 $\mu\text{g}/\text{animal}$. In animals exhibiting spontaneous oviductal activity, $\text{PGF}_{1\alpha}$ and $\text{PGF}_{2\alpha}$ administered at i.v. doses of 50, 100, and 200 $\mu\text{g}/\text{animal}$ evoked a sustained increase in tubal tone (Spilman and Harper, 1972). However, subcutaneous injections of PGE_1 (1 mg/kg) given to mice on various days after mating had no effect on the rate of ovum transport in the reproductive tract (Horton and Marley, 1969).

Prostaglandins have also been shown to alter oviduct motility in humans. Intravenous injection of PGE_2 (100 μg) resulted in a marked inhibition of tubal motility and $\text{PGF}_{2\alpha}$ (100 μg) stimulated the human oviduct (Coutinho and Maia, 1971). Contrasting effects of PGE_2 and $\text{PGF}_{2\alpha}$ were also observed when these compounds were injected directly into the lumen of the human oviduct (Coutinho and Maia, 1971). Using the Rubin-uterotubal insufflation technique, Eliasson and Posse (1965) studied the effects of prostaglandins on the hindrance of gas flow through the oviducts and uterus of infertile women at midcycle. Intravaginal application of 150-200 units of partially purified prostaglandin from human seminal fluid caused a marked increase in the resistance of gas flow in some patients while no change was seen in other patients (Eliasson and Posse, 1965).

In addition to steroids and prostaglandins, other biologically active substances have been shown to affect oviduct motility. Ovarian follicular fluid has been reported to contain a substance that acts on oviduct smooth muscle (Ramwell et al., 1969). A kinin-like polypeptide was responsible for this smooth muscle stimulating activity, and follicular kinins have been shown to decrease the tone of rabbit and bovine oviducts in vitro (Ramwell et al., 1969). Detection of a kinin-forming fluid from bovine oviducts has led Ramwell and his colleagues to suggest that increased smooth muscle activity may result from contact of follicular fluid with the tubal lumen.

Effect of adrenergic stimulation on oviduct motility

After conducting the first pharmacological studies on the oviduct in 1927, Kok was convinced that the nerve supply to the oviduct played a major role in control of tubal motility (Kok, 1927, as cited by Brundin, 1969). Despite this early observation, the sympathetic nervous system has only recently been implicated in the control of muscular activity of the oviduct. Using an in vitro technique to measure motility of the human Fallopian tube, Sandberg et al. (1960) found that the oviduct responded to acetylcholine, adrenaline and noradrenaline with an increase in tone and amplitude of contraction. Employing a fluorescent method for the detection of catecholamines Brundin and Wirsén (1964a,b) found the isthmus of the oviduct to be highly innervated by adrenergic nerve terminals, while innervation of the ampulla was poor. This observation was confirmed by Owman and Sjöberg (1966) who, in addition, found the isthmoampullary junction to have greater innervation than the rest of the isthmus. In

a series of studies involving the rabbit oviduct, Brundin demonstrated the presence of a functional occlusive mechanism in the isthmo-ampullary junction (Brundin, 1964) and found high amounts of noradrenaline in the isthmus of the oviduct (Brundin, 1965). He concluded that the isthmus of the rabbit oviduct can be regarded as a sphincter with adrenergic mechanisms probably responsible for keeping the isthmic lumen constricted.

The presence of adrenergic receptors has been demonstrated in sheep (Holst et al., 1970), rabbit (Longley et al., 1968; Brunton, 1972), and in human (Rosenblum and Stein, 1966; Cibils et al., 1971) oviducts. Holst et al. (1970) examined portions of sheep oviduct and found that the noradrenaline content of the isthmus (1.05 µg/gm wet tissue) was significantly higher than in the ampulla (0.20 µg/gm wet tissue). Measuring the trans-membrane potential and short-circuit current of the rabbit oviduct in vitro, Brunton (1972) demonstrated the presence of beta-adrenergic receptors associated with secretory cells of the oviduct. Longley et al. (1968) demonstrated that the circular muscle of the rabbit oviduct in vivo responds to adrenergic stimulation with alpha receptors affecting contraction and beta receptors affecting relaxation. Similar results were obtained in an in vitro study by Levy and Lindner (1972). Cibils et al. (1971) reported that the local administration of small amounts of norepinephrine (1.5 to 10 µg) into the lumen of the human oviduct caused strong tubal contractions. Nakanishi and Wood (1968) investigated the effects of various adrenergic stimulating and blocking agents on human Fallopian tube motility in vitro. They observed that noradrenaline admini-

stration as well as nerve stimulation resulted in tubal contractions while pre-treatment with alpha-blocking agents depressed these contractile responses. The Fallopian tubes of pregnant women were less responsive than those of nonpregnant women to both nerve stimulation and noradrenaline (Nakanishi and Wood, 1968). Epinephrine and norepinephrine have a stimulatory effect on the human oviduct in vivo except during the luteal phase of the menstrual cycle (Coutinho et al., 1970a). Coutinho and colleagues have suggested that a local release of norepinephrine at nerve endings may be responsible for the spontaneous outbursts of increased contractility characteristic of tubal activity. The reduced sensitivity of human oviducts to epinephrine and norepinephrine during the luteal phase of the menstrual cycle corresponds with the disappearance of the spontaneous outbursts of contractile activity during this period of the cycle (Coutinho et al., 1970a). Coutinho and co-workers have extended their studies to the rabbit to examine the role of ovarian steroids in regulating the activity of the adrenergic receptors (Coutinho et al., 1971). The tubal response to all adrenergic compounds was enhanced by endogenous or exogenous estrogen; progesterone treatment depressed alpha receptor sensitivity while increasing the reactivity of the beta receptors. Coutinho et al. (1971) have proposed that enhancement of tubal adrenergic responsiveness by estrogen maintains closure of the uterotubal junction in rabbits, thus preventing premature egg transport into the uterus. Progesterone reduces the sensitivity of the alpha receptors to stimuli while enhancing beta receptor responsiveness, creating an environment conducive to the passage of the ovum through the isthmus

and uterotubal junction (Coutinho et al., 1971). Woodruff and Pauerstein (1969) have suggested that an alteration of the estrogen-progesterone ratio, allowing beta receptor dominance, might be responsible for the final passage of ova into the uterus. Bodkhe and Harper (1972) have reported that the content of norepinephrine in the distal tubal isthmus of rabbits was significantly lower after insemination than in estrous animals; exogenous estrogen or progesterone at doses that blocked and accelerated ovum transport, respectively, resulted in significant increases in the content and concentration of norepinephrine in the distal isthmus as compared to control animals. Bodkhe and Harper (1972) concluded that changes in free norepinephrine or hormonal changes not affecting noradrenergic activity may control ovum transport through the oviduct.

The prostaglandins have also been implicated in the regulation of adrenergic nerve activity. Prostaglandin E₁ (PGE₁) has been shown to inhibit the response of the rabbit oviduct to noradrenergic nerve stimulation in vivo (Brundin, 1968). Hedqvist and von Euler (1972) have reported that endogenous PGEs modulate the effector response to nerve activity in sympathetically-innervated tissues of the guinea pig vas deferens. A potentiated contractile response of seminal vesicles to catecholamines and acetylcholine in the presence of prostaglandins has been demonstrated (Eliasson and Risley, 1966; Risley and Stahl, 1972).

The effect of neurohypophyseal hormones on oviduct motility has also been investigated. Coutinho and Maia (1970b) found that human Fallopian tubes in vivo are more sensitive to oxytocin stimulation

than to vasopressin in contrast to the uterus which is more responsive to vasopressin. Coutinho and Maia (1970b) also found that ovarian steroids reduced the activity and sensitivity of the oviducts to both oxytocin and vasopressin.

Although the isolated effects of ovarian steroids, prostaglandins, catecholamines on tubal motility and egg transports are partially described, the integrated response of the oviduct to these control agents are not yet well understood. The objective of the research described herein is to show, in more detail than has been done, the effects of prostaglandins $F_{2\alpha}$ and E_1 upon the rate of egg transport through the rabbit oviduct, upon oviduct motility as measured by indwelling catheters and, in addition, to examine the effects of ovarian steroids upon prostaglandin-mediated changes in oviduct motility.

MATERIALS AND METHODS

Animals

Adult, Dutch-belted female rabbits (1.8 to 3.0 kg) were used throughout this study. Rabbits were individually housed under conditions of controlled temperature (75°F) and lighting (12 hr. on, 12 hr. off); laboratory rabbit chow and water were provided ad libitum. Animals were generally obtained at least three weeks before experimental use.

Measurement of Oviduct Motility

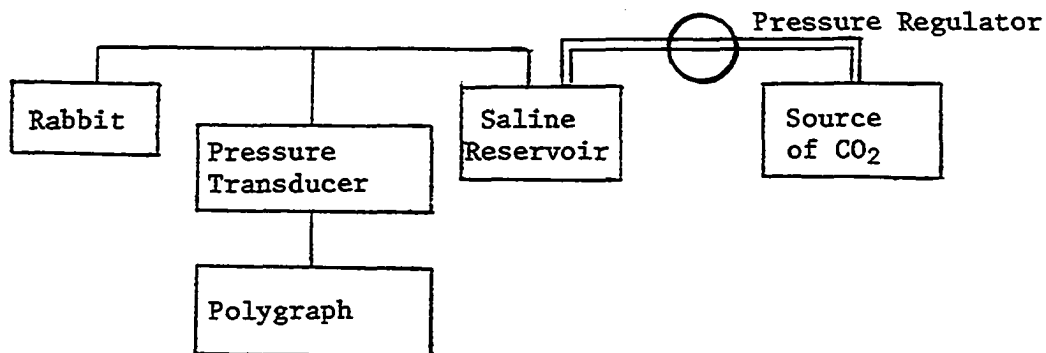
Cannulas used to measure oviduct motility were patterned after the aorta cannula of Weeks and Jones (1960). The subcutaneous portion of the cannula was constructed of polyethylene tubing PE 10 (.011" I.D.; .024" O.D.) and PE 20 (.015" I.D.; .043" O.D.) joined to the oviductal portion of silicone rubber tubing (.025" O.D.). A detailed description of cannula construction is given in Appendix A.

Rabbits were anesthetized with sodium pentobarbital, 40 mg/kg i.p., (Diabutal, Diamond Laboratories, Des Moines, Iowa) and supplemented as needed with ether for the surgical insertion of oviduct cannulas. A midline abdominal incision was made and the left uterine horn and the corresponding oviduct were exposed. The cannula was inserted into the uterine horn through an incision made with a 20 gauge needle; care was taken to avoid uterine blood vessels. The tip of the cannula was placed into the isthmus of the oviduct and anchored in place with a single u-

terine suture. The peritoneal segment of the cannula was passed through the psoas muscle with the use of a trocar, and then the cannula was guided subcutaneously to an area between the shoulder blades, exteriorized, and anchored with a single suture. The exterior end of the cannula was stoppered with a small metal pin when not in use. Location of the cannula in the oviduct was verified at autopsy.

Recordings of tubal motility were taken repeatedly over several months in five adult, intact rabbits and in one ovariectomized rabbit using the constant perfusion technique described by Horton et al. (1963) and Brundin (1965). Saline was perfused into the oviduct at a rate of approximately $2\frac{1}{2}$ μ l/min and tubal motility was recorded with a P23 Statham pressure transducer and a 2-channel Grass Model 79C polygraph. Chart speed (10 mm/min) and amplifier sensitivity were kept constant for all experiments. Changes in intraluminal pressure were taken as an index of motility of the oviduct; the polygraph was calibrated in millimeters of mercury by means of a manometer applied to the transducer. A schematic illustration of the recording system is showed in Figure 2.

Figure 2. Sketch of recording system used for measuring oviduct motility.



Effect of Prostaglandins on Ovum Transport

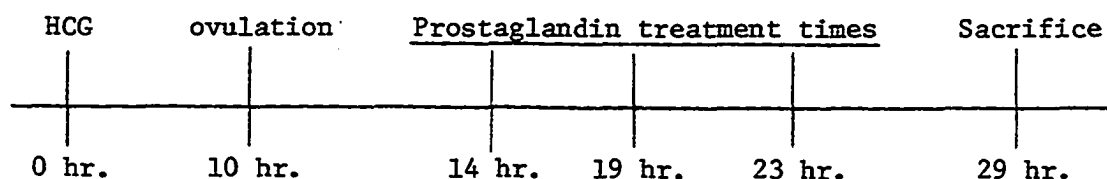
Experiments were conducted to test the hypothesis that prostaglandins $F_{2\alpha}$ and E_1 (PGs) could alter ovum transport through the rabbit oviduct. The general experimental design employed in these studies is shown in Figure 3. Ovulation was induced in intact, estrous rabbits by intravenous injection (i.v.) of 100 I.U. of human chorionic gonadotrophin (HCG) (Nutritional Biochemicals Corporation, Cleveland, Ohio); ovulation occurs approximately 10 hr. after mating or HCG treatment (Greenwald, 1961). Animals were sacrificed at various times after prostaglandin treatment by an overdose (i.v. or cardiac puncture) of sodium pentobarbital; the oviducts were quickly removed, divided into three equal segments, and flushed with saline. Recovered ova were counted using a dissecting scope (16 X) and the number of ova compared with the number of ovulation points on the respective ovary.

All prostaglandins (The Upjohn Company, Kalamazoo, Michigan) were dissolved in phosphate buffer or saline as needed; in the case of PGE_1 , this compound was dissolved in absolute ethanol and diluted appropriately with phosphate buffer. For purposes of this discussion, the time of prostaglandin treatment will be given in reference to the time of ovulation.

Outline of Experiments

This investigation involved two areas of study: ovum transport studies and the measurement of oviduct motility. A brief outline of the experiments undertaken in each of these areas is given on the following page.

Figure 3. Experimental design for ovum transport studies.



Ovum transport studies

Experiments were conducted to determine the rate of egg transport through the oviduct and to test the hypothesis that prostaglandins could alter ovum transport in the rabbit. A brief description of the experiments conducted is given in Table 1.

Oviduct motility studies

Oviduct motility experiments were conducted for the following reasons:

- 1) Evaluate oviduct motility in the intact, estrous rabbit.
- 2) Determine the effects of prostaglandins on oviduct motility and correlate these observations with any alteration of ovum transport by prostaglandins.
- 3) Observe oviduct motility in the ovariectomized rabbit and determine the effects of prostaglandins on the motility of the oviduct.
- 4) Determine the effects of exogenous progesterone on prostaglandin-induced contractions of the oviduct in the ovariectomized rabbit.

Table 1. Outline of ovum transport experiments.

<u>Experiment</u>	<u>Treatment^a</u>	<u>Time of sacrifice^b hours after ovulation</u>	<u>No. of Animals</u>
Exp. 1. Distribution of ova during passage through the oviduct in untreated rabbits.	None	2,14,38,60 hrs.	10
Exp. 2. Effect of PGE ₁ and PGF _{2α} on ovum transport.	PGE ₁ or PGF _{2α} (5 mg) at 13 hr. post-ovulation	19 hr.	21
Exp. 3. The location of ova 1 hr. after PGF _{2α} administration.	PGF _{2α} (5 mg) 13 hr. post-ovulation	14 hr.	2
Exp. 4. Effect of repeated injections of PGE ₁ on ovum transport.	PGE ₁ (1 mg) given at ovulation, 2, and 4 hr. after ovulation	17 hr.	2
Exp. 5. Effect of PGE ₁ and PGF _{2α} in the cumulus cell mass.	PGE ₁ and PGF _{2α} (5 mg) given at 4 hr. after ovulation	9 hr.	19
Exp. 6. Effect of PGF _{2α} on ovum transport when administered 9 hr. after ovulation.	PGF _{2α} (5 mg) given at 9 hr. after ovulation	14 hr.	5
Exp. 7. Effect of a reduced dose of PGF _{2α} (2 mg) on ovum transport.	PGF _{2α} (2 mg) given at 13 hr. post-ovulation	19 hr.	5

^aAll animals given 100 I.U. of HCG intravenously to induce ovulation.

^bAll animals sacrificed with an overdose (i.v. or cardiac puncture) of sodium pentobarbital (Diabital).

RESULTS

Effect of Prostaglandins on Ovum Transport

A series of experiments were performed to determine whether prostaglandins, by stimulating smooth-muscle, could alter ovum transport through the rabbit oviduct.

Experiment 1 was undertaken to determine the distribution of ova in the oviducts of rabbits not treated with prostaglandins. Ovulation was induced in 10 intact, estrous rabbits and the location of ova at various times after ovulation was determined. Table 2 summarizes the results of the first experiment. All ova were found in the second segment of the oviduct within 2 hr. after ovulation. At 14 hr. and 38 hr. after ovulation 25 out of 33 (25/33) and 12 out of 13 (12/13) ova were found in the second and third segments of the oviduct, respectively. By 60 hr. post-ovulation only 4/9 ova were recovered from the oviduct.

Experiment 2 was designed to test the hypothesis that PGE_1 and $\text{PGF}_{2\alpha}$, by inhibiting and stimulating oviduct contractility (see later), respectively, could alter ovum transport through the oviduct. PGE_1 , $\text{PGF}_{2\alpha}$, or a control injection of phosphate buffer was administered subcutaneously to 21 rabbits 13 hr. post-ovulation; animals were sacrificed six hr. after treatment. Subcutaneous administration of PGE_1 to animals at a dose of 5 mg, resulted in ataxia, rapid breathing, and diarrhea; animals treated with $\text{PGF}_{2\alpha}$ were not affected by drug administration. The injection of phosphate buffer as a control

Table 2. Distribution of ova during passage through the oviduct of untreated rabbits.

Time of Sacrifice After Ovulation	Position of Ova in Reproductive Tract				
	Oviduct ^a			Uterus	"Missing" ^b
	1st Segment	2nd Segment	3rd Segment		
2 hr. post ovulation (2 animals)		8/8			
14 hr. post ovulation (4 animals)		25/33	3/33		5/33
38 hr. post ovulation (2 animals)			12/13		1/13
60 hr. post ovulation (2 animals)			4/9		5/9

^aOviduct divided into three equal segments; first segment is proximal to the ovary, most distal segment corresponds to the isthmus.

^bMissing ova - The number of ovulation points on respective ovary minus number of ova recovered.

^cNumber of ova recovered/total number of ova (i.e. number of ovulation points).
(a, b, and c are the same for all experiments).

vehicle was also without effect.

The results shown in Table 3 demonstrate accelerated ovum transport in animals treated with prostaglandins. In 7 control animals, 47/48 ova were recovered from the second segment of the oviduct; one ovum was found in the third segment. In animals treated with PGE_1 and $\text{PGF}_{2\alpha}$, 13/48 and 5/42 ova, respectively, were found in the second segment of the oviduct. The majority of eggs in prostaglandin-treated animals (35/48 for E_1 ; 37/42 for $\text{F}_{2\alpha}$) were found in the distal third of the oviduct, the uterus, or were not recovered.

Experiments designed to measure oviduct motility were performed concurrently with the ovum transport studies. These studies suggested that subcutaneous administration of prostaglandin exerted an effect on oviduct motility very rapidly. In view of this, Experiment 3 was conducted to examine oviducts of rabbits one hour after treatment with $\text{PGF}_{2\alpha}$ for any indications of altered ovum transport. Subcutaneous injections of $\text{PGF}_{2\alpha}$ (5 mg) were given to two rabbits at 13 hr. after ovulation; oviducts were examined one hr. later. The results shown in Table 4 indicate that no ova were recovered from the second segment while 4/17 and 5/17 ova were recovered from the third segment and uterus, respectively; 8/17 ova were not recovered. Experiment 4 was conducted to test the effect of repeated injections of low doses of PGE_1 on ovum transport. One mg of PGE_1 was administered subcutaneously to 2 rabbits at ovulation and 2 hr. after ovulation; an additional mg of PGE_1 was given to rabbit No. 2 4 hr. post-ovulation. Both animals were sacrificed 7 hr. after ovulation. As summarized in Table 5, all ova (13/13) were found in the second segment. Examination of ova

Table 3. The effect of prostaglandin E_1 and $F_{2\alpha}$ on ovum transport (Experiment 2).

Treatment ^a	Position of Ova in Reproductive Tract				
	Oviduct			Uterus	"Missing"
	1st Segment	2nd Segment	3rd Segment		
Control (7 animals)		47/48	1/48		
PGE_1 (9 animals)		13/48	17/48	8/48	10/48
$PGF_{2\alpha}$ (5 animals)		5/42	0/42	9/42	28/42

^aAll treatments given subcutaneously 13 hr. after ovulation with examination of oviducts 6 hr. later.
Control injection of 1 ml of phosphate buffer; prostaglandins (5 mg) given in 1 ml of phosphate buffer.

Table 4. The location of ova 1 hr. after $\text{PGF}_{2\alpha}$ administration (Experiment 3).

Treatment ^a	Position of Ova in Reproductive Tract				
	Oviduct			Uterus	"Missing"
	1st Segment	2nd Segment	3rd Segment		
$\text{PGF}_{2\alpha}$ (2 animals)		0/17	4/17	5/17	8/17

^aSubcutaneous injection of 5 mg $\text{PGF}_{2\alpha}$ given at 13 hr. after ovulation with examination of oviducts 1 hr. later.

Table 5. The effect of repeated injections of PGE_1 on ovum transport (Experiment 4).

Rabbit No.	Total Dose ^a mg	Number & (Location of ova) ^b
1	2 mg	6/6 (2nd segment)
2	3 mg	7/7 (2nd segment)

^aAll injections 1 mg PGE_1 subcutaneously given at ovulation and two hr. after ovulation; Rabbit 2 was given an additional injection 4 hr. after ovulation.

^bBoth animals were sacrificed 7 hr. after ovulation.

from rabbit No. 2 revealed that the majority of ova were free of the cumulus cell mass.

Experiment 5 was carried out to study the effect of prostaglandins on the premature removal of the cumulus cell mass from ova. Control vehicle, PGE₁ (5 mg) or PGF_{2α} (5 mg) was administered to 19 rabbits 4 hr. after ovulation; all animals were sacrificed 5 hr. after treatment. The results are summarized in Table 6. Neither PGE₁ or PGF_{2α} (49% and 53% of ova in cumulus cell mass, respectively) had a significant effect on ova in the cumulus cell mass when compared to control values (57% of ova in cumulus cell mass). Table 6 also illustrates the effect of prostaglandin administration on ovum transport when given 4 hr. after ovulation. The majority of ova in each of the control (34/39), PGE₁ (55/55), and PGF_{2α} (38/41) treated animals were found in the second segment of the oviduct.

Experiment 6 was designed to test the effect of subcutaneous administration of PGF_{2α} (5 mg) at 9 hr. after ovulation. The results from five animals are presented in Table 7. In four animals the majority of ova (23/28) were located in the second segment while in one rabbit only 3/9 ova were found in the second segment of the oviduct; in this one rabbit 3/4 ova were recovered in the right oviduct.

Experiment 7 was undertaken to determine the effect of a reduced dose of PGF_{2α} on ovum transport. Subcutaneous injection of 2 mg of PGF_{2α} was given to 5 animals 13 hr. after ovulation, with sacrifice of animals 6 hr. later. As seen in Table 8, the majority of ova (16/19) from 3 rabbits were found in the second segment. However in the two remaining rabbits only 2/16 ova were recovered from the second segment; the majority of eggs (14/16) were not recovered.

Table 6. The effect of prostaglandins on ova in the cumulus cell mass (Experiment 5).

Treatment ^a	Position of Ova in Reproductive Tract					Eggs in Cumulus: % and (number)
	Oviduct			Uterus	"Missing"	
	1st Segment	2nd Segment	3rd Segment			
Control (6 animals)		34/39			5/39	57% (20/35)
PGE ₁ (8 animals)		55/55				49% (27/55)
PGF _{2α} (5 animals)		38/41 ^(c)			3/41	53% (19/36)

^aAll treatments given subcutaneously 4 hr. after ovulation with examination of oviducts 5 hr. later. PGE₁ and PGF_{2α} (5 mg) were administered in 1 ml of phosphate buffer.

Table 7. The effect of $\text{PGF}_{2\alpha}$ on ovum transport when administered 9 hr. after ovulation (Experiment 6).

Treatment ^a	Position of Ova in Reproductive Tract				
	Oviduct			Uterus	"Missing"
	1st Segment	2nd Segment	3rd Segment		
$\text{PGF}_{2\alpha}$ (5 animals)		26/37			11/37

^aSubcutaneous injection of 5 mg $\text{PGF}_{2\alpha}$ given 9 hr. after ovulation with examination of oviducts 5 hr. later.

Table 8. The effect of a reduced dose (2 mg) of $\text{PGF}_{2\alpha}$ on ovum transport (Experiment 7).

Treatment ^a	Position of Ova in Reproductive Tract				
	Oviduct			Uterus	"Missing"
	1st Segment	2nd Segment	3rd Segment		
Group A ^b (3 animals)		16/19	2/19	0/19	1/19
Group B ^c (2 animals)		2/16	0/16	0/16	14/16
Total (5 animals)		18/35	2/35	0/35	15/35

^aAll animals given 2 mg of $\text{PGF}_{2\alpha}$ subcutaneously 13 hr. after ovulation with examination of oviducts 6 hr. later.

^bAnimals that showed no alteration in ovum transport.

^cAnimals that showed possible alteration in ovum transport.

Oviduct Motility Studies

Representative recordings of oviduct motility in two intact, estrous rabbits are presented in Figure 4. The frequency of contractions ranged from 2 to 10/min. with amplitude of contractions varying from 2 to 25 mm of mercury. While spontaneous bursts of increased contractile activity were often seen, each animal exhibited a characteristic pattern of oviduct motility.

The effects of prostaglandin on oviduct motility are shown in Figure 5. Within minutes of a subcutaneous injection of 1 mg of $\text{PGF}_{2\alpha}$, the resting tone and both the amplitude and frequency of contractions increased dramatically. A subcutaneous injection of 5 mg of PGE_1 produced a decrease in tone, and a decrease in the frequency and amplitude of contractions. Subcutaneous injections of 5 mg of either PGE_1 or $\text{PGF}_{2\alpha}$ affected oviduct motility for 45 to 90 minutes. None of the PGE_1 or $\text{PGF}_{2\alpha}$ injections resulted in the death of any animals.

Typical responses to various intravenous doses of $\text{PGF}_{2\alpha}$ and PGE_1 are shown in Figures 6 and 7, respectively. Generally $\text{PGF}_{2\alpha}$ produced an increase in tubal tone and an increase in the frequency and amplitude of contractions in both intact and ovariectomized rabbits. PGE_1 , as illustrated in Figure 7, inhibited tubal motility in all animals. The tubal response of the ovariectomized rabbit to injections of both $\text{PGF}_{2\alpha}$ and PGE_1 is shown in Figure 7c; the sustained contraction induced by $\text{PGF}_{2\alpha}$ (25 μg) is abolished by a subsequent injection of PGE_1 (26 μg). Similar results were also seen in the intact animal.

Characteristic recordings of oviduct motility from a single rabbit at various times after ovariectomy are presented in Figure 8.

With increasing time after ovariectomy, the pattern of tubal motility is one of regular contractions with generally little variation in frequency or amplitude of contractions.

The effect of progesterone on prostaglandin-induced alteration of oviduct motility is illustrated in Figure 9. In two tests $\text{PGF}_{2\alpha}$ and PGE_1 were intravenously administered before, 12-14 hr. after, and 4 days after progesterone treatment. In both cases progesterone was administered to an ovariectomized rabbit as a 10 mg subcutaneous injection in cottonseed oil. The oviduct motility pattern in untreated and treated animals is shown in Figures 9a and b with typical responses to $\text{PGF}_{2\alpha}$ presented in Figures 9c and d. The response to 25 μg of $\text{PGF}_{2\alpha}$ i.v. was very similar in both the untreated and progesterone-treated animal; PGE_1 appeared to be slightly less effective in relaxing tubal contractility in the rabbit treated with progesterone (not shown). There was no significant difference in tubal response to prostaglandins between treated and untreated animals on day 4 after progesterone treatment.

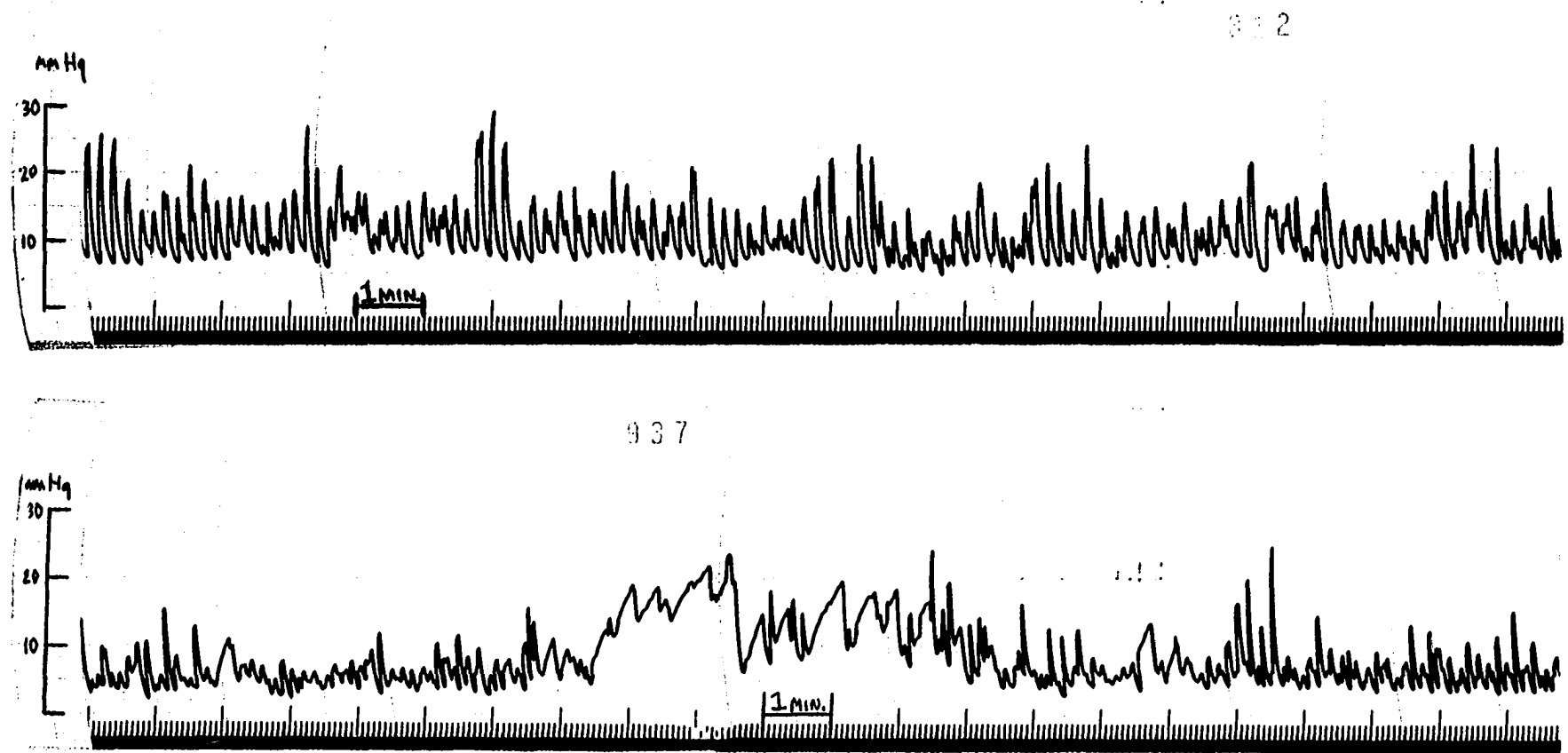


Figure 4. Motility of the rabbit oviduct. In vivo control recordings from two different animals.

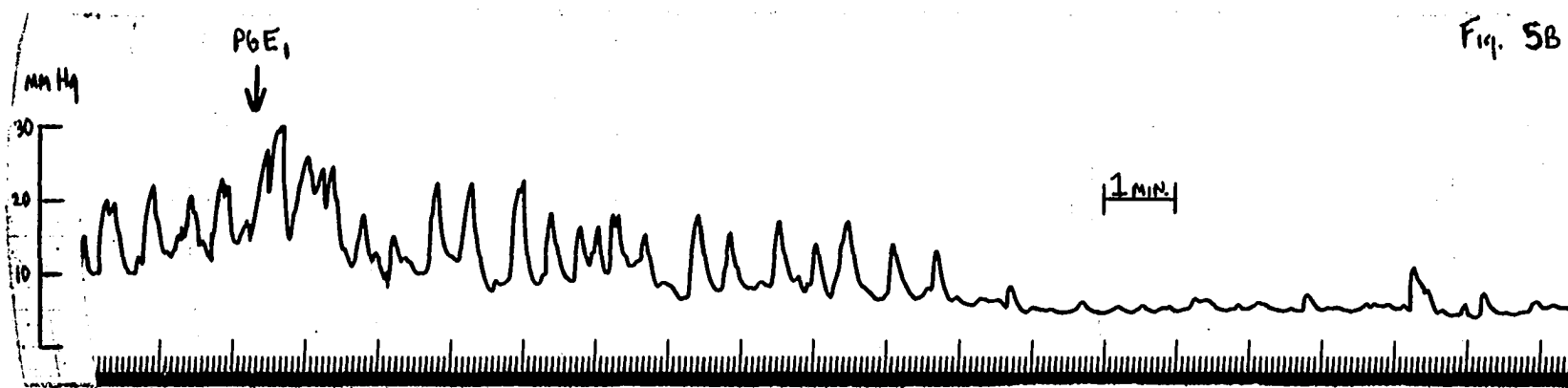
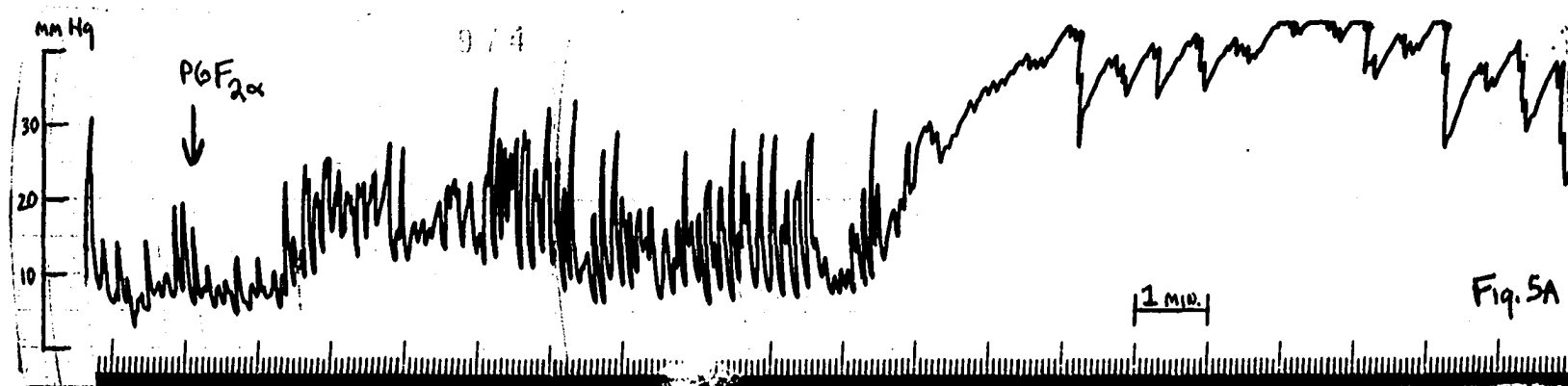


Figure 5. The response of the rabbit oviduct to $\text{PGF}_{2\alpha}$ and PGE_1 in vivo. The prostaglandins were injected subcutaneously as indicated by the arrows.

Figure 5a. $\text{PGF}_{2\alpha}$ (1 mg) treatment.

Figure 5b. PGE_1 (5 mg) treatment.

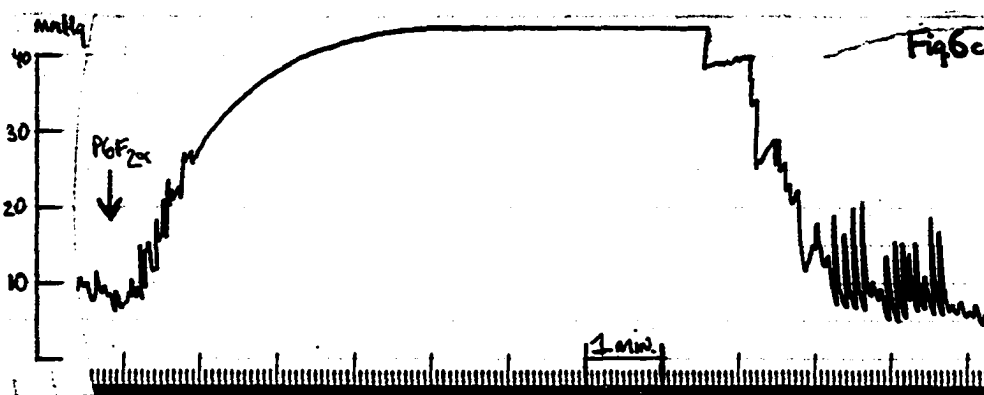
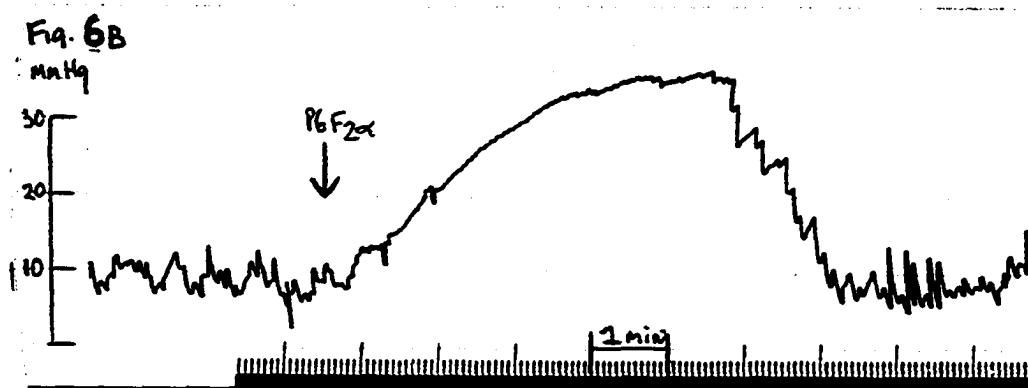
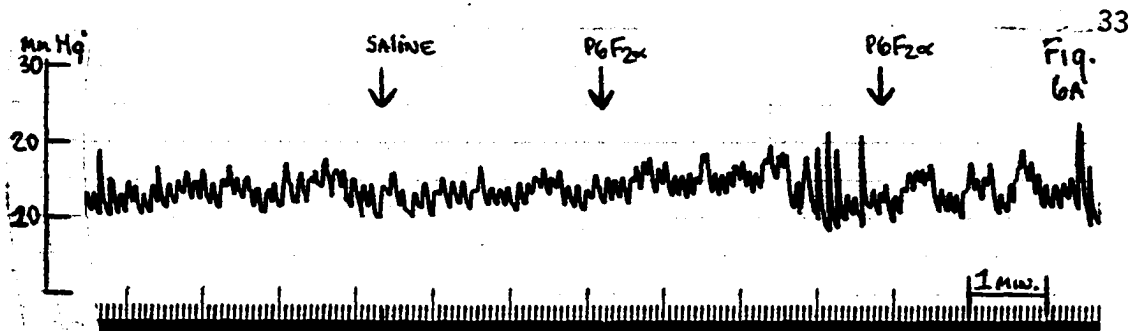


Figure 6. The response of the rabbit oviduct to intravenous administration of $\text{PGF}_{2\alpha}$. All injections indicated by arrows.

Figure 6a. Intact estrous rabbit. Saline (0.1 ml) and $\text{PGF}_{2\alpha}$ injections (5 μg) given i.v.

Figure 6b. Intact estrous rabbit. $\text{PGF}_{2\alpha}$ (10 μg).

Figure 6c. Ovariectomized rabbit. $\text{PGF}_{2\alpha}$ (5 μg).

Fig. 7A

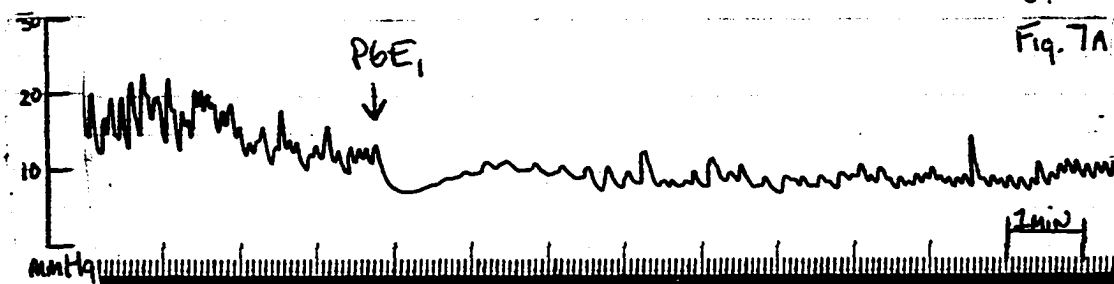


Fig. 7B

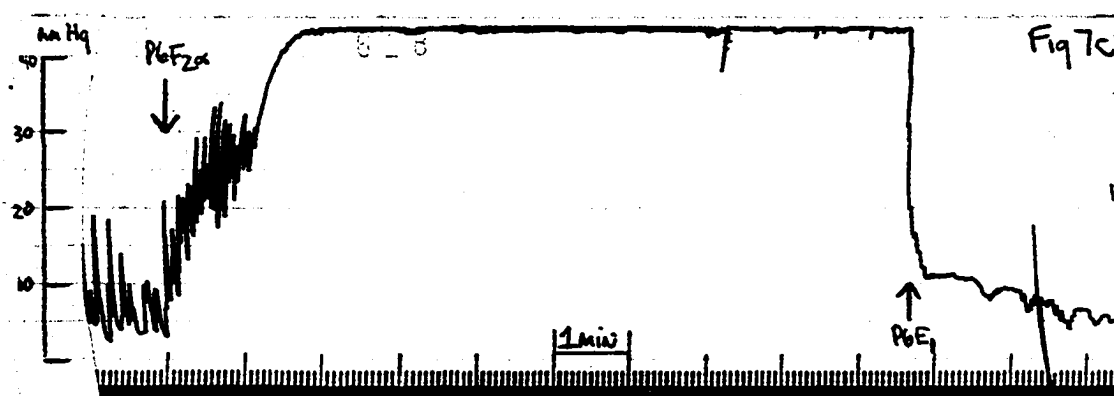
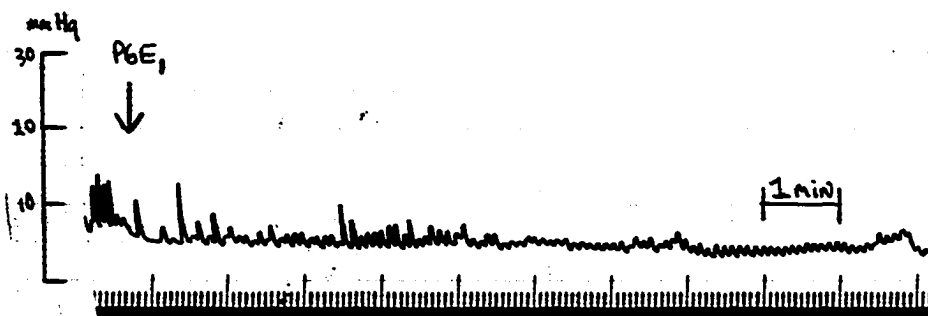


Figure 7. The response of the rabbit oviduct to intravenous administration of PGE_1 . All injections indicated by arrows.

Figure 7a. Intact estrous rabbit PGE_1 (26 μ g).

Figure 7b. Intact estrous rabbit PGE_1 (5 μ g).

Figure 7c. Ovariectomized rabbit $PGF_{2\alpha}$ (25 μ g) PGE_1 (26 μ g)

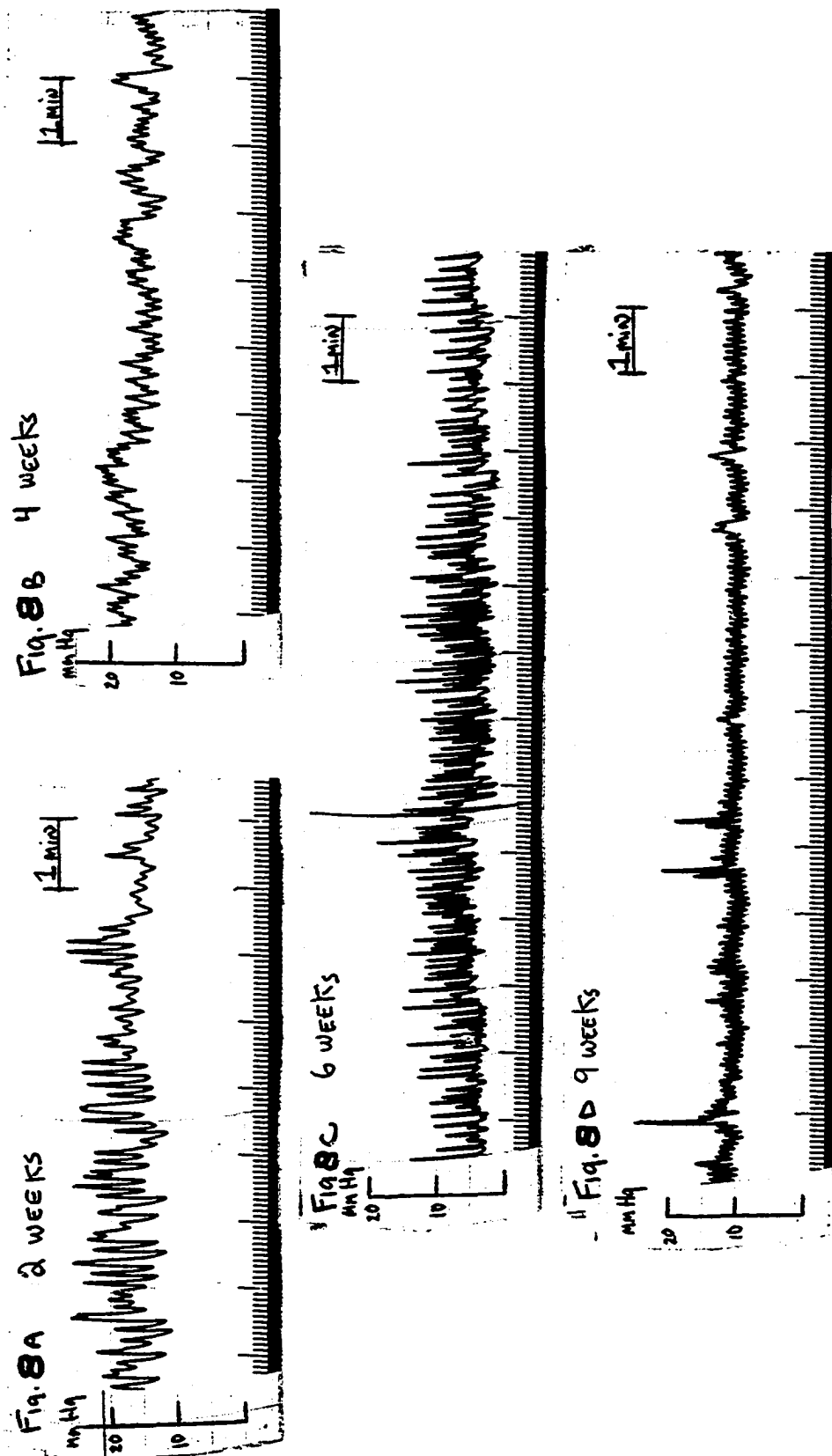


Figure 8. Effect of ovariectomy on tubal motility of the rabbit. Recordings were taken at 2, 4, 6, and 9 weeks after ovariectomy (Figures 8A, 8B, 8C, 8D, respectively). Note the lack of variation in tubal motility during the 9th week after ovariectomy.

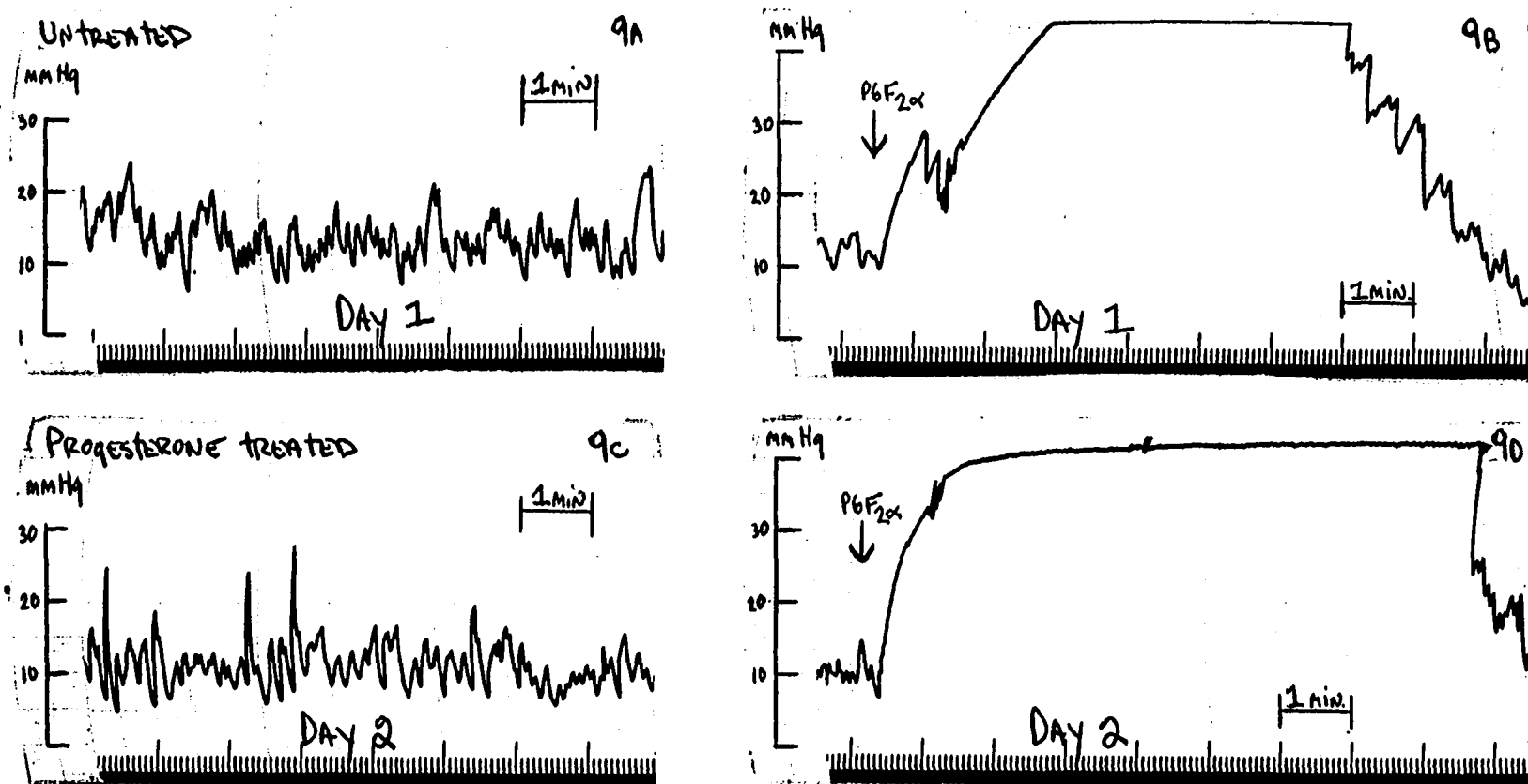


Figure 9. Oviduct recordings from an intact rabbit showing the response to an intravenous injection of PGF₂α before treatment with progesterone (Day 1) and during the progesterone effect (Day 2). PGF₂α treatment on both days was 25 µg.

DISCUSSION

Muscular activity of the mammalian oviduct has long been recognized as playing a major role in ovum transport; however, the mechanism of regulation of tubal activity remains essentially unknown. Quite appropriately, the literature contains a multitude of reports implicating various endocrine, neural, and anatomical factors in the regulation of both ovum transport and oviduct motility. More recently, the prostaglandins, due to their ubiquity and ability to alter smooth muscle contractility, have been implicated in many reproductive processes. It has been the purpose of this investigation to examine possible effects of prostaglandins on ovum transport through the rabbit oviduct.

Effect of Prostaglandins on Ovum Transport

It is concluded from the results of Experiment 2 that both PGE_1 and $\text{PGF}_{2\alpha}$ are capable of accelerating ovum transport through the rabbit oviduct; this conclusion is based on the following evidence: (1) the presence of ova in both the uterus and the third segment of the oviduct at a time when ova are normally found in the second segment of the oviduct; and (2) the large number of unrecovered ova (assumed to be in the uterus or outside of the reproductive tract) in animals treated with prostaglandins as compared to 100 per cent recovery of ovulated eggs in untreated animals. It is further concluded that this prostaglandin-induced acceleration of ovum transport occurs within one hr. of injection (Exp. 3) due to a rapid, direct effect on oviduct

smooth muscle (see motility discussion). The results obtained in this investigation are in agreement with reports in the literature; Chang and Hunt (1972) have reported that subcutaneous injections of $\text{PGF}_{2\alpha}$ (5 mg/kg) one day after insemination resulted in the elimination of ova from the oviducts and uterus of rabbits.

The results obtained in Experiments 5 and 6 suggest that prostaglandins are probably not effective in altering ovum transport prior to 10 to 13 hr. after ovulation. The administration of either PGE_1 or $\text{PGF}_{2\alpha}$ (5 mg s.c.) at four (Exp. 5) and nine (Exp. 6) hours after ovulation had no effect on the location of ova; the majority of eggs were recovered from the second segment of the oviduct. Based on the results obtained with prostaglandin administration at 4, 9, and 13 hr. after ovulation, it is postulated that the effectiveness of prostaglandin treatment at 13 hr. post-ovulation corresponds with the opening of the ampullary-isthmic junction; treatment prior to this time is ineffective due to constriction of the junction. Many investigators have recognized the importance of the ampullary-isthmic junction for the oviductal retention of ova, however reports differ as to the length of time the ovum transport is arrested. Chang (1951) studied egg transport shortly after ovulation and found that during the first 3 hr. after ovulation a high percentage of the eggs (43%) were in the upper half of the oviduct; by 8-11 hr. post-ovulation 16, 54, and 30 per cent of the eggs were in the ovarian half of the tube, and in the first and second third of the isthmus, respectively. Harper *et al.* (1960) reported similar results although they observed a somewhat slower rate of ovum transport at 8 hr. after ovulation; however, they suggested

that egg movement is very rapid between 8 and 11 hr. post-ovulation. Blandau (1961, 1969) reported that mammalian eggs are retained at the ampullar-isthmic junction for 15-18 hr., at which time they begin movement through the isthmus. However, Greenwald (1961) reported that ova are delayed at the ampullary-isthmic junction until at least 48 hr. after coitus (38 hr. after ovulation).

Probably even more puzzling than the regulation of ovum transport, is the mechanism of ovum delay at the ampullary-isthmic junction and/or the uterotubal junction of the mammalian oviduct. The importance of this delay to the process of fertilization is well established (Chang, 1950); however, there is divergent opinion on both the mechanism and length of time of this tubal arrest of ovum transport. It is apparent that further investigation into this aspect of egg transport is warranted.

Experiments 4 and 7 were conducted using smaller doses of prostaglandin; the repeated injections of PGE_1 (up to 3 mg) had no effect on ovum transport (Exp. 4). In Experiment 7 subcutaneous injections of 2 mg of $\text{PGF}_{2\alpha}$ were administered at 13 hr. after ovulation. It is concluded from the results of this experiment that 2 mg of $\text{PGF}_{2\alpha}$ approaches the minimal effective dose of $\text{PGF}_{2\alpha}$ that alters ovum transport when administered at this time; this conclusion is based on an apparent lack of effect in 3 animals while in two additional rabbits a large number of ova were not recovered.

Effect of Prostaglandins on Oviduct Motility

The acceleration of ovum transport by prostaglandins could be ef-

fects by several mechanisms: (1) A rapid increase in oviductal secretion; (2) A stimulation of ciliary movement; or (3) the alteration of tubal muscular activity. Although oviductal secretion and ciliary activity play a role in ovum transport, their mechanism of action and the effect of prostaglandins on these processes is unknown. However, the pronounced circular muscle of the isthmus, and the potent effects of prostaglandins on smooth-muscle, strongly suggest that prostaglandin-induced acceleration of ovum transport is due to alteration of oviduct muscular activity. Accordingly, studies were undertaken to determine the effect of prostaglandins on oviduct smooth-muscle.

Oviduct motility was measured by a constant perfusion method (Horton et al., 1963; Brundin, 1965); the validity of this technique for the measurement of contractile activity has recently been demonstrated by Talo and Brundin (1971). By recording spontaneous electric activity before and during perfusions, they concluded that flow rates of 1.4 to 5.8 $\mu\text{l}/\text{min}$. did not cause any detectable stimulation of the oviduct or produce any measurable change in spontaneous activity of the oviduct. The results obtained here are in agreement with the observations seen using other types of cannulas; both the rate and amplitude of oviductal contractions are similar to those reported by other investigators (Maia and Coutinho, 1968; Salomy and Harper, 1971).

It is concluded from the oviduct motility studies that PGE_1 inhibits and $\text{PGF}_{2\alpha}$ stimulates oviduct motility in vivo in the rabbit. These results are identical to those reported in the literature (Horton et al., 1963, 1965; Brundin, 1965, 1968; Horton and Main, 1965; Spilman

and Harper, 1972). Horton et al. (1965) demonstrated that the effect of prostaglandins on the oviduct is direct, and not secondary to their effects on blood pressure or the central nervous system. While PGE₁, acetylcholine and bradykinin produced marked vasodepressor responses in anesthetized rabbits, only PGE₁ reduced oviduct motility; PGE₁ likewise inhibited oviduct motility in rabbits pithed under the effects of ether (Horton et al., 1965). In vitro experiments also suggest that the effect of prostaglandins is directly on the oviduct (Horton et al., 1965; Ingelman-Sundberg et al., 1971).

Intravenous injection of 15 µg or more per animal of either PGE₁ or PGF_{2α} consistently altered oviduct motility in the unanesthetized, intact rabbit; occasionally lower doses of either prostaglandin modified oviduct motility. Similarly, Spilman and Harper (1972) reported that i.v. injection of PGE₁ (25 µg/animal) and PGF_{2α} (50 µg/animal) caused suppression and stimulation, respectively, of oviduct motility in the unanesthetized rabbit. Horton and Main (1965) and Horton et al. (1965) found that in anesthetized rabbits the threshold dose for PGF_{2α} was approximately 5 µg/kg while PGE₁ in doses of 0.5 µg/kg or more i.v. lowered intraluminal pressure and reduced the size and frequency of spontaneous contractions.

At doses of PGE₁ and PGF_{2α} that accelerated ovum transport, (5 mg, subcutaneously) inhibition and stimulation of oviduct motility, respectively, were seen for 45 to 90 minutes. This period of stimulation is sufficient to accelerate egg transport. This conclusion is supported by the results obtained in Experiment 3 where no ova were recovered in the oviduct one hour after prostaglandin treatment.

It is concluded that prostaglandins, as in the intact animal, are capable of altering oviduct motility in the ovariectomized rabbit. At times the tubal contractile response of the ovariectomized rabbit appeared to be more sensitive to prostaglandin than the response seen in the intact animal; however no definite conclusions can be made because only one rabbit was used. On occasion the same animal, whether intact or ovariectomized, would respond to a given injection of prostaglandin differently at various recording sessions. Since the intact rabbits were selected at random, without regard to the phase of the estrous cycle, it seems probable that hormonal secretion could cause peaks of tubal activity, and thus influence the contractile response to prostaglandins; however steroid hormone support of the oviduct is not essential for oviductal muscle activity. It is interesting to note that Spilman and Harper (1972) found that $\text{PGF}_{1\alpha}$ and $\text{PGF}_{2\alpha}$ had no effect in animals showing no spontaneous oviduct activity; they postulated that the action of these two prostaglandins may be related to other tubal regulatory mechanisms.

Progesterone treatment appeared to have no effect on the response of the oviduct to prostaglandins in the ovariectomized animal (Fig. 9). However, Porter and Behrman (1971) reported that progesterone treatment of intact rabbits inhibited prostaglandin-induced myometrial activity in vivo. Progesterone treatment has been shown to have contrasting effects on the uterus and the oviducts; while uterine motility is depressed by progesterone, the tubal response to this hormone is stimulatory (DeMattos and Coutinho, 1970).

The interaction of ovarian steroids and prostaglandins has been

studied in several different species. Hawkins et al. (1968) found that approximately the same concentration of various prostaglandins was needed to elicit a uterine response from ovariectomized and non-estrous rats. They also reported that estradiol treatment of ovariectomized animals markedly reduced the sensitivity of the uteri to prostaglandins as compared with untreated animals; progesterone treatment and adrenalectomy had no effect on uterine sensitivity to prostaglandins. However, in the same study the uterine response to PGE₁ in vitro was inhibited by the addition of either progesterone or estradiol (20 µg/ml) to the organ bath. In contrast, Anggard and Bergstrom (1963) found that pre-treatment of rats with estrogen increased the sensitivity of the isolated uterus to a different prostaglandin, F_{2α}, by 10 to 50 times. Sullivan, studying the response of the electrically-stimulated rat and guinea pig uterus to PGE₁ and PGF_{2α}, found no significant difference in uterine sensitivity to prostaglandins between diestrous and estrous animals. Sullivan also reported that progesterone addition to the organ bath caused a depression of the prostaglandin-induced excitatory effects, while Bygdeman (1964) found that the effect of PGE₁ on the system might be reduced or increased by the addition of progesterone to the organ bath. Recently, Blatchley et al. (1971) demonstrated that guinea pigs pretreated with estrogen had higher plasma concentrations of PGF_{2α} than untreated controls. Similarly, Wilks et al. (1972) reported that uterine tissue from estrous rabbits synthesized greater quantities of PGF_{2α} than did tissue from pseudopregnant animals.

An interaction between ovarian steroids and prostaglandins in several different species and tissues is apparent. Therefore further

studies on the oviductal contractile response to prostaglandins, in both the intact and ovariectomized rabbit, is warranted.

Possible Physiological Role for Prostaglandins in the Oviduct

The transport of eggs through the mammalian oviduct appears to depend largely on the smooth muscle activity of the oviduct. Although ovarian steroids, prostaglandins, and sympathomimetic drugs have all been shown to alter oviduct motility, the mechanism of regulation of this smooth muscle activity remains a mystery. It seems likely that further investigation may elucidate a regulatory mechanism of oviduct activity that includes physiological roles for all of the above hormones.

It has been suggested that the prominent adrenergic innervation localized in the circular musculature of the isthmus may have a regulatory influence on oviduct activity by altering contractility and maintaining a sphincteric action in the isthmus; the sympathetic nervous system has been implicated to have a role in both ovum transport and ovum delay, respectively (see literature review). Coutinho *et al.* (1970) have postulated that the outbursts of increased contractile activity often seen in the human oviduct might be produced by a local release of norepinephrine. It seems equally reasonable that these periods of increased contractile activity may be due to prostaglandins; the contractile pattern of the oviduct might be maintained by the local release of prostaglandins, with PGFs stimulating and PGEs inhibiting smooth muscle activity. It has been shown in this work and by others (Spilman and Harper, 1972) that PGF_{2α} and PGE₁ are both capable of

abolishing the contractile response induced by the other. Naturally before prostaglandins can be given a physiological role in oviduct function, there is a definite need for quantitative analysis of the prostaglandin content of oviductal tissue. However it is interesting to note that the rabbit oviduct is capable of synthesizing $\text{PGF}_{2\alpha}$ (personal communication, Wilks, 1972).

The literature contains many interesting, but often conflicting reports concerning the results of adrenergic stimulation of the mammalian oviduct. Coutinho et al. (1970) reported that the stimulatory response of the human Fallopian tube in vivo to a single injection of either epinephrine or norepinephrine was followed by a period of quiescence when tubal contractility was below pre-injection levels. Similarly, Cibils et al. (1971) found that the local administration of minute amounts of norepinephrine into the oviduct in situ had a strong stimulatory effect on motility; however, on many occasions this effect was followed by a transient period of markedly diminished or inhibited contractility. Other investigators have not reported seeing this period of brief inhibition after adrenergic stimulation (Levy and Lindner, 1972). While Coutinho and colleagues (1970) suggested that the relaxant aftereffect of adrenergic stimulation might be due to exhaustion of energy stores, Cibils et al. (1971) postulated that this period of inhibition seen after norepinephrine injection might be due to the presence of active adrenergic β receptors (subserving relaxation of oviduct smooth muscle) which can also be stimulated by norepinephrine. Further comparison of these two studies reveal that while Coutinho's group found diminished sensitivity of the oviducts to catecholamines

during the luteal phase of the menstrual cycle, Cibils and co-workers found no change in the sensitivity of the oviduct to norepinephrine throughout the cycle; in addition, Cibils et al. could not correlate the biphasic nature of the tubal contractile response with dose of norepinephrine injected.

It is evident that a strong biological relationship exists between prostaglandins and the sympathetic nervous system. Shaw (1966) and Ramwell and Shaw (1966) reported that prostaglandin is released from rat epididymal fat pads in vitro upon sympathetic nerve stimulation, while Hedqvist and von Euler (1972) have recently shown that the guinea-pig vas deferens releases prostaglandin in response to nerve stimulation. It is suggested here that local stimulation of the circular muscle cells or nerve endings in the oviduct musculature causes the release of endogenous prostaglandin, most likely the E prostaglandins, which then antagonize the contractile response of adrenergic stimulation and/or the F prostaglandins. In support of this theory, Talo and Brundin (1971) have recently reported that the presence of ova in the isthmus of the oviduct stretches the muscle wall. It is also interesting to note that Brundin (1965) found that in mated rabbits there was lower opening perfusion pressure and smaller effects of nerve stimulation and exogenous noradrenaline observed at the time of passage of fertilized ova through the isthmus of the oviduct. That prostaglandins, especially of the E series, can modify adrenergic stimulation has been demonstrated in several different species and tissues. Brundin (1968) reported that PGE₁ inhibited the constrictory response of the rabbit oviduct to both nerve stimulation

and i.v. injection of noradrenaline. Hedqvist and von Euler (1972) found that neuromuscular transmission in the guinea-pig vas deferens is facilitated after inhibition of prostaglandin synthesis; they postulated that endogenous prostaglandin of the E series modulate nerve activity in sympathetically innervated tissues. Clegg (1966) reported that both PGFs and PGEs depress the response of various isolated smooth muscle preparations to sympathomimetic substances; muscle bath concentration of $\text{PGF}_{2\alpha}$ as low as 10^{-12} g/ml antagonized the effects of noradrenaline on the guinea-pig uterus. Clegg (1966) suggested that prostaglandin, although not occupying the receptor site, may bind the sympathomimetic to the receptor, leading to an elimination of available receptor sites. Smythies (1972) has recently presented possible models for the β -adrenergic receptor that includes a prostaglandin-protein complex. He suggests that the α and β receptors would have the same molecular structure with and without an attached prostaglandin, respectively; thus it would be possible to convert β to α receptor by removing or inactivating the prostaglandin and to convert α to β receptor by adding the appropriate prostaglandin (Smythies, 1972).

While exogenous prostaglandins alter both ovum transport and smooth muscle activity of the rabbit oviduct, any physiological significance of endogenous prostaglandins in the normal activities of the oviduct remains to be elucidated. However, until the regulatory mechanism of oviduct function is known, further investigation into the role of prostaglandins in oviduct physiology is both warranted and necessary.

SUMMARY

- (1) The subcutaneous administration of $\text{PGF}_{2\alpha}$ or PGE_1 (5 mg) 13 hr. after ovulation resulted in altered ovum transport; the majority of eggs were found in the distal third of the oviduct, the uterus, or were not recovered.
- (2) In both ovariectomized and intact estrous rabbits, $\text{PGF}_{2\alpha}$ and PGE_1 caused an increase and decrease, respectively, in tubal tone, and in amplitude and frequency of contractions.
- (3) The subcutaneous injection of $\text{PGF}_{2\alpha}$ or PGE_1 (5 mg) at 4 or 9 hr. after ovulation had no effect on the location of ova when the oviducts were examined 5 hr. post-treatment.
- (4) Subcutaneous injection of 2 mg of $\text{PGF}_{2\alpha}$ approximates the minimum effective dose that will alter ovum transport when administered 13 hr. post-ovulation.
- (5) Progesterone treatment had no effect on the contractile response of the oviduct to $\text{PGF}_{2\alpha}$ in the ovariectomized rabbit.
- (6) It is concluded that PGE_1 and $\text{PGF}_{2\alpha}$, by inhibiting and stimulating smooth muscle contractility, respectively, can accelerate ovum transport in the rabbit.

APPENDIX A. PREPARATION OF OVIDUCT CANNULAS

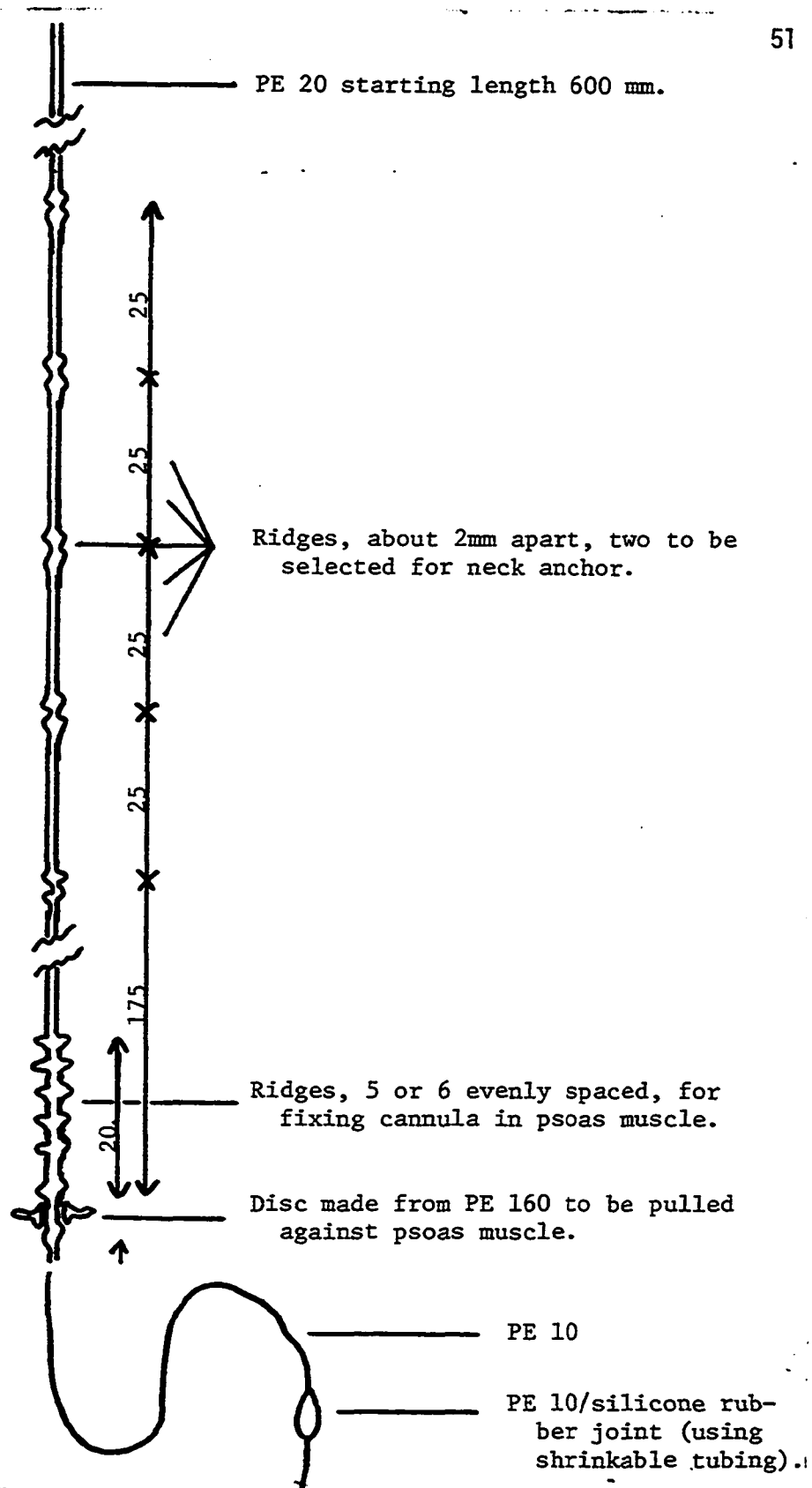
A completed cannula is illustrated in Figure 10. General instructions for the preparation of these cannulas are given below.

1. Approximately 600 mm of PE 20 and 100 mm of PE 10 are cut and a steel wire (0.010 in.) is passed through the lumens of both as a mandrel.
2. A disc (see below) is slipped over the PE 20 and then the PE 10 is fused to the PE 20 by rotating in a stream of hot air; the disc is then pushed against the ridge formed at the PE 10/20 joint.
3. A ridge is formed in the PE 20 next to the disc serving to lock it in place.
4. Starting at the disc, 5 or 6 ridges are raised about 3 mm apart in the PE 20. These hold the cannula in the psoas muscle.
5. Five pairs of ridges beginning 175 mm from the disc are formed on the PE 20 about 2 mm apart and spaced at about 25 mm intervals. The most convenient of these ridges acts to anchor the cannula to the neck muscles.
6. A 5 mm piece of 3/64 in. shrinkable tubing is passed over the PE 10.
7. Approximately 60 mm of silicone rubber tubing is cut and one end of this tubing is placed in chloroform until it swells sufficiently to slip over the PE 10; approximately 5 mm of the silicone tubing is passed over the PE 10.
8. The shrinkable tubing is placed at the end of the PE 10 so that 2 mm of the PE 10 remains visible through the silicone rubber tubing. A hot air stream is then applied to the point where the end of the PE 10 emerges from inside the silicone rubber tubing, thus locking the rubber tubing to the polyethylene tubing.
9. The remainder of the shrinkable tubing is heated in order to adhere it to the PE 10. When this joint is cool, the wire mandrel is carefully removed.
10. Another 5 mm piece of 3/64 in. shrinkable tubing is then slipped over the silicone rubber tubing. This is not attached for it serves as an anchor for the single uterine suture.

Preparation of the disc at the joint between the PE 10 and 20:

1. Cut a 25 mm segment of PE 160 and insert approximately 6 in. of 19 gauge hypodermic tubing in the lumen as a mandrel.
2. Cut two pieces (20 to 25 mm long) of Tygon tubing (3/16 in. o.d. x 1/16 in. i.d.) and put a small brass washer (3/16 in. o.d.) and one of the Tygon segments over each end of the mandrel.
3. Insert each end of the PE 160 through a washer and about 5 mm into the Tygon tubing.
4. Melt the PE 160 between the washers, pushing together slightly to allow it to gather. Remove the amount from the heat and push the washers together firmly forming a disc of polyethylene.
5. Remove the disc from the mandrel and cut the PE 160 nearly flush with the disc.

Figure 10. Chronic Oviduct Cannula for measuring tubal motility in rabbits.
(Cannula instructions and drawing modified from Weeks and Jones, 1960).



BIBLIOGRAPHY

- Änggård, R. and Bergström, S. 1963. Biological effects of an unsaturated trihydroxy acid (PGF_{2α}) from normal swine lung. *Acta. Physiol. Scand.* 58:1.
- Blandau, R. J. 1961. Biology of eggs and implantation, Chap. 14, p. 797. In: *Sex and Internal Secretions*. W. C. Young, Ed. Williams and Wilkins Company, Baltimore.
- Blandau, R. J. 1969. Gamete transport-comparative aspects, p. 129. In: *The Mammalian Oviduct*. E.S.E. Hafez and R. J. Blandau, Eds. University of Chicago Press, Chicago.
- Blatchley, F. R., Donovan, B. T., Poyser, N. L., Horton, E. W., Thompson, C. J., and Los, M. 1971. Identification of Prostaglandin F_{2α} in the utero-ovarian blood of guinea-pig after treatment with oestrogen. *Nature* 230:243.
- Bodkhe, R. R. and Harper, M.J.K. 1972. Changes in the amount of adrenergic neurotransmitter in the genital tract of untreated rabbits, and rabbits given reserpine or iproniazid during the time of egg transport. *Biol. of Reprod.* 6:288.
- Boling, J. L. 1969. Endocrinology of oviductal musculature, p. 163. In: *The Mammalian Oviduct*. E.S.E. Hafez and R. J. Blandau, Eds. University of Chicago Press, Chicago.
- Boling, J. L. and R. J. Blandau. 1971. Egg transport through the ampullae of the oviducts of rabbits under various experimental conditions. *Biol. of Reprod.* 4:174.
- Boling, J. L. and Blandau, R. J. 1971b. The role of estrogens in egg transport through the ampullae of oviducts of castrate rabbits. *Fert. and Steril.* 22:544.
- Borell, U., Nilsson, O., and Westman, A. 1957. Ciliary activity in the rabbit Fallopian tube during estrus and after copulation. *Acta. Obstet. Gynec. Scand.* 35:35.
- Brundin, J. 1964. An occlusive mechanism in the Fallopian tube of the rabbit. *Acta. Physiol. Scand.* 61:219.
- Brundin, J. 1964. The distribution of noradrenaline and adrenaline in the Fallopian tube of the rabbit. *Acta. Physiol. Scand.* 62:156.
- Brundin, J. 1965. Distribution and function of adrenergic nerves in the rabbit Fallopian tube. *Acta. Physiol. Scand.* 66:Suppl. 259, p. 1.

- Brundin, J. 1968. The effect of prostaglandin E_1 on the response of the rabbit oviduct to hypogastric nerve stimulation. *Acta. Physiol. Scand.* 73:54.
- Brundin, J. and Wirsén, C. 1964a. The distribution of adrenergic nerve terminals in the rabbit oviduct. *Acta. Physiol. Scand.* 61:203.
- Brundin, J. and Wirsén, C. 1964b. Adrenergic nerve terminals in the human Fallopian tube examined by fluorescence microscopy. *Acta. Physiol. Scand.* 61:505.
- Brunton, W. J. 1972. Beta-adrenergic stimulation of transmembrane potential and short circuit current of isolated rabbit oviduct. *Nature New Biology* 236:12.
- Burdick, H. O. and G. Pincus. 1935. The effect of oestrin injections upon the developing ova of mice and rabbits. *Am. J. Physiol.* 111:201.
- Bygdeman, M. 1964. The effect of different prostaglandins on human myometrium in vitro. *Acta. Physiol. Scand.* 63:Suppl. 242, p. 1.
- Chang, M. C. 1950. Development and fate of transferred rabbit ova or blastocysts in relation to the ovulation time of recipients. *J. Exp. Zool.* 114:197.
- Chang, M. C. 1951. Fertility and sterility as revealed in the study of fertilization and development of rabbit eggs. *Fert. and Steril.* 2:205.
- Chang, M. C. 1966a. Transport of eggs from the Fallopian tube to the uterus as a function of oestrogen. *Nature* 212:1048.
- Chang, M. C. 1966b. Effects of oral administration of medroxyprogesterone acetate and ethinyl estradiol on the transportation and development of rabbit eggs. *Endocrinology* 79:939.
- Chang, M. C. and M.J.K. Harper. 1966. Effect of ethinyl estradiol on egg transport and development in the rabbit. *Endocrinology* 78:860.
- Chang, M. C. and Hunt, D. M. 1972. Effect of prostaglandin $F_{2\alpha}$ on the early pregnancy of rabbits. *Nature* 236:120.
- Cibils, L. A., Sica-Blanco, Y., Remedio, M. R., Rozada, H., and Gil, B. E. 1971. Effect of sympathomimetic drugs upon the human oviduct in vivo. *Am. J. Obstet. Gynec.* 110:481.
- Clegg, P. C. 1966. Antagonism by prostaglandins of the responses of various smooth muscle preparations to sympathomimetics. *Nature* 209:1137.

- Corner, G. W. 1928. Physiology of the corpus luteum. *Am. J. Physiol.* 86:74.
- Coutinho, E. M., DeMattos, C.E.R. and DaSilva, A. R. 1971. The effect of ovarian hormones on the adrenergic stimulation of the rabbit Fallopian tube. *Fert. and Steril.* 22:311.
- Coutinho, E. M. and Maia, H. S. 1970b. The influence of the ovarian steroids on the response of the human Fallopian tubes to neurohypophyseal hormones in vivo. *Am. J. Obstet. Gynec.* 108:194.
- Coutinho, E. M. and Maia, H. S. 1971. The contractile response of the human uterus, Fallopian tubes, and ovary to prostaglandins in vivo. *Fert. and Steril.* 22:539.
- Coutinho, E. M., Maia, H. S., and Filho, J. A. 1970a. Response of the human Fallopian tube to adrenergic stimulation. *Fert. and Steril.* 21:590.
- DeMattos, C.E.R. and Coutinho, E. M. 1971. Effects of the ovarian hormones on tubal motility of the rabbit. *Endocrinology* 89:912.
- Eliasson, R. and Posse, N. 1965. Rubin's test before and after intravaginal application of prostaglandin. *Int. J. Fert.* 4: 373.
- Eliasson, R. and Risley, P. L. 1966. Potentiated response of isolated seminal vesicles to catecholamines and acetylcholine in the presence of PGE₁. *Acta. Physiol. Scand.* 67:253.
- Greenwald, G. S. 1961. A study of the transport of ova through the rabbit oviduct. *Fert. and Steril.* 12(1):80.
- Harper, M.J.K. 1961. Egg movement through the ampullar region of the Fallopian tube of the rabbit, p. 375. In: *Proceedings of IV Int. Congress of Animal Reprod.*, The Hague.
- Harper, M.J.K., Bennett, J. P., Boursnell, J. C., and Rowson, L.E.A. 1960. An autoradiographic method for the study of egg transport in the rabbit Fallopian tube. *J. Reprod. Fert.* 1:249.
- Hartman, C. G. 1962. In: *Science and the Safe Period*, p. 78. Williams and Wilkins Company, Baltimore.
- Hawkins, R. A., Jessup, R., and Ramwell, P. W. 1968. Effects of ovarian hormones on response of the isolated rat uterus to prostaglandins. In: *Prostaglandin Symposium of the Worcester Foundation for Exp. Biology*. P. W. Ramwell and J. E. Shaw, Eds. Interscience Publishers, New York.

- Hedqvist, P. and von Euler, V. S. 1972. Prostaglandin controls neuromuscular transmission in guinea-pig vas deferens. *Nature New Biology* 236:113.
- Holst, P. J., Cox, R. I., and Braden, A.W.H. 1970. The distribution of noradrenaline in the sheep oviduct. *Aust. Exp. Biol. Med. Sci.* 48:563.
- Horton, E. W. and Main, I.H.M. 1965. A comparison of the actions of prostaglandins $F_{2\alpha}$ and E_1 on smooth muscle. *Brit. J. Pharmacol.* 24:470.
- Horton, E. W., Main, I.H.M., and Thompson, C. J. 1963. The action of intravaginal prostaglandin E_1 on the female reproductive tract. *J. Physiol.* 168:54-55P.
- Horton, E. W., Main, I.H.M., and Thompson, C. J. 1965. Effects of prostaglandins on the oviduct, studied in rabbits and ewes. *J. Physiol.* 180:514.
- Horton, E. W. and Marley, P. B. 1969. An investigation of the possible effects of prostaglandins E_1 , $F_{2\alpha}$ and $F_{2\beta}$ on pregnancy in mice and rabbits. *Brit. J. Pharm.* 36:188-189P.
- Ingelman-Sundberg, A., Sandberg, F., Rydén, G., Molfese, A. 1971. The effect of prostaglandin E_1 on the circular and longitudinal musculature of the human oviduct in vitro. *Acta Obstet. Gynec. Scand.* 50:51.
- Kok, 1927, cited by Brundin, J. 1969. In: *Pharmacology of the Oviduct, The Mammalian Oviduct*. E.S.E. Hafez and R. J. Blandau, Eds, p. 251. University of Chicago Press, Chicago.
- Labhsetwar, A. P. 1972. Effects of prostaglandin $F_{2\alpha}$ on some reproductive processes of hamsters and rats. *J. Endo.* 53:201.
- Levy, B. and Lindner, H. R. 1972. The effects of adrenergic drugs on the rabbit oviduct. *Eur. J. Pharm.* 18:15.
- Longley, W. J., Black, D. L., and Currie, G. N. 1968. Oviduct circular muscle response to drugs related to the autonomic nervous system. *J. Reprod. Fert.* 17:95.
- Maia, H. and Coutinho, E. M. 1968. A new technique for recording human tubal activity in vivo. *Amer. J. Obstet. Gynec.* 102:1043.
- Maia, H. and Coutinho, E. M. 1970. Peristalsis and anti-peristalsis of the human Fallopian tube during the menstrual cycle. *Biol. of Reprod.* 2:305.

- Nakanishi, H. and Wood, C. 1968. Effects of adrenergic blocking agents on human Fallopian tube motility in vitro. J. Reprod. Fert. 16:21.
- Neri, A., Marcus, S. L., and Fuchs, F. 1972. Motility of the oviduct in the Rhesus monkey. Obst. and Gynec. 39:205.
- Nilsson, O. and Reinuis, S. 1969. "Light and Electron Microscopic Structure of the Oviduct," p. 57. The Mammalian Oviduct, E.S.E. Hafez and R. J. Blandau, Eds. University of Chicago Press, Chicago.
- Nutting, E. F. 1969. Antifertility activity of prostaglandin E₂ in hamsters, rabbits, and rats. Proc. Soc. Study Reprod. 2nd Meeting, (Abstract).
- Nutting, E. F. and P. S. Cammarata. 1969. Effects of prostaglandins on fertility in female rats. Nature 222:287.
- Owman, C. and Sjöberg, N. O. 1966. Cited by Brundin in 1969. Pharmacology of the Oviduct, p. 251. In: The Mammalian Oviduct. E.S.E. Hafez and R. J. Blandau, Eds. University of Chicago Press, Chicago.
- Porter, D. G. and Behrman, H. R. 1971. Prostaglandin-induced myometrial activity inhibited by progesterone. Nature 232:627.
- Ramwell, P. W., Shaw, J. E., and Jessup, S. J. 1969. Follicular fluid kinin and its action on Fallopian tube. Endo. 84:931.
- Risley, P. L. and Stahl, P. 1972. Effects of prostaglandins on hamster seminal vesicle responses to catecholamines and acetylcholine. Biol. of Reprod. 6:224.
- Rosenblum, I. and Stein, A. 1966. Autonomic responses of the circular muscles of the isolated human Fallopian tube. Am. J. Physiol. 210:1127.
- Salomy, M. and Harper, M.J.K. 1971. Cyclical changes of oviduct motility in rabbits. Biol. of Reprod. 4:185.
- Sandberg, F., Ingelman-Sundberg, A., Lindgren, L., and Ryden, G. 1960. In vitro studies of the motility of the human Fallopian tube. Part I. The effects of acetylcholine, adrenaline, noradrenaline and oxytocin on the spontaneous motility. Acta. Obstet. Gynec. Scand. 39:506.
- Shaw, J. E. 1966. Prostaglandin release from adipose tissue in vitro evoked by nerve stimulation or catecholamines. Proc. Fed. Amer. Soc. Exp. Biol. 25:770.

- Smythies, J. R. 1972. The adenylyl cyclase complex: A model of its mechanism of action in relation to the α - and β -adrenergic receptors. *Eur. J. Pharm.* 19:18.
- Spilman, C. H. and Harper, M.J.K. 1972. Effect of prostaglandins on oviduct motility in conscious rabbits. Abstract, 5th Annual Meeting, Society for the Study of Reproduction, Michigan State University, East Lansing, Michigan.
- Sullivan, J. J. 1966. Response of the mammalian uterus to prostaglandins under differing hormonal conditions. *Brit. J. Pharmacol.* 26:678.
- Talo, A. and Brundin, J. 1971. Muscular activity in the rabbit oviduct: A combination of electric and mechanic recordings. *Biol. of Reprod.* 5:67.
- Weeks, J. R. and Jones, J. A. 1960. Routine direct measurement of arterial pressure in unanesthetized rats. *Proc. Soc. Exp. Biol. Med.* 104:646.
- Wilks, J. W. 1972. Personal communication. The Upjohn Company, Kalamazoo, Michigan.
- Wilks, J. W., Hunter, K. K., and Norland, J. F. 1972. Prostaglandin $F_{2\alpha}$: Synthesis by the rabbit ovary, uterus, and uterine cervix. Abstract, 5th Annual Meeting, Society for the Study of Reproduction, Michigan State University, East Lansing, Michigan.
- Wislocki, G. B. and F. F. Synder. 1933. The experimental acceleration of the rate of transport of ova through the Fallopian tube. *Bull. Johns Hopkins Hosp.* 52:379.
- Woodruff, J. D. and Pauerstein, C. J. 1969. *The Fallopian Tube.* Williams and Wilkins Company, Baltimore.