Action of Some Sympatholytic Agents on Pregnancy in the Rat. (24695)

F. Bovet-Nitti and D. Bovet (Introduced by M. C. Shelesnyak)
Laboratorio di Chimica Terapeutica, Instituto Superiore di Sanità, Rome, Italy

Shelesnyak(1-3) showed that ergot alkaloids, especially ergokryptine and ergocornine terminated early (pre-implantation) pregnancy and inhibited formation of deciduomata in rats. That these effects were overcome by progesterone led the author to believe that they appear to be exerted on hormonal balance (estrogen-progesterone)(2,3). Chambon(4) demonstrated that chlorpromazine induced abortion in pregnant rat, and similar action by reserpine has been reported (5). Abortive action of both drugs could be prevented by progesterone treatment. Many clinical observations led Cranston(6) to examine action of tranquilizing drugs on normal estrus rhythm of mice. For pharmacologists these hitherto unknown aspects of action of some antagonists of neurovegetative nervous system mediators have great interest because 1) they show a new area of action of these drugs and 2) make evident their particular toxicity in this field. There are, however, very few systematic researches in the field of drugs which act on the neurovegetative nervous system associated with reproductive functions. It is from the standpoint of their pharmacological relationship that we carried out these experiments to examine the action exerted by them on fertility and fecundity of the female rat. Seventeen compounds were tested, many known sympatholytic drugs, and others belonging to other series formerly described by us(7-11). Compounds selected were: 1) for sympatholytic effects, a tetra hydro-β-naphtylamine derivative, N-(2-tetralyl) N-methyl-N'ethyl-β-alaninamide (916IS)(7,8); piperoxan hydrochloride (933F) and 3 of its derivatives, N-(2-methyl - 1,4-benzodioxan)-N' methyl-β-alaninamide (1205IS)(9). 2) for hypotensive properties, N - piperidine (2-aminomethyl - 1, 4 - benzodioxan) acetamide (1659IS) and 3) for central effects N-morpholine-2-aminomethyl 1,4-benzodioxan-acetamide (1656IS)(10,11).

Methods. In Group I (Table I) females in proestrus were mated with males whose fertility had been established. Presence of sperm in vaginal smear on the next morning was considered evidence of impregnation and onset of pregnancy. On 4th day of pregnancy (5th after coitus) intramuscular injections were given. In Group II (Table II) females were selected as in Group I, but drugs were administered orally for a period of 7 days beginning on the 3rd day after coitus. The animals were in individual cages with especially designed drinking vessels which contained the drugs and which were weighed daily to ascertain the water intake. In Group III, females with established regularity of the sex cycle as determined by vaginal smears, were used to study the action of some drugs on the cycle periodicity. Drugs were administered either intramuscularly or orally, and smears were examined daily during treatment and for 10 subsequent days. Comparison of the number of estrus cycles during 10 post-treatment days with the control number formed the basis for judging the effectiveness of the drug.

Results. In summary the effects of a single intramuscular injected on the 5th *post coitum* (Table I) are: 1) Amphetamine and yohimbine failed to alter the course of pregnancy or litter size. 2) Infundin and pyrilamin acted on the fetus, so that at normal parturition malformed or dead fetuses were expelled, or those which were viable died, soon after birth. 3) Ergotoxin interrupted early pregnancy with the appearance of estrus smears within 72 hr after injection as demonstrated by Shelesnyak (1,2). 4) Quinine caused generalized intoxication. Large doses took rapid effect on early pregnancy—and were fatal to mother; lower doses caused foetal damage. 5) Chlorpromazine and reserpine disturbed the late stages of pregnancy as reported by Chambon(4) and Tuchmann-Duplessis *et al.*(5). 6) With some synthetic derivatives of tetrahydro-β-naphtylamine (621IS; 916IS) and 2-aminomethyl-benzodioxan series (1205IS; 1656IS; 1659IS)

TABLE I. Effect of Single Muscular Injection of Some Drugs on Early Pregnancy in Rat.

	Dose, i.m. (mg/kg)	Normal	Aborted*	Lethal effects†‡		Gestations terminated§
				On mother	On litter	
A Amphetamine	10	6/8		2/8		
Yohimbine	20	8/8				
Infundin	1 U.	4/8			3/8	1/8
Pyrilamine	50	3/8			4/8	"
Thonzylamine	"	6/8				2/8
Strychnine	0.5	6/8			1/8	1/8
Chloropromazine	20	4/8			2/8	2/8
Reserpin	0.5	10/16		1/16	2/16	3/16
B Quinine	10	7/16	3/16		1/16	5/16
	100	5/8		1/8		2/8
	250	4/8		2/8	1/8	1/8
C Ergotoxine	20	1/8				7/8
D THN	20	5/8			1/8	2/8
621 I.S.	100	7/16	1/16	1/16	4/16	3/16
916 I.S.	"	6/16	4/16	2/16	1/16	"
E Piperoxan	250	9/12		1/12		2/12
1205 I.S.	100	3/8	1/8	2/8		2/8
1656 I.S.	20	5/8			2/8	1/8
	100	9/16			2/16	5/16
	250	5/16			2/16	9/16
1659 I.S.	100	6/8				2/8
Controls		7.2/8 (avg of 200 rats)				

* *Aborted:* Expulsion of non-viable fetuses between day 12 and 17 of pregnancy.
† *Lethal effects on mother:* Maternal death during course of fetal abortion; or maternal death at term accompanied with massive uterine haemorrhage, prolapse, or retention of litter.
‡ *Lethal effects on litter:* Entire litter dead at parturition or within 24 hr thereafter.
§ *Gestations terminated:* Assignable to failure to implant, degeneration of blastocyst, or hormonal disturbance.

various degrees of disturbance of pregnancy were observed which were partly associated with toxicity related with oxytocic properties.

Results from Group II (Table II) revealed that reserpine was equally effective by injection and mouth, and that 100-160 mg/k/d of 933F, and 150-265 mg/k/d of 1656IS terminated pregnancy in 6/10 to 9/10 of the groups.

From results in Group III it appears that 933F maintains estrus while 1656IS diestrus.

Conclusions. These experiments permitted screening of various drugs, affecting the neurovegetative nervous system, for their action on

TABLE II. Effect of Oral Administration of Drugs during Early Pregnancy in Rat.

	Daily oral dose					
	Conc. in drinking water, mg/100 cc	Avg dose absorbed (7 days), mg/kg/day	Normal	Toxic effects		Gestations terminated
				On mother	On litter	
Reserpin	2.5	2.5	1/10		3/10	6/10
Piperoxan	200	105	4/10			"
	500	100	1/10		1/10	8/10
	"	164	0/10	1/10*		9/10
1656 I.S.	200	104	7/10		"	2/10
	500	266	1/10			9/10
	"	148	2/10		"	7/10
	"	175	"			8/10
Controls			9/10 (avg of 30 rats)			

* Died on 10th day of pregnancy—undetermined cause.

early and middle pregnancy in the rat. Where effects are noted, they were, mainly, in that pregnancy did not proceed normally. In some instances there was evidence of abortion, in others of toxic action on the mother, or on the foetuses (with resulting death or malformation) or recurrence of estrus (*e.g.*, ergotoxine) or simple persistence of diestrus. No effort was made in these preliminary experiments to pin-point the site or mechanism of action on the course of pregnancy.

The findings of other workers(1-4) were confirmed. Rats treated with 2 drugs of our series, 1656IS and 933F, revealed significant percent of failure to achieve successful pregnancy, but the mechanism of action remains to be elicited.

It appears that pharmacologically active substances may have significantly selective effects on the sexual cycle and on early pregnancy. This is an area of investigation which until now has remained mainly in the domain of endocrinology.

Summary. Drugs acting on the neurovegetative nervous system, particularly certain derivatives (sympatholytic) of the β-tetra hydronaphthylamine and 2-aminomethylbenzodioxan series, were tested for their action on gestation in the rat. Certain agents showed interference with normal pregnancy, but the mechanism of action remains to be explored.

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Effect of Endotoxin on Gastrointestinal Mucosa of the Rat.* (24696)

SELWYN A. BROITMAN, ALYCE L. BEZMAN, MARGARET M. HAZEL AND NORMAN ZAMCHECK (Introducd by E. H. Kass)
Mallory Inst. of Pathology and Gastro-Intestinal Clinic, Boston City Hospital and Dept. of Pathology, Boston University School of Medicine

Pathogenesis of the gastrointestinal congestion and hemorrhage caused by endotoxin poisoning(1,2) is not clearly understood. The present investigation was undertaken to study alterations in morphology and biochemical activity of the gastrointestinal tract of the rat during acute endotoxin intoxication. Measurements of succinoxidase activity, an enzyme abundantly distributed in the normal rat gastrointestinal mucosa(3) were used as an indication of aerobic metabolism. An inhibitor of the succinoxidase system in the rat intestinal mucosa has been described by Nakamura *et al.*(4). It was necessary, therefore, to ascertain whether any changes in activity were due to alterations of the inhibitor rather than to changes in enzyme activity *per se*. In addition, parallel studies were carried out to determine if the mucosal barrier to microorganisms was impaired by endotoxin. Invasion by intestinal microorganisms resulting from chemical irritation of intestinal mucosa and other types of gastrointestinal trauma has been observed(5,6) while transmural migration of microorganisms, or products thereof,

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