Journal of Pharmaceutical Sciences

JUNE 1976
VOLUME 65 NUMBER 6

REVIEW ARTICLE

Progesterone: An Overview and Recent Advances

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Keyphrases □ Progesterone—production, metabolism, mechanism of action, effects, clinical use, toxicity, review □ Hormones—progesterone, production, metabolism, mechanism of action, effects, clinical use, toxicity, review □ Metabolism—progesterone, biosynthesis, concentration in body fluids and tissues, review □ Pharmacokinetics—progesterone, receptor characterization, nuclear interactions, receptor concentration, review □ Toxicity—progesterone, cell growth inhibition, prenatal and neonatal exposure, review □ Contraceptives—progesterone, metabolism, mechanism of action, effects, toxicity, review

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Because of its major function in reproduction, the physiological role of progesterone has been widely studied in the human and various animal species for over 30 years. Endogenous as well as exogenous progesterone has specific and pronounced hormonal effects on the reproductive tract and, either directly or indirectly, exerts influence beyond the utero-vaginal locus. The primary emphasis in this review is on the role of progesterone in the regulation of human fertility.

Although several reviews have been written on compounds with progestational activity, only two recent texts address themselves specifically to progesterone rather than the synthetic analogs (1, 2); much has been reported, however, since the publication of these reviews 5 years ago. Rather than a broad comprehensive review of all progestational compounds and actions, this article gives an overview of the physiological effects of progesterone and selected recent studies that are significant and relevant to the

Table I—Progesterone Production Rate in Humans

Source	Production Rate (Range), mg/day	Reference
Males	0.75	6
Ovariectomized women	1.2	6
Follicular phase	0.75–2.5	7
	2.3–5.4	8
	4	6
Luteal phase	22–43	8
	30	6
	15–50	7
Pregnancy:		
15 weeks	92	9
27–40 weeks	334 (188–563)	8
27–31 weeks	263	9
35–36 weeks	250	10
Third trimester	322 (188–563)	9
Third trimester	210 (132–288)	7

role of progesterone in human reproduction. Recent developments relating to the mechanism of action of progesterone and the clinical application of its physiological and pharmacological properties have been included also.

PRODUCTION RATE AND METABOLISM

Production Rate in Humans—Progesterone is secreted by the ovaries (3), the placenta (4), and the adrenal glands of both male and female (5). The rate of production, estimated by isotopic dilution techniques with ^{14}C- or ^{3}H-labeled progesterone, ranges from mean values of 0.75 mg/day for young males and 1.2 mg/day for ovariectomized females to about 250 mg/day in late pregnancy when placental contribution is most substantial. The rate of production is 2.3–5.4 mg/day during the follicular phase of the menstrual cycle and 22–43 mg/day during the luteal phase. These progesterone production rates are summarized in Table I.

Biosynthesis—In several mammalian species, progesterone is synthesized from both tissue and circulating cholesterol, the tissue cholesterol being derived from acetate (11, 12). Cholesterol is transformed to pregnenolone, the immediate precursor of progesterone. Pregnenolone is then converted to progesterone by a combined dehydrogenase and isomerase reaction.

Ovarian Synthesis—The human ovarian biosynthesis of progesterone has been studied by *in vitro* incubations of slices or homogenates in the presence of various labeled precursors and, more recently, by *in vivo* perfusion methods (13–15). A conversion of acetate to progesterone has been shown in luteinized rat ovarian tissue (16, 17), in bovine luteal tissue (18, 19), and in human corpora lutea (19). This biogenesis in the ovary is not limited to the corpus luteum but occurs also in the human graafian follicle (20, 21).

A correctly timed action of the anterior pituitary gonadotropic hormones, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) seems essential for the biogenesis of progesterone in the corpus luteum. Luteinizing hormone injection rapidly increases ovarian synthesis of progesterone and its release in the circulation (13) by stimulation of the enzymes responsible for the conversion of cholesterol to progesterone.

Table II—Progesterone Concentrations in Human Peripheral Plasma

Source	Concentration, μg/100 ml of Plasma	Reference
Males	0.028 ± 0.013	6
Ovariectomized women	0.039 ± 0.010	6
Follicular phase	0.023 ± 0.010	33
	0.032 ± 0.025	34
	0.040 ± 0.005	35
	0.12 ± 0.02	36
	0.113 ± 0.049	6
Luteal phase	1–2	34
	0.94 ± 0.093	35
	0.83 ± 0.58	36
	0.828 ± 0.634	33
	1.04 ± 0.32	6
Pregnancy:		
8th week	2.1 ± 0.8	37
19th week	4.0 ± 0.5	38
20th week	5.2 ± 0.5	37
34th week	19.7 ± 5.2	39
34th week	14.3 ± 0.6	38
34th week	12.7 ± 4.4	37
24 hr postpartum	1.9 ± 0.3	39

Placental Synthesis—The progesterone required for maintenance of human pregnancy originates in the placenta after the 2nd month of gestation (22, 23), reaching levels of 1–4 μg/g of tissue (4, 24, 25). Placental biosynthesis has been shown to occur in the absence of fetal organism (26) and maternal ovaries (27). The precursors for the synthesis of progesterone in the placenta are fetal pregnenolone (28, 29), fetal pregnenolone sulfate (30), and, possibly, maternal blood cholesterol (31).

Concentration in Body Fluids and Tissues—Newer methods of analysis have provided a clear measure of progesterone plasma levels during numerous physiological events. Uterine tissue concentrations have received less attention but do not seem to follow a distinct pattern.

Plasma Concentrations—The concentration of progesterone in human peripheral plasma is about 0.035 μg/100 ml for both males and ovariectomized females. In normal young women, the plasma hormone level is 0.03–0.12 μg/100 ml during the follicular phase of the cycle; after ovulation, it rises to a maximum of 1–2 μg/100 ml. This concentration is maintained until approximately 24 hr before the onset of menstruation, when it falls to the preovulatory value.

Luteal function can be estimated routinely by the determination of plasma progesterone. The plasma progesterone level increases gradually during pregnancy, reaching 12–20 μg/100 ml of plasma near term and dropping to 1.9 μg/100 ml of plasma 24 hr postpartum. No mean change in the plasma progesterone level is observed throughout labor (32). These data are summarized in Table II.

Because progesterone is produced by the corpus luteum, the progesterone concentration is substantially higher in human ovarian vein blood than in peripheral plasma. Progesterone in ovarian venous blood is less than 2 μg/100 ml of plasma during the follicular phase but rises to about 60 μg/100 ml of plasma during the luteal phase, a concentration comparable to

Table III—Progesterone Concentrations in Human Ovarian and Uterine Vein Blood

Phase of Menstrual Cycle	Concentration, μg/100 ml of Plasma	Reference
Follicular phase	<2 (ovarian)	40
	0.2–1.5 (ovarian)	41
Luteal phase	56.1 (ovarian)	40
	0.7–186 (ovarian)	41
Pregnancy:		
First half	8–97 (uterine)	42
8 weeks	14.8 (uterine)	43
8 weeks	34 (ovarian)	43
11.5 weeks	63 (ovarian)	43
23 weeks	30 (ovarian)	43
40 weeks	13 (ovarian)	43
40 weeks	100–310 (ovarian)	44
40 weeks	200–710 (uterine)	44

the highest level found during pregnancy at 11.5 weeks. During late gestation, levels of progesterone in the venous blood of the ovary are 30–300 μg/100 ml of plasma. The progesterone content of uterine venous blood reaches 14.8 μg/100 ml of plasma during the 8th week of pregnancy, exceeding the value in peripheral blood; later in gestation, it ranges from 8 to 710 μg/100 ml of plasma (Table III).

Uterine Tissue Concentrations—Efforts to measure the progesterone content of the myometrium during pregnancy have produced a range of concentrations of 4–63 μg/100 g of tissue (Table IV). The variations may reflect differences in assay methods or in local concentrations within the uterus or may result from time-varying concentrations during pregnancy (45). Progesterone levels have not been determined in nonpregnant myometrial tissues.

Progesterone concentrations in the human endometrium range from 0.5 to 16.8 μg/100 g of tissue during the menstrual cycle and from 8 to 58.9 μg/100 g of tissue during pregnancy (Table V). At any given time in the cycle, the measured level of progesterone in endometrial tissue depends upon several factors, such as the overall corpora lutea function and enzymatic activity controlling metabolic pathways and rates. Therefore, alterations from normal tissue concentrations of progesterone might be used to determine abnormal endometrial functions (52).

Metabolism—The absorption of exogenous progesterone in humans is rapid, irrespective of the route of administration. Because progesterone is almost completely metabolized in one passage through the GI mucosa and the liver, however, low doses administered orally are ineffective. Intramuscular injection of 25 mg of progesterone in oil or administration of 100 mg by the vaginal or rectal route achieves plasma levels equivalent to those seen during the luteal phase (53).

Table IV—Progesterone Concentrations in Human Myometrium during Pregnancy

Gestational Age	Concentration, μg/100 g of Tissue	Reference
10–19 weeks	11.1 ± 8.1	45
11 weeks	4.7, 20.7	46
12–41 weeks	5–16	47
Undated, pooled material	31–63	47
12–41 weeks	4–52	48
4th month	9	49
10th month	7–22	49
33–38 weeks	12.6 ± 9.7	45
35–40 weeks	19–57	50
40 weeks	1.7–7.9	46
39–42 weeks	12.4 ± 7.3	45

Table V—Progesterone Concentrations in Human Endometrium

Phase of Menstrual Cycle	Concentration, μg/100 g of Tissue	Reference
Follicular phase	2.5, 3.1	46
	0.5, 1.5	51
Luteal phase	4.8, 16.8	46
	1.2, 3.0	51
Pregnancy:		
11 weeks	58.9	46
40 weeks	8–18.5	46

In the bloodstream, endogenous and exogenous progesterone binds to plasma proteins. Early investigations on the binding of progesterone to serum components, using equilibrium dialysis, indicated a high affinity of the hormone for human serum albumin (88.9%) (54). Extremely low amounts of progesterone are found in erythrocytes (55) or platelets (54). It was shown more recently that pregnant guinea pig serum contains a progesterone-binding globulin (PBG), which is distinct from corticosteroid-binding globulin (CBG or transcortin) (56).

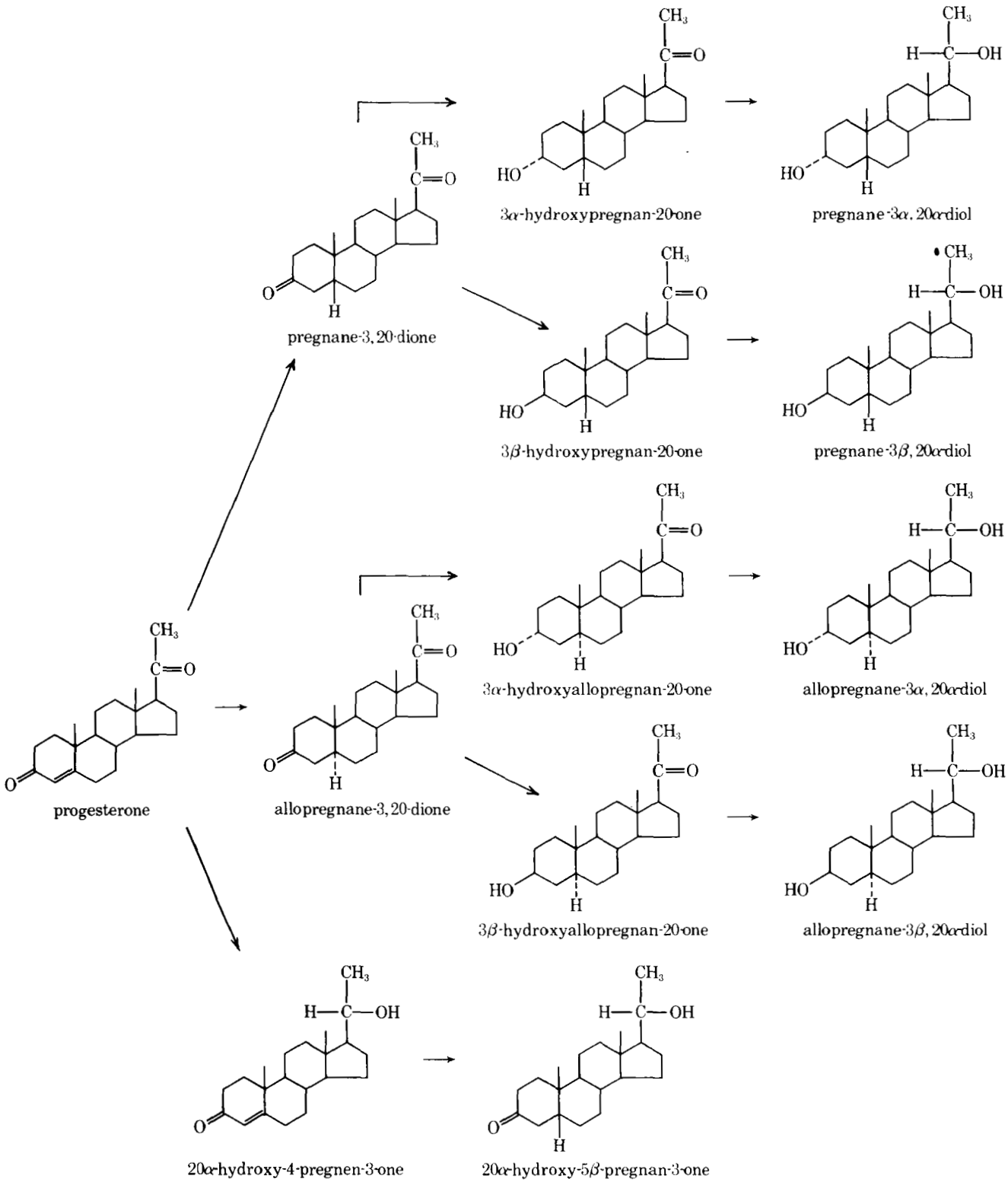
Progesterone-binding globulin has been purified to homogeneity and found to be a glycoprotein with high (48.7%) carbohydrate content, a molecular weight of 77,500 daltons, and an isoelectric point in the range of pH 2.8–3.6 (57, 58). The relative binding affinities of various steroids for the guinea pig progesterone-binding globulin have been determined (59); compounds displaying high affinity include 5α-pregnan-3,20-dione, 20α-hydroxypregn-4-en-3-one, and 21-hydroxypreg-4-en-3,20-dione as well as progesterone. An equilibrium association constant of $9 \times 10^8\ M^{-1}$ is calculated at 4.0° for the progesterone–progesterone-binding globulin 1:1 complex.

The reported half-life of intravenously injected progesterone in the human ranges widely, from 3 (10) to 90 (60) min. These and other half-life determinations were discussed by Thijssen and Zander (61) and by Fylling (62), who obtained plasma half-life values of 27 and 45 min, respectively. The metabolic clearance rate (MCR) of progesterone, determined from both single-injection and continuous infusion methods, ranges between 2510 and 2800 liters/day in normal women and remains constant through the menstrual cycle (63–65).

In spite of the large ovarian production of progesterone, its concentration in uterine tissues is low, primarily due to metabolism by the liver, since blood flow from the ovaries leads to systemic circulation. The low uterine concentration is also due to the high rate of metabolism of progesterone by the endometrium and myometrium. Based on the percent of progesterone metabolized in an *in vitro* incubation, the metabolic rate for proliferative human endometrial tissue is 0.99 μg of progesterone/(g of tissue-hr); human myometrial tissue metabolizes 0.11 μg/(g of tissue-hr) (66). Uterine weights vary greatly, depend-

ing on parity, race, and age. A mature female uterus, which may be considered to weigh approximately 110 g (67), metabolizes approximately 3 mg of progesterone/day.

Species- and sex-dependent variations occur in the metabolism of progesterone. Its human metabolism consists of various conversions, including reduction, hydroxylation, cleavage, and conjugation (60, 68). The reductive metabolism of progesterone is depicted in Scheme I. In humans, progesterone is mainly metabolized by the liver to 5β-pregnane-3α,20α-diol (pregnanediol). This and other metabolites are then conjugated in the liver with glucuronic acid and excreted by the kidney. Liver metabolism accounts for approximately two-thirds of all metabolic pathways.



Scheme I—Major in vivo *human metabolic pathways of progesterone*

Following the injection of labeled progesterone, 50–60% of the excretion of progesterone metabolites is *via* the kidney; the second major excretory pathway, approximately 10%, is *via* the bile and feces (60). Overall recovery of labeled material accounts for up to 70% of an administered dose, the remainder being unaccounted for (69).

A highly significant correlation exists between serum progesterone concentration and urinary excretion of pregnanediol during the menstrual cycle (70). In some clinical investigations, only pregnanediol is measured as an index of progesterone secretion. For the detection of luteal activity, however, most clinical laboratories are abandoning the measurement of pregnanediol for the more definitive progesterone radioimmunoassay (70, 71). When labeled progesterone is injected in humans, a range of 6–27% is eliminated as urinary pregnanediol regardless of the dose of progesterone injected (72).

Hydroxylation of steroids by liver microsomes is affected by the same parameters that affect drug oxidation, suggesting that drugs and steroids are substrates for the same microsomal enzymes (73). Environmental chemicals [1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) and chlordane] and drugs (phenobarbital) increase progesterone hydroxylase activity, resulting in a decrease in the concentration of progesterone and its metabolites in the brain and total body of the rat (74). This increase in metabolism is manifested *in vivo* by altered physiological responses, such as a decrease in the anesthetic action of large doses of progesterone.

In the human skin, metabolism of the hormone is accounted for by subcellular fractions shown to contain membrane-bound 5α-reductase and soluble 20α-hydroxysteroid dehydrogenase activity (75). Similar enzyme activities are observed in the rat pituitary gland (76). The metabolism of progesterone in the adrenal cortex leads to the production of corticosteroids (*e.g.*, cortisol and aldosterone). The formation of additional metabolites (hydroxylations and keto and alkene reductions) was reviewed by Kincl (77).

Among nonhuman primates, progesterone is also a major secretory product of the ovary. Its metabolism, however, differs from species to species. In the rhesus monkey, the diurnal change in progesterone secretion is a composite of fluctuations of ovarian and adrenal progesterone governed by different factors (78). In this species, the major urinary metabolite is androsterone, accounting for 6% of the progesterone administered (79); pregnanediol is isolated only in trace amounts (80). In the pigtail monkey, androsterone is the progesterone metabolite of quantitative importance (81).

Data for the chimpanzee and the baboon, on the other hand, show a progesterone metabolism pattern closer to that observed for humans. In immature chimpanzees, 7% of the injected dose of progesterone is recovered as pregnanediol (82). The chimpanzee placenta can also convert pregnenolone to progesterone (83). In the baboon, the major identified metabolites from intravenously administered progesterone are 11.7% androsterone and 31.4% for the 5α- and 5β-isomers of 3α,20α-pregnanediol (84, 85).

MECHANISM OF ACTION

A large body of accumulating evidence tends to support a unitary theory for the mechanism of action of steroid hormones. According to this theory, the steroids elicit a sequence of events, starting with the uptake of the steroid molecule into the target cell where the steroid binds to a specific cytoplasmic "receptor" protein. This receptor protein–steroid complex is then translocated to the nucleus where it binds to specific sites on the genome, thus inducing the transcription for a new, specific RNA. This RNA, in turn, results in the ribosomal synthesis of new proteins, which become the physiological expression of the specific steroid hormone. Recent reviews comprehensively cover the data on the various steps involved in the interaction of female steroid hormones with their target cells (86–88).

Receptor Characterization—The target cells responsive to progesterone contain high affinity, saturable cytoplasmic receptor proteins. Considerable evidence supports the hypothesis that the physiological manifestations of progesterone result from an initial interaction of the hormone with this specific receptor in the cytosol of the target cell. The identification of such a receptor must rely on the high specificity and high affinity of its interaction with progesterone.

The molecular interactions between progesterone and its receptor site are best studied with highly purified forms of the hormone–receptor complex. The isolation and partial purification of the progesterone receptor from various mammalian, including human, uterine tissues were recently reported (89–91). Subsequent to purification, the receptor–progesterone complex in human oviduct nuclei still retains its capacity for translocation and nuclear binding. Experiments are yet to be performed, however, where the hormone is removed from the receptor complex while the activity of the receptor is retained. Future work on the characterization and isolation of the progesterone receptor would be advanced by the use of identification ligands having optimal affinity for the receptor (92).

Partial characterization of the endometrial and myometrial progesterone–receptor complex indicates the binding macromolecules to be protein in nature. Much work recently has been performed to resolve whether the progesterone receptor is not, in fact, the corticosteroid-binding globulin (93, 94). Binding affinity studies (90, 95, 96) allow one to conclude that the endometrial and myometrial progesterone receptor is of tissue origin and has binding affinity distinct from that of corticosteroid-binding globulin.

Similarly, synthetic progestational agents show little affinity for corticosteroid-binding globulin but compete with progesterone for the cytosol binding site. This finding supports the suggestion that synthetic progestational agents act, at least in part, by interacting with receptors in target organs (95–97). Verma and Laumas (90), however, could not obtain

any competitive binding when using orally active progestational steroids. These results may be due to prolonged dialysis in the absence of glycerol, leading to rapid loss of high affinity progesterone binding activity (95, 98). In the hamster uterus, progesterone itself, not its metabolite 5α-pregnane-3,20-dione, mediates the progestational response by binding to the receptor site, indicating that initiation of the progestational response does not require conversion to this metabolite (99).

Ultracentrifugation in sucrose density gradients provides a practical means to differentiate among various forms of the receptor. The use of sedimentation rates to characterize receptor transformation for the estrogen–receptor complexes has been described (87). Even though the sedimentation behavior of steroid–receptor complexes varies according to concentration and ionic strength, it serves as a useful method to identify steroid–receptor complexes.

The sedimentation coefficient for the cytosol–progesterone receptor is about 4 S in sucrose density gradient centrifugation in the presence of 0.3 *M* KCl (90, 94). At low ionic strength (no potassium chloride), the aggregation occurs at 5 S and 8 S. Reported molecular weights for the receptor molecule monomer, calculated by various techniques, range between 60,000 and 110,000 daltons (89, 90). Binding is not covalent since the steroids are completely extractable with organic solvents. Published affinity constants vary between 1.0 and $3.4 \times 10^9\ M^{-1}$ (92, 96).

Nuclear Interactions—The nuclear steroid–receptor complex seems derived from the cytosol complex since cytosol receptor contents decrease as nuclear binding increases. The progesterone–receptor complex appears to bind the chick oviduct nuclei (a specific target tissue for progesterone) only after a time- and temperature-dependent transformation occurs. This transformation can be followed with ^{3}H-progesterone; the steroid–receptor complex becomes associated with the chromatin fractions (86).

The details of the molecular interactions between the receptor complex and chromatin fractions are not yet known, nor is the mechanism by which such interaction results in gene expression. Conceivably, the progesterone receptor consists of subunits that could play complementary roles in binding to the chromatin components responsible for acceptor activity (86, 88, 100).

In the estrogen-primed chick, progesterone increases the rate of synthesis of messenger RNA in the oviduct, an effect prevented by the administration of actinomycin D, an inhibitor of DNA-dependent RNA synthesis. If the biosynthesis of RNA is allowed to proceed, the oviduct synthesizes the hormone-dependent protein avidin.

After progesterone initiation of RNA biosynthesis, the hormone no longer seems necessary to evoke the resulting morphological changes. Consequently, total RNA extracted from progesterone-stimulated chick oviducts can induce the synthesis of avidin in estrogen-primed chicks. If no progesterone contamination is assumed, such a transfer method supports the concept that progesterone acts on the nucleus of target cells to promote synthesis of RNA (101). The morphological effects of progesterone (stimulation of cilia formation and secretory activity) can also be obtained by transfer of RNA extracted from progesterone-stimulated oviducts. The oviducts of the RNA-treated animals are almost indistinguishable from those that have undergone progesterone treatment (101).

Receptor Concentration—Theoretical and experimental approaches for the analysis of receptor concentration have been discussed (102). The concentration of progesterone receptor present in crude cytosol is approximately 3×10^{-9} mole/mg of protein (89, 103). The progesterone receptor concentration varies throughout the estrous cycle and is dependent on the action of both estrogen and progesterone (104, 105).

A single injection of estradiol (100 μg/kg) in castrated guinea pigs results in an eightfold increase in basal concentration of receptors after 20.5 hr (102). Similar results were obtained after diethylstilbestrol treatment in the chick oviduct (106). The established observation that, in most circumstances, progesterone can exert its biological effects only after estrogen priming is now understood in terms of the following scheme: estrogen → synthesis of progesterone receptor → progestational response. This increase in progesterone receptors after estradiol injection does not occur when actinomycin D or cycloheximide (an inhibitor of protein synthesis) is injected 15 min prior to the estradiol. Neither actinomycin D nor cycloheximide has any effect on receptor concentration when injected 20.5 hr after estradiol (time corresponding to maximum receptor concentration) (102). Following the estradiol treatment, the increase in concentration of progesterone receptor seems dependent on RNA and protein syntheses. The subsequent decrease in progesterone receptor is slow, with a receptor half-life of about 5 days.

The precise mechanism of receptor degradation is not understood. The injection of progesterone (1–10 mg) into estrogen-primed guinea pigs results in a rapid decrease in concentration of progesterone receptor. Very low concentrations of progesterone receptor are reached within 24 hr of progesterone injection and only slowly return to basal levels (102). This decrease in progesterone receptor concentration is not due to nuclear translocation (107) but may result either from an inactivation of the receptor protein or from changes in its binding behavior (since binding, not absolute receptor concentration, is measured).

The high levels of progesterone receptor during the follicular phase may, therefore, reflect the estrogen-dominated environment. On the other hand, a progesterone-dominated environment (*i.e.*, during the luteal phase) results in low levels of progesterone receptor. These observations are substantiated by the low concentrations of progesterone receptor present in subjects receiving oral contraceptives and during pregnancy.

In endometrial carcinoma, the concentration of progesterone receptor is low in undifferentiated tumors but relatively high in well-differentiated tu-

mors (108). Understanding the function of the receptor during the process of tumor differentiation may allow the prediction of the therapeutic response of tumor cells to treatment with progestational agents or other endocrine therapy. In human breast cancer, preliminary clinical results provide strong evidence for the hypothesis that only breast tumors containing progesterone receptors will show objective remission in response to endocrine therapy, *e.g.*, hypophysectomy or oophorectomy (109). During the malignant transformation of hormonal target tissue, the cells may not retain their ability to synthesize the hormone receptors. Patients with tumors containing both estrogen and progesterone receptors appear more likely to respond to endocrine therapy than if the tumors are without these receptors or only with estrogen receptors.

EFFECTS ON REPRODUCTIVE TISSUES AND FUNCTIONS

Hypothalamic–Pituitary–Ovarian Axis—Progesterone plays a relatively minor role during the early follicular stage of the menstrual cycle. Follicle-stimulating hormone secretion increases, promoting growth of the ovarian follicle. Follicular growth results in estrogen secretion and estrogen, in turn, seems to stimulate further follicular growth. Near the middle of the menstrual cycle, estrogen secretion peaks and stimulates or enhances the sudden release of luteinizing hormone. This transient increase in luteinizing hormone secretion results in high plasma luteinizing hormone levels causing ovulation. Accompanying the luteinizing hormone ovulatory surge, plasma follicle-stimulating hormone sharply rises. Luteinizing hormone seems to act directly on the follicle to cause release of the egg.

Following ovulation, the empty follicle rapidly becomes the corpus luteum, which secretes both progesterone and estrogen. In the human, increased progesterone synthesis may actually begin before ovulation (110, 111); it has been shown that by the time follicle-stimulating hormone and luteinizing hormone exhibit their peaks, the serum progesterone already has increased significantly (112). The ripe follicle is the probable source of this preovulatory progesterone (113), which at this point in the cycle may facilitate the release of luteinizing hormone. During the functional life of the corpus luteum (the luteal phase), the progesterone it produces reaches levels that inhibit hypothalamic cells controlling the formation or release of luteinizing hormone in the pituitary (114, 115).

We lack a cohesive understanding of which pituitary gonadotropin is most essential for the maintenance of the human corpus luteum. Luteinizing hormone can stimulate progesterone secretion and extend luteal life, yet other factors are involved since continuous treatment with luteinizing hormone or human chorionic gonadotropin (HCG) can extend luteal life for only a few days, the corpus luteum regressing during treatment. Regression of the corpus luteum abolishes the hormonal support provided to the secretory endometrium (116), leading to the endometrial sloughing of menstruation.

During pregnancy, the production of progesterone by the placenta (117–119) and the corpus luteum (3, 120) suppresses gonadotropin secretion and inhibits ovulation. The suppression of pituitary activity attained by progesterone administration includes adrenocorticotropin and growth hormone as well as gonadotropins. Such a broad range of pituitary inhibition suggests that the increased progesterone production during pregnancy is one major factor eliciting the shift from pituitary to placental dominance.

Progesterone exerts both stimulatory and inhibitory effects on ovulation (121). In some mammals (*e.g.*, rabbits and rats), progesterone, if given at a critical interval and dose, induces ovulation. This stimulatory effect of progesterone has been reviewed in detail (122). More emphasis, however, has been placed on progesterone's inhibition of ovulation, a concept that was a starting point for the development of oral contraception (123). Oral contraceptives containing both estrogenic and progestational analogs may interfere with fertility in several ways, but it is well established that, as presently used, their contraceptive action in humans results from suppression of follicle-stimulating hormone and luteinizing hormone and inhibition of ovulation.

Continuous administration of a progestational agent alone in sufficient doses also inhibits ovulation and abolishes the menstrual cycle for as long as therapy is continued. Smaller doses of progestational agents, as in the "mini-pill," also provide a contraceptive effect but do not disturb the menstrual cycle or ovulation. Progesterone injections, even in high doses, do not affect follicular maturation except in the late preovulation phase.

Autoradiograms of the hypothalamus of guinea pigs demonstrate a selective concentration of progesterone or its metabolites in the nuclei of certain neurons of the brain, providing supportive evidence for the presence of progesterone-sensitive sites in the hypothalamus (124). Nuclear binding of progesterone in hypothalamic neurons is further suggested as necessary for the production of the central hormonal action of progesterone.

Rat and baboon pituitary glands have the capacity to metabolize progesterone *via* 5α-reductase and 20α-hydroxysteroid dehydrogenase activity (125). This enzymatic activity within a target tissue has been interpreted as representing a mechanism by which progesterone may modulate certain pituitary and central nervous system (CNS) functions (76, 125).

Another approach in the elucidation of the interactions between hormonal and neural parameters responsible for estrus behavior has been to investigate the effects of ovarian steroids on the neuronal activity of brain monoamines (126). However, no clear picture has yet emerged from such studies due to experimental and interpretative problems.

Uterus—The primary target tissue for progesterone is the uterus. The sites of action are both the mucosal (endometrium) and muscular (myometrium)

portions. Progesterone enhances overall uterine growth (especially endometrial) resulting from estrogen priming. Subsequently, the endometrium differentiates and becomes ready for implantation of the blastocyst (secretory endometrium).

During the luteal phase of the menstrual cycle, the corpus luteum secretes estrogen and progesterone, causing the endometrium to become more tortuous and to produce a more mucous secretion with a high glycogen content. Endometrial growth is largely due to estrogen, while progesterone is responsible for the stromal changes and the increase in glycogen and glycoprotein in the glandular epithelium. These changes peak 7–8 days after ovulation, coincident with maximal progesterone secretion.

If implantation of a fertilized blastocyst does not occur, the secretory activity of the corpus luteum decreases, resulting in a measurable drop in progesterone production. This drop also may be partly due to an increase in ovarian 20α-hydroxysteroid dehydrogenase. With the fall in progesterone, the secretory endometrium can no longer be maintained, and it is sloughed (menstruation).

Endometrial Histology—Progesterone is considered responsible for the conversion of proliferative to secretory endometrium *in vivo* during the menstrual cycle. By adding progesterone (10 μg/ml) to a culture medium, glandular cells in the endometrial tissue are stimulated to secrete, and subnuclear vacuolation appears after 2–3 days. As the culture continues, the vacuoles disappear and secretion of mucopolysaccharides into the lumen of the glands occurs (127). Similar subnuclear vacuolation appears in the glandular cells of the endometrium in oophorectomized women after progesterone treatment.

Histochemically, this secretory effect is manifested by the increase in glycogen granules present in the cytoplasm and by changes in the apical villous borders of cells (128, 129). Glycogen granules first concentrate in the basal portion of the epithelial cells and then enter the secretory domes from which they detach as secretion globules. The substrates contained in the wall of the glandular epithelial cells are neutral or predominantly acid mucoids. These endometrial changes are well documented and have served historically as the basis of several bioassays for screening progestational agents.

After extended progestational therapy, the histochemical picture is one of focal pseudodecidual transformation of the stroma with glycogen accumulation and involution of the glands.

Protracted therapy provides a variety of changes encountered on a localized basis, including atypical secretion, exhaustion, and regression alternating with each other (129). Associated with the conversion of the endometrium to its secretory phase is an increase in the activity of most endometrial tissue enzymes (130–133).

Intrauterine Leukocytes—In most animal models (estrous, ovariectomized, and pseudopregnant), progesterone is generally found either to reduce or not to affect leukocyte levels in the uterus (134–137). Neutrophils and mononuclear cells are abundant in endometrial tissue during the menstrual flow, and mononuclear cells increase in association with the pseudodecidual stromal reaction occurring in the luteal phase.

Other observations have shown, however, that progesterone may also increase the number of the leukocytes present in oviductal tissues of cattle; such leukocytes release their products into the uterus at the start of the follicular phase, giving the uterus, under the influence of estrogen, its bactericidal properties. These leukocyte-like cells penetrate the lumen during early luteal stages of the estrous cycle and at early stages of pregnancy. The specific origin of these cells has not been determined; their morphology differs from the eosinophilic and neutrophilic polymorphonuclear cells present in genital tissues during inflammation (138).

Myometrial Activity—Human myometrial activity has been reviewed extensively (139, 140). As described by Moawad and Bengtsson (140), from Day 6 to Day 18 of a normal 28-day menstrual cycle the same type of activity is found, *i.e.*, frequent contractions (two to four per minute) of low amplitude (3–10 mm Hg) and short duration. After the 8th day preceding the next period, contractions of another type appear, with lower frequency (every 2–3 min), higher amplitude (around 25 mm Hg), and longer duration (1–2 min). These contractions gradually increase to a "prelabor-like" pattern 4 days before the next period. A further increase to "labor-like" activity is observed around the onset of bleeding.

The relative importance of the combined action of estrogen and progesterone is not known. The prelabor-like pattern corresponds with the presence of both estrogen and progesterone, whereas the labor-like pattern corresponds with the withdrawal of both hormones. In the nonpregnant woman, exogenous progesterone also induces the prelabor-like pattern of myometrial activity, resulting in contractions of lower frequency, longer duration, and higher amplitude (141).

In the pregnant uterus, most experiments indicate a depression of myometrial activity. Placental contribution of progesterone to the myometrium rather than the peripheral plasma progesterone may be responsible for this depression of myometrial activity (50, 142). In the rabbit, in which progesterone is known to have a blocking action on the myometrium, treatment with progesterone inhibits the myometrial stimulations caused by prostaglandin $F_{2\alpha}$ (dinoprost) (143). Agreement is still lacking on the physiological parameters that precipitate the onset of labor and, in particular, on the role (if any) of progesterone in the complex process of initiation and control of labor. In the human, the mean plasma progesterone remains unchanged prior to and throughout normal labor (32). In the case of premature labor, however, Csapo *et al.* (144) attributed the onset to a decrease in progesterone levels, caused perhaps by a failure in placental growth and function.

Electrophysiologically, progesterone has been suggested to act by inhibiting the movement of ions through the myometrial cell membrane (145). Like-

wise, inhibition of enzymes that are coupled to ionic movements and that are responsible for uterine muscle contraction would provide an alternative explanation. *In vitro,* progesterone does inhibit creatine phosphokinase activity (146) and, at high concentrations, adenosine triphosphatase activity (147).

Cervix—During the preovulatory phase of the cycle or following estrogen priming, the endocervical mucus is highly elastic and displays well-formed ferning (crystallized sodium chloride) upon drying. The rheological properties of this estrogenic mucus make it suitable for sperm penetration and survival. During the luteal phase, progesterone decreases the total volume of estrogenic mucus present in the endocervical canal (148), increases mucus viscosity, and decreases its "Spinnbarkeit" (length of the mucus thread) (149). Concomitant clouding of the mucus is due to the presence of polymorphonuclear leukocytes.

Progesterone (30 mg/week im), when administered without estrogen priming in ovariectomized women, causes no observable effect on the cervical mucosa. After an intramuscular injection of progesterone (5–10 mg), spermatozoa have difficulty in penetrating the mucus and in maintaining their motility. Progesterone, in oral doses of 10 mg/day to normal women, decreases both sperm population and sperm motility in the endocervical mucus following sexual intercourse (150). Intracervical silicone elastomer devices releasing progesterone display the expected progesterone effects; they inhibit secretion of preovulatory human cervical mucus, lower its Spinnbarkeit, and increase its viscosity (148).

Sperm Migration and Capacitation—Inhibition of sperm motility by progesterone is usually ascribed to secretory changes in the mucus production by the cervical crypts. In addition, progesterone released *in vitro* into cervical mucus inhibits sperm migration, suggesting that progesterone has a direct spermiostatic action (151). The relevance of this direct effect of progesterone on the regulation of fertility is not, however, established. Other factors that may play a role in the rate of sperm transfer have been studied: ciliary actions in the genital system, serotonin (152), oxytocin (153), and prostaglandins (154–156).

A specific hormonal balance seems necessary for sperm capacitation, a process involving changes in the spermatozoa necessary for penetration into eggs (157). An anticapacitating effect of progesterone was initially observed in rabbits (158). Further evidence was derived from experiments in which spermatozoa were incubated in the uterus of estrous rabbits pretreated with progesterone. In the progesterone-treated rabbits, only 2.1% of the ova were fertilized, as opposed to 63% after incubation in estrous rabbits without progesterone. Sperm capacitation was inhibited only in the uterus and not in the fallopian tubes.

Implantation and Blastocyst Development—The fertilized mammalian ovum generally reaches the uterus between 3 and 5 days after ovulation; in the uterus, the ovum requires a special environment, which is highly dependent on hormonal factors. Implantation of the fertilized ovum results in a rapid growth and differentiation at the implantation site, characterized by increased rates in the synthesis of nucleic acids and proteins. Results of reported studies are difficult to correlate due to species and experimental differences.

In the rabbit, for instance (159), survival of unimplanted fertilized eggs in the uterus depends on the presence of progesterone acting on the uterine epithelium and enabling the eggs to implant at the correct time. In most species, however, progesterone *per se* does not seem required for implantation but is essential for the initiation and maintenance of the decidualization and for the survival of the embryo. Ovariectomy in early pregnancy in the guinea pig does not prevent implantation, but subsequent degeneration of the decidua, ascribed to progesterone deficiency, results in embryonic death (160). If, however, progesterone administration is given following ovariectomy, pregnancy is maintained. Concurrent administration of small quantities of estrogen often reduces the amount of progesterone required (161).

In the rat, some inhibition of uterine receptivity occurs whenever the basic progesterone–estrogen sequence is disturbed. Receptivity in the uterus appears to be a local phenomenon, in that implantation can be inhibited in one part of the organ due to local administration of hormones while progressing normally in the rest of the uterus (160).

In spayed rats, the blastocyst can survive in the uterine lumen for several days in the absence of exogenous hormones (162). If progesterone (10 mg) is injected in such spayed rats, the blastocyst may survive for several weeks without implanting. This induction of dormancy in the blastocyst has been suggested to result from a hypothetical inhibitor produced by the uterus under the influence of progesterone as a protection to the embryo. A small dose of estrogen (1 μg) subsequent to progesterone injection removes the inhibition and leads to implantation. Normal development occurs provided progesterone treatment is continued.

Direct Exposure of Uterine Lumen—The direct exposure of the uterine lumen to exogenous progesterone has a contraceptive effect. Progesterone-filled silicone elastomer capsules inserted in the uterine horn of mature rabbits inhibit implantation of fertilized ovum (163). Similar capsules have also served as a contraceptive in human volunteers (164–166). Clinical efficacy studies with an intrauterine device that releases progesterone will be discussed later.

Morphological changes in the endometrium were observed in women having the progesterone-releasing system *in utero* but not in women wearing placebo devices (*i.e.,* containing no progesterone). The latter showed the usual endometrial picture of stromal edema and sometimes inflammatory cells. Delivery of progesterone to the endometrium causes a decidual transformation with a depression of the glandular development. The progesterone-releasing uterine system increases endometrial progesterone levels and decreases endometrial estradiol levels but causes no detectable change in the peripheral plasma levels of these steroids (51).

The specific mechanism of the contraceptive activity of intrauterine progesterone administration is unknown. Myometrial activity is unaffected in humans (167). Furthermore, no systemic effects from progesterone have been observed in rabbits (163), baboons (168), or humans (169). Contraceptive efficacy appears to depend on one or more changes within the uterine milieu: alteration of cervical mucus (170), disturbance of sperm capacitation (171–173), reduction of egg fertilization (171), endometrial suppression (170), and/or inhibition of nidation. Although the latter two effects seem the most likely mechanisms, the other factors may participate.

Vagina—Following estrogen priming, progesterone causes desquamation in the human vagina (174, 175). Desquamation occurs in clumps, the superficial cells being replaced by cells with basophilic cytoplasm and vesicular nuclei (149). In addition to shedding superficial layers, the thickness of the epithelium increases and progesterone may inhibit estrogen-induced vaginal cornification (176). The significance of an increase in the number of polymorphonuclear leukocytes, observable after 12 hr of an intravenous drip infusion of progesterone, is not known (177).

Mammary Gland—Mammary gland growth is a complex process involving other endocrine tissues besides the ovaries and the placenta (*e.g.*, pituitary and adrenals). Progesterone by itself, in sufficiently large doses, causes full development of the ductal and lobuloalveolar system of the mammary glands in intact and castrated rats, mice, and guinea pigs (178–180); priming by estrogen is not necessary to attain full development. Daily injections of 5–20 mg of progesterone in rhesus monkeys increase the size and number of lobules (181).

In the human, the alveolar proliferation caused by progesterone is most evident during pregnancy but is also operative during each luteal phase. The differences reported in the literature on this effect are partially due to marked species differences and to the inability to distinguish, in castrated but nonhypophysectomized animals, between a direct effect of progesterone on the mammary growth or an indirect action *via* the pituitary. In most experimental animals, the pituitary must remain intact if estrogen and progesterone are to affect mammary growth (180).

OTHER EFFECTS

As might be expected from its milligram per day production and wide body distribution, progesterone has sundry effects in addition to those on the reproductive organs. The effects of major interest in humans are summarized here. Reviews dealing with the effects of progesterone on other organ systems, including the effects on hepatic metabolism (182), the liver (183), respiration (184, 185), and the skin (186), have been published.

CNS—Progesterone exerts various effects on the CNS. The effect of progesterone on the hypothalamic–pituitary–ovarian axis has already been described. Sawyer *et al.* (187) reviewed the central effects of various hormones as they pertain to animal sexual behavior. Traditionally, the sharp falls in progesterone levels occurring at the end of each menstrual cycle and at the end of pregnancy have been implicated in premenstrual and postpartum disturbances in behavior (188–190).

The occurrence of depression or puerperal psychosis increases significantly during the 3 postpartum months (191). Serious psychological disturbances due solely to increased progesterone levels are, however, unlikely (192). Rather than investigating the role played by a unique agent (*i.e.*, progesterone) in pregnancy-related psychological phenomena, a more integrated approach encompassing a multiplicity of agents may better indicate possible correlations.

One clinical survey on the relationship between the incidence of migraine attacks and the stage of the menstrual cycle showed that the attacks occur regularly just before or during menstruation only in 13 out of 138 migraine patients (193). Most women with migraine, however, exhibited elevated plasma concentrations of both progesterone and estrogen throughout the menstrual cycle as compared to healthy migraine-free controls. This elevation in migraine patients was more marked in the late luteal phase. It must be kept in mind, however, that additional nonhormonal factors may be responsible for such results.

When progesterone (35 mg) is injected intraperitoneally into female rats, a deep anesthesia occurs within 15 min; if given subcutaneously, however, 100 mg is without effect (194, 195). A single intraperitoneal injection of progesterone (5 mg) into estrogen-primed rats shortens the periods of wakefulness and induces, in the hippocampal area, the appearance of EEG spikes similar to those of sleep (196).

Studying the uptake of labeled progesterone and two of its metabolites (pregnanolone and pregnanedione), Raisinghani *et al.* (197) concluded that pregnanolone mediates the anesthetic effect of progesterone. The median anesthetic dose in mice is 89 mg/kg iv (198). In the human, this effect has not had any practical application, although Merryman *et al.* (199) reported sleep induction in women within the first 15 min of an intravenous infusion of progesterone (500 mg). The hypnotic effect lasts for several hours and is dose dependent.

Progesterone increases, and estradiol decreases, the seizure threshold for rats given electroshock-induced convulsions (200). The administration of 5 mg/kg/day of progesterone significantly raises the seizure threshold in female rats but is without effect in males. This anticonvulsant effect in females is transient; after 20 days of treatment, a mild convulsant response is observed in both males and females. Progesterone is also effective in protecting dogs against induced convulsions.

Clinical studies with human epileptic patients appear consistent with animal results; the number of seizures definitely declines during the luteal phase of the menstrual cycle and increases immediately before, during, and just after menstruation. This exacerbation is thought to result from the drop in the progesterone secretion. Activations of abnormal EEG

patterns and precipitation of seizure occur with exogenous estrogen whereas a decrease in seizures is observed with premenstrual progesterone therapy (201, 202). This effect of progesterone on the CNS has not been clinically exploited, however, since other more advantageous therapeutic compounds are available.

Progesterone is associated with an increase in basal body temperature. In women, the basal body temperature is usually higher during the luteal phase of the cycle; the initial rise in temperature is widely assumed to coincide with ovulation. The pattern of basal body temperature, however, varies greatly from subject to subject. In addition, no increase in basal body temperature with ovulation is obtained in 12% of otherwise normal cycles (203). These factors indicate that this thermogenic effect cannot be used reliably for predicting ovulation. Body temperature also generally increases during the first 4 months of pregnancy (204).

The increase in basal body temperature is not mediated by the uterus, since this effect is also seen in males and hysterectomized females and there is no evidence of local uterine inflammation. After a single 10–15-mg injection of progesterone to males, temperature rises 0.3–0.9° (0.5–1.5°F) for 1–4 days (205). A minimum dose (~10 mg) is required to elicit this rise, beyond which, however, the response is not dose dependent. In the rat, the intact pituitary seems essential in eliciting this thermogenic action; it has been suggested that the hypothalamic thermoregulating centers are involved. On the other hand, neither ovariectomy nor thyroidectomy has any effect (206). It is assumed that the hypothalamic centers lose their responsiveness after extended exposure to progesterone because body temperature falls to pregestational follicular levels after the 4th month of pregnancy (204).

Cardiovascular System—High doses of exogenously administered progesterone can either elevate or lower blood pressure in various species. Daily subcutaneous doses of progesterone reduce blood pressure in rats (15 mg/kg) and dogs (20 mg/kg) with experimental nephrogenic hypertension (207). In studies with patients suffering from either primary or renal hypertension, progesterone (50–200 mg/day im for 10–16 days) significantly decreases blood pressure without loss of sodium (208, 209).

On the other hand, Horrobin (210) reported that prolonged treatment (60 days) of rabbits with large daily doses (25–50 mg) of progesterone results in a moderate (15–25 mm Hg) rise in systolic arterial pressure and causes renal lesions. This effect could be explained partially by considering the increase in aldosterone secretion that accompanies high doses of progesterone, whereas low doses of progesterone are ineffective in increasing aldosterone secretion (211). Moreover, progesterone is a precursor in the biosynthesis of aldosterone and other corticosteroids, a fact that may also explain the clinical finding that some Addisonian patients do well with little or no corticoid therapy during pregnancy.

A rise of systolic blood pressure in the range of 10 mm Hg is observed in certain women taking combined estrogen–progestogen oral contraceptives. A rise of similar magnitude observed with intravenous infusion of estrogens strongly suggests that the estrogen component is responsible for this effect observed with combined oral contraceptives (212).

Exogenous progesterone does not influence the plasma fibrinogen level in the rat, and no changes in platelet number can be observed (213).

Skeletal Growth and Weight Regulation—Injection of progesterone into intact mice (three weekly doses of 10 μg) retards growth, cartilage development, and ossification. In castrated mice of either sex, progesterone somewhat counteracts the effect of gonadectomy by restoring a more regular course of ossification (214). The treatment of rats with progesterone (1 mg/day im for 7 days) markedly decreases the rate of growth of their teeth (215). Plasma growth hormone concentrations after glucose and insulin administration are decreased significantly in normal subjects following progesterone administration (300–400 mg/day im for 3–5 days). Progesterone also impairs growth hormone response to arginine (216). Such observations suggest that placental production of progesterone contributes to the suppression of pituitary release of growth hormone observed in late human pregnancy.

Experiments with female rodents given progesterone at levels closely approximating those of pregnancy (217) indicate the following effects: water retention, protein anabolism (increased nitrogen retention), and appetite stimulation. It has been suggested that these actions are related to the direct influence of progesterone on the hypothalamic food-regulating centers (218). In rats, these effects of progesterone administration on the weight and composition of the body are not present in either males or castrated females (219) but are seen after ovary implantation (220). Hypophysectomy drastically reduces the weight response to progesterone; adrenalectomy, on the other hand, markedly increases it (221, 222).

In humans, nitrogen excretion (as urea) increases with a daily dose of 50 mg of progesterone. This catabolic effect, seen in both sexes and in hypophysectomized and ovariectomized subjects, has been attributed to an increased utilization of amino acids by the liver (223). Progesterone (100 mg/day im) has been used in conjunction with a low calorie diet, digitalis, and diuretics in the treatment of obese patients with alveolar hypoventilation. The therapeutic benefits from progesterone did not appear necessarily associated with weight loss from the treatment but were the result of stimulated ventilation and improvement in the pulmonary status of the obese patients (224).

Microorganisms—Antibacterial action against Gram-positive microorganisms is shown *in vitro* by progesterone (10–20 μg/ml). Progesterone exerts its bacteriostatic action on staphylococci primarily during the first 8 hr of incubation; the effect is reduced by the presence of oxygen (225). In the presence of 20 μg of progesterone/ml, there is a significant decrease in the oxidation by resting staphylococcal suspensions or utilization by staphylococci of pyruvate as an energy source during growth.

The effect of progesterone on Gram-negative organisms seems restricted to members of the genus *Neisseria;* strains of *N. gonorrhoeae* and *N. meningitidis* are sensitive to growth inhibition by progesterone (40 μg/ml) (226). The site of progesterone action appears to be in the cell membrane, where the hormone may bind to proteins (227). Although other factors could contribute, this growth inhibitory effect of progesterone correlates with the observation that, during the menstrual cycle, the lowest isolation rate for *N. gonorrhoeae* from cervical cultures occurs at the peak of progesterone activity (228).

Tumor Growth—A review by Kramer *et al.* (229) concluded that progesterone inhibits the growth of estrogen-induced tumors, except for enhancing the growth of pituitary adenoma. Lipschütz (230) was the first to demonstrate that the subcutaneous implantation of a progesterone pellet in guinea pigs (average absorption calculated to be 40 mg/day over 2 months) reduces the development of estradiol-induced tumors. Continuous administration of progesterone (20-mg pellets sc) also prevents the appearance of mammary tumors in rats exposed to the synergistic carcinogenic effect of radiation (800 Rads) and estrogen (231). In these experiments, progesterone had a protective effect against both the estrogen and combined estrogen–radiation treatments, because fewer tumors occurred on both the irradiated side and the nonirradiated side.

In experimental tumor induction with known carcinogens, tremendous variation in results has been observed, depending on the animal species and strain used and the methods of administering the carcinogens and hormones (232). Prolonged and high doses of progesterone (45 mg/mouse for 9 weeks) or synthetic progestational agents, if administered at a critical time, increased the effect of known carcinogens on the endocervical mucosa. Histological results indicated that parenteral administration of progesterone influences the maturation of 20-methylcholanthrene-induced endocervical carcinoma in mice. Progesterone had, however, no effect on the maturation of induced invasive carcinoma from the vagina and the exocervix (233, 234).

Progesterone (6 mg/week sc for 17 weeks) increased the frequency of metastasis when mammotropic pituitary tumors were transplanted in mice (235). Poel (236) found that progesterone (0.25 ml of 5% progesterone in peanut oil sc/week for 19 weeks) accelerated the development of 20-methylcholanthrene-induced mammary tumors in mice. When 7,12-dimethylbenz[*a*]anthracene (DMBA) was used as a carcinogen, mammary tumorigenesis was significantly enhanced by progesterone treatment if begun just before or after carcinogen administration in intact rats (237) or if given continuously after dimethylbenzanthracene treatment in hypothyroid rats (238). When, on the other hand, progesterone was administered before feeding dimethylbenzanthracene, it prevented the onset of mammary cancers (239) as shown by a reduction in tumor yield; continuation of progesterone after carcinogen administration, however, lessened this reduction in tumor yield (240).

The results of studies on the growth of malignant cells during progesterone administration in susceptible animal strains have questionable relevance in humans. Progesterone and progestational agents have been used successfully in humans in the treatment of endometrial carcinoma (241–246) and with more limited success in the treatment of mammary carcinoma (246). Animal testing, moreover, provides little evidence suggesting that progesterone is tumorigenic *per se.* Evidence that it enhances chemically induced tumorigenesis is at best debatable, considering the variation in response based on pharmacological factors, such as route of administration and local concentration of progesterone, and tumoral factors, such as homogeneity, degree of differentiation, and genetically determined hormonal responsiveness of the tumor cell population.

CLINICAL USE

Progesterone, with its short half-life and extensive degradation following ingestion, has been inconvenient to use effectively in the clinic. Because of these problems, orally effective, synthetic progestational agents frequently have been substituted (247, 248), perhaps unwisely in some cases, since synthetic progestogens recently have been linked with abnormal fetal development (249, 250). Recent successful clinical uses of progesterone have utilized its local administration to a given area, thereby reducing the loss of progesterone to systemic metabolism.

Carcinoma—The role of sex steroids in the development of carcinoma of the endometrium has been the subject of considerable investigation over the past 30 years. It has been suggested that, in some individuals, unopposed, protracted estrogen stimulation of the endometrium may eventually result in carcinoma (251, 252). Because progesterone has a profound modifying effect on the estrogen-prepared endometrium, progesterone has been investigated as a prophylactic and therapeutic drug in the overall management of patients with endometrial or breast cancer and adenomatous hyperplasia.

Patients with metastatic endometrial carcinoma were treated from 3.5 weeks to 4.5 years with progesterone (50 mg three times/week) or hydroxyprogesterone caproate (up to 1 g weekly) (253). In 32% of the cases, objective remissions were obtained, lasting from 1 month to 9 years. Remission rates were similar in studies using progestational agents for the treatment of recurrent endometrial adenocarcinoma (241–246). Regression of endometrial carcinoma following progesterone therapy is ascribed to a direct effect upon the cancer cell rather than to an indirect inhibition of pituitary tropic hormone release.

Progesterone treatment has proved of only limited value, with a success rate of 10%, in the regression of advanced mammary carcinomas (254). The hypothesis that estrogenic stimulation in the absence of sufficient progesterone secretion provides a favorable setting for mammary carcinoma (255) has not been tested epidemiologically.

In early studies on the use of progesterone therapy

for cervical carcinoma, Hertz (256, 257) administered intramuscular injections of 250 mg/day of progesterone to 17 women over periods ranging from 10 to 149 days (a total of 1.5–42.5 g of progesterone/patient). The regressive changes observed were not considered sufficient to justify the use of progesterone as a therapeutic agent in carcinoma of the cervix.

Preliminary studies with the use of progesterone suppositories for vaginal adenosis have been more promising. Using this local mode of hormone administration, five out of five patients achieved regression of their adenosis and a striking reduction in associated redness and inflammation while maintaining normal ovulatory function (258).

Habitual Abortion—The effectiveness of progesterone in protecting pregnancy is not established. Nevertheless, progesterone therapy is sometimes initiated in pregnant women with a history of habitual abortion and in pregnant women who experience blood staining, with or without abdominal cramps. Several medications and different routes of administration may be used, including vaginal, rectal, intramuscular, or intra-amniotic (259, 260). Progesterone (1000 mg/day) has also been administered orally to these patients from the beginning of pregnancy through at least the 36th week of gestation. Of the 52 women receiving oral progesterone and completing the study, 38 were able to maintain pregnancy and deliver full-term infants (261). Synthetic progestogens should not be substituted for progesterone because of their association with fetal masculinization (249) and teratogenicity (250).

Gynecological Disorders—Progesterone and synthetic progestogens have a wide clinical application in the treatment of gynecological disorders such as dysmenorrhea, amenorrhea, and dysfunctional uterine bleeding (247, 248, 262). Synthetic progestogens are used occasionally to attain less painful episodes in patients with primary dysmenorrhea. Progesterone is generally successful in the treatment of secondary amenorrhea. Such steroid therapy is essentially substitutive, replacing the missing endogenous ovarian hormones. For diagnosis of the cause of amenorrhea, a suitable test dose is 50 mg of progesterone injected twice (48 hr apart). Subsequent withdrawal bleeding indicates the production of endogenous estrogen, a responsive endometrium, and a nonpregnant state. Repeated induction of artificial menses usually requires an estrogen for 20 days, followed by a progestational agent for 5 days (248).

The underlying principle of progesterone therapy in the control of dysfunctional uterine bleeding is to raise the blood level of the steroid to a point capable of preventing further disintegration of the bleeding endometrium and then to withdraw the steroid abruptly, causing a rapid exfoliation of the superficial layers and nonsurgical curettage. An intramuscular injection of progesterone (25 mg/day for 5 days) is used to control uterine bleeding.

Contraception—Early studies on its use as an oral contraceptive showed that, at 300 mg/day (5th to 25th day of the menstrual cycle), progesterone was effective in preventing ovulation through four cycles (263). The related effect of larger doses of progesterone on gonadotropin excretion also has been investigated. Rothchild (264) found that continuous or intermittent intravenously administered progesterone (100–400 mg/day) for 10 days depressed the total amount of gonadotropin excreted into the urine. However, Paulsen *et al.* (265) found that oral progesterone at 1000 mg/day for 87 days did not have a significant effect on urinary gonadotropin excretion. The efficacy of progesterone as an oral contraceptive was never fully tested, because synthetic progestational agents, which were orally effective, were available.

Direct administration of progesterone to the uterine lumen, however, has been found a convenient and effective method of contraception (266, 267). In a preliminary clinical study, silicone elastomer devices releasing progesterone were placed in 109 women for two to 13 cycles (a total of 755 woman months). No pregnancies occurred with a functional device *in situ*. Two pregnancies did occur: one when the device was displaced into the cervix and the other when the device was not releasing progesterone. The devices caused suppression in the superficial portion of the endometrium, but a regular menstrual cycle was preserved (164–166).

This method of contraception has since been improved and extensively tested in over 4000 women. Progesterone is released at a rate of 65 μg/day from a T-shaped uterine system[1] for 1 year. At the end of the year, the system is replaced. The efficacy of the uterine system compares favorably with oral contraceptives (267) and it causes no extrauterine systemic steroid effects (169).

TOXICITY

Cell Growth Inhibition—Addition of high concentrations of progesterone (50–200 μg/ml) to tissue cultures of endometrial carcinoma cells is associated with inhibition of DNA synthesis, which results in a decrease in cell survival (246, 268). With adrenal cells, 50% inhibition of growth is accomplished with 7 μg/ml of progesterone (269). The cell growth inhibition value for chick heart ventricular cell cultures is 4 μg/ml of progesterone (270).

Animal Toxicity Studies—The intravenous LD_{50} of progesterone in propylene glycol (20 mg/ml) in rabbits is 26.5 mg/kg. The animals exhibit respiratory convulsions and opisthotonos; the primary cause of death is acute hypoxia (271). Such results, however, cannot reliably represent the acute toxicity of intravenously administered progesterone since propylene glycol itself has an intravenous LD_{50} of 3.2 ml/kg of rabbit body weight (271). The intraperitoneal LD_{100} of progesterone in peanut oil in rats is 327 mg/kg (272).

Oral administration (40 or 160 mg/kg/day) or subcutaneous injections (4 or 16 mg/kg/day) of progesterone suspended in 0.25% carboxymethylcellulose

[1] Progestasert System, Alza Corp., Palo Alto, CA 94304

were carried out for 26 weeks with both male and female rats (273). Mortality in tested animals did not differ from a control group. Gonads were atrophied in both males (prostate) and females (uterus) receiving the high subcutaneous dosage. Hematological values determined throughout the experiment were unremarkable, as were microscopic examinations of organ tissues at termination of the experiment. In males, body and organ weights did not differ from those of controls. The only significant changes at these dose levels occurred in female animals receiving subcutaneous treatment. These animals exhibited an increase in body and liver weights. This increase in liver weight was not significant, however, when expressed as a ratio to body weight.

Prenatal Exposure—Using an egg transfer technique, Dickmann (274) determined the effect of progesterone on the survival of rat morulae. Morulae degenerated in the uteri of recipients that had been ovariectomized and injected daily with 2 mg of progesterone. No deleterious effect to the blastocyst could be observed. Progesterone concentrations below 2 μg/ml produced no noticeable effects on the development of the mouse ova *in vitro*; concentrations above 4 μg/ml inhibited ova development by blocking cleavage, particularly at the blastula stage (275). This action was reversible, with ova resuming cleavage when placed in progesterone-free media.

Using subcontraceptive levels of progesterone in rabbits (2 mg sc near ovulation), Allen and Foote (276) concluded that progesterone suppressed the development of zygotes into blastocysts, but that once implanted successfully, all treated embryos developed normally and were equivalent to controls during their postnatal development. The mechanism of this action of progesterone on mammalian ova *in vitro* seems to result from an inhibition in transfer of amino acids or soluble proteins across the cell membrane, thereby inhibiting protein synthesis within the ovum (277).

Various progesterone effects on the fetus occur in the pregnant rat, depending upon dosage and time of administration. For instance, progesterone (5 mg/day im) injected on Days 16 through 19 had no effect, but the same dosage on Days 20 through 23 caused fetal death (278, 279). There is no agreement on the hypothesis that fetal death is related to the prolonged delay of parturition due to progesterone administration (279). In the pregnant swine, progesterone (2 mg/kg/day sc) between Day 0 and Day 25 of gestation did not increase the expected embryonic survival rate, indicating that early embryonal mortality is not due to a deficiency of progesterone in this species (280, 281).

In a study of the effects of some known teratogens (*e.g.*, ergocornine) on the course of gestation in rats, it was concluded that the mechanism for teratogenic action is mediated, at least in part, by a progesterone deficiency resulting from the use of the teratogen (282). The administration of 1 mg of ergocornine on the 8th day seriously disturbed pregnancy and increased the incidence of fetal malformations. Progesterone treatment (5 mg/day) given concomitantly with the teratogen allowed pregnancy to proceed according to a more normal pattern (282). The embryolethal effect of certain drugs, such as actinomycin D, is also decreased by progesterone treatment. For instance, subcutaneous injections of progesterone (4 mg/day between the 8th and 21st day of gestation) in actinomycin D-treated rats increased the number of live fetuses and reduced the number of nonviable implantations (283).

The possibility of fetal masculinization by progesterone treatment has been reviewed and experimentally investigated (284). Pregnant rats were treated from the 16th to the 19th day of gestation with 4–274 mg of progesterone (1–75 mg/day). All female fetuses exhibited normally developed genitalia, and it was concluded that there is little or no risk of masculinization of female infants.

Some cases of human female pseudohermaphroditism were reported following administration of synthetic progestogens during gestation to mothers treated for habitual or threatened abortion (285). These data describe synthetic progestogens that exhibit masculinizing properties and in no way argue against the use of progesterone (249). This virilizing effect of synthetic progestogens upon the female fetus seems to be attributable to the androgenic properties of the steroids, since it is well established that the administration of androgens during pregnancy leads to masculinization in both laboratory animals and humans (286).

Hagler *et al.* (287) summarized the effect of steroid administration to mothers during early pregnancy on the incidence of male pseudohermaphroditism. At that time (1963), there were only three cases where progesterone was given alone (37.5–200 mg iv weekly for up to 17 weeks), and in none did male pseudohermaphroditism occur. One infant was anencephalic, but there is no reason to believe that malformation was due to a progesterone effect.

Progesterone therapy, sometimes initiated in pregnant women, causes no adverse effect to the fetus. On the other hand, synthetic progestogens or estrogen–progestogen combinations—given in cases of threatened abortions, pregnancy tests, or as oral contraceptives—have been associated with a variety of congenital abnormalities. These include hypospadia (288), transposition of the great vessels (289), CNS malformation (290, 291), and other anomalies (292–294). These preliminary clinical findings clearly indicate the need to ascertain the absence of pregnancy before initiation of oral contraception (estrogen and/or synthetic progestogen) and strongly suggest that hormonal agents are contraindicated as pregnancy tests (250).

Studies of fetal development under the influence of progestational agents point out the need to differentiate clearly between the use of synthetic progestogens and progesterone (295). Progesterone, which is secreted in large quantities during gestation, is necessary to maintain the early stages of pregnancy. Progesterone has not been found harmful to the developing fetus and, in fact, may be beneficial to it (295, 296). Infants born to women using an intrauterine

device that releases progesterone to the uterine lumen have been normal[2].

Neonatal Exposure—Early postnatal damage in neonate rodents caused by estrogens or androgens can be blocked by progesterone. Progesterone (3 mg im) prevented the alteration of gonadal function produced by injecting androgen into female rats and estrogen into male rats (297). Such observations suggest that certain human hypogonadal syndromes or infertility may result in part from decreased or abnormal steroidogenesis during fetal life. The neonate mouse is highly sensitive to progesterone. The following pattern is observed: between 0 and 24 hr, LD_{50} = 70 mg/kg; between 49 and 72 hr, LD_{50} = 1200 mg/kg; and between 121 and 168 hr, LD_{50} = 2700 mg/kg (298).

These results suggest that the neonate mouse does not have the enzymatic ability necessary to metabolize the injected progesterone and that anatomical barriers preventing elevated concentrations in certain organ systems (*e.g.*, CNS) are not yet fully developed. The injection of a single dose of progesterone (1 mg) to 5-day-old female mice resulted in a delay in sexual maturity and a decrease in fertility of the animals, although estrous cycles were normal (299). Even though no dose–effect relationship has been established, proper progesterone level during the neonatal period appears essential for the adequate gonadal development and function.

REFERENCES

(1) "Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents," vol. I, International Encyclopedia of Pharmacology and Therapeutics, sect. 48, M. Tausk, Ed., Pergamon, New York, N.Y., 1971.

(2) "The Gestagens," Handbook of Experimental Pharmacology, vol. XXII/I, K. Junkmann, Ed., Springer-Verlag, New York, N.Y., 1968.

(3) J. Zander, F. Forbes, A. von Münstermann, and R. Neher, *J. Clin. Endocrinol. Metab.*, **18,** 337(1958).

(4) E. Diczfalusy, *Acta Endocrinol.*, **10,** 373(1952).

(5) A. M. Moses, J. Lobotsky, and C. W. Lloyd, *J. Clin. Endocrinol. Metab.*, **19,** 987(1959).

(6) A. Riondel, J. F. Tait, S. A. S. Tait, M. Gut, and B. Little, *ibid.*, **25,** 229(1965).

(7) T. J. Lin, S. C. Lin, F. Erlenmeyer, I. T. Kline, R. Underwood, R. Billiar, and B. Little, *ibid.*, **34,** 287(1972).

(8) O. V. Dominguez, G. D. Francois, M. Watanabe, and S. Solomon, *Proc. Meet. Endocrine Soc., 44th*, **35,** 17(1962).

(9) S. Solomon, M. Watanabe, O. V. Dominguez, M. J. Gray, C. I. Meekey, and E. A. H. Sims, *Excerpta Med. Found. Int. Congr. Ser.*, **51,** 267(1962).

(10) W. H. Pearlman, *Ciba Found. Colloq. Endocrinol.*, **11,** 233(1957).

(11) K. Block, *J. Biol. Chem.*, **157,** 661(1945).

(12) D. B. Bartosik and E. B. Romanoff, "The Gonads," K. W. Mc Kerns, Ed., North-Holland Publishing Co., Amsterdam, The Netherlands, 1969, p. 211.

(13) S. Dell'Acqua, S. Mancuso, M. Catelli, and A. Bompiani, *Acta Endocrinol.*, **75,** 368(1974).

(14) N. R. Mason and K. Savard, *Endocrinology*, **75,** 215(1964).

(15) B. I. Tamaoki and G. Pincus, *ibid.*, **69,** 527(1961).

(16) W. Y. Huang and W. H. Pearlman, *J. Biol. Chem.*, **237,** 1060(1962).

(17) B. F. Rice and A. Segaloff, *Acta Endocrinol.*, **51,** 131(1966).

(18) K. Savard and G. Telegdy, *Steroids, Suppl. II*, **1965,** 205.

(19) M. L. Sweat, D. Berliner, M. Bryson, C. Nabors, J. Haskell, and E. Holmstrom, *Biochim. Biophys. Acta*, **40,** 289(1960).

(20) K. J. Ryan and Z. Petro, *J. Clin. Endocrinol. Metab.*, **26,** 46(1966).

(21) K. J. Ryan and O. W. Smith, *J. Biol. Chem.*, **236,** 705(1961).

(22) M. E. Davis and E. J. Plotz, *Recent Progr. Horm. Res.*, **13,** 347(1957).

(23) H. W. Jones and P. G. Weil, *J. Amer. Med. Ass.*, **111,** 519(1938).

(24) H. A. Salhanick, M. W. Noall, M. X. Zarrow, and L. T. Samuels, *Science*, **115,** 708(1952).

(25) W. H. Pearlman and E. Cerceo, *Endocrinology*, **53,** 599(1953).

(26) O. Cassmer, *Acta Endocrinol., Suppl.*, **45,** 1(1959).

(27) E. Diczfalusy and U. Borell, *J. Clin. Endocrinol. Metab.*, **21,** 1119(1961).

(28) R. B. Jaffe, *Excerpta Med., Series No. 111*, **1966,** 547.

(29) R. Pion, R. B. Jaffe, G. Eriksson, N. Wiqvist, and E. Diczfalusy, *Acta Endocrinol.*, **48,** 234(1965).

(30) R. Palmer, G. Eriksson, N. Wiqvist, and E. Diczfalusy, *ibid.*, **52,** 598(1966).

(31) K. J. Ryan, R. A. Meigs, and Z. Petro, *Amer. J. Obstet. Gynecol.*, **96,** 676(1966).

(32) D. M. Okada, D. Tulchinsky, J. W. Ross, and C. J. Hobel, *ibid.*, **119,** 502(1974).

(33) S. Furuyama and C. A. Nugent, *Steroids*, **17,** 663(1971).

(34) E. D. B. Johansson, *Acta Endocrinol.*, **61,** 592(1969).

(35) C. M. Cargille, G. T. Ross, and T. Toshimi, *J. Clin. Endocrinol. Metab.*, **29,** 12(1969).

(36) C. Fassorra and M. Luisi, *Hormones*, **2,** 153(1971).

(37) E. D. B. Johansson, *Acta Endocrinol.*, **61,** 607(1969).

(38) A. Csapo, E. Knobil, H. Van der Molen, and W. Wiest, *Amer. J. Obstet. Gynecol.*, **110,** 630(1971).

(39) J. L. Llauró, B. Runnebaum, and J. Zander, *ibid.*, **101,** 867(1968).

(40) G. Mikhail, J. Zander, and W. M. Allen, *J. Clin. Endocrinol. Metab.*, **23,** 1267(1963).

(41) C. W. Lloyd, J. Lobotsky, D. T. Baird, J. H. McCracken, J. Weisz, M. Pupkin, J. Zanartu, and J. Puga, *ibid.*, **32,** 155(1971).

(42) F. Fuchs, A. R. Fuchs, and R. V. Short, *J. Endocrinol.*, **27,** 333(1963).

(43) G. Mikhail and W. M. Allen, *Amer. J. Obstet. Gynecol.*, **99,** 308(1967).

(44) W. J. LeMaire, P. W. Conly, A. Moffett, and W. W. Cleveland, *ibid.*, **108,** 132(1970).

(45) B. Runnebaum and J. Zander, *Acta Endocrinol., Suppl.*, **150,** 5(1971).

(46) I. Nilsson, *Acta Obstet. Gynecol. Scand.*, **51,** 117(1972).

(47) A. C. Barnes, D. Kumar, and J. A. Goodno, *Amer. J. Obstet. Gynecol.*, **84,** 1207(1962).

(48) D. Kumar and A. C. Barnes, *ibid.*, **92,** 717(1965).

(49) J. Zander and B. Runnebaum, *Acta Endocrinol.*, **54,** 19(1967).

(50) W. G. Wiest, *Steroids*, **10,** 279(1967).

(51) K. Hagenfeldt and B. M. Landgren, *J. Steroid Biochem.*, **6,** 895(1975).

(52) H. Grundsell, I. Nilsson, and S. Nordqvist, *Lancet*, **1,** 888(1973).

(53) E. D. B. Johansson, *Acta Obstet. Gynecol. Scand., Suppl.*, **19,** 17(1972).

(54) U. Westphal, B. D. Ashley, and G. L. Selden, *Arch. Biochem. Biophys.*, **92,** 441(1961).

(55) R. V. Short, *J. Endocrinol.*, **16,** 415(1958).

(56) R. M. Burton, G. B. Harding, N. Rust, and U. Westphal, *Steroids*, **17,** 1(1971).

(57) G. B. Harding, R. M. Burton, S. D. Stroupe, and U. Westphal, *Life Sci.*, **14,** 2405(1974).

(58) E. Milgrom, P. Allouch, M. Atger, and E. E. Baulieu, *J. Biol. Chem.*, **248,** 1106(1973).

(59) E. Milgrom, P. Allouch, and M. Atger, *Methods Enzymol.*, **36,** 120(1975).

(60) A. A. Sandberg and W. R. Slaunwhite, *J. Clin. Endocrinol. Metab.*, **18,** 253(1958).

[2] Alza Corp., Palo Alto, CA 94304, unpublished results.

(61) J. H. H. Thijssen and J. Zander, *Acta Endocrinol.*, **51,** 563(1966).
(62) P. Fylling, *ibid.*, **65,** 284(1970).
(63) T. J. Lin, R. B. Billiar, and B. Little, *J. Clin. Endocrinol. Metab.*, **35,** 879(1972).
(64) B. Little, R. B. Billiar, J. Bougas, and J. F. Tait, *ibid.*, **36,** 1222(1973).
(65) W. H. Pearlman, *Excerpta Med. Found. Int. Congr. Ser.*, **51,** Abst. 11, 15(1962).
(66) M. L. Sweat and M. J. Bryson, *Amer. J. Obstet. Gynecol.*, **106,** 193(1970).
(67) P. L. Langlois, *J. Reprod. Med.*, **4,** 31(1970).
(68) K. Fotherby, *Vitam. Horm. (N.Y.)*, **22,** 153(1964).
(69) M. E. Davis, E. J. Plotz, G. V. LeRoy, R. G. Gould, and H. Werbin, *Amer. J. Obstet. Gynecol.*, **72,** 740(1956).
(70) H. Askalani, M. Smuk, J. Sugar, P. Delvoye, C. Robyn, and J. Schwers, *ibid.*, **118,** 1054(1974).
(71) G. E. Abraham, G. B. Maroulis, and J. R. Marshall, *Obstet. Gynecol.*, **44,** 522(1974).
(72) R. A. Harkness, D. W. Davidson, and J. A. Strong, *Acta Endocrinol.*, **60,** 221(1969).
(73) A. H. Conney and J. J. Burns, *Science*, **178,** 576(1972).
(74) A. H. Conney, M. Jacobson, W. Levin, K. Scheidman, and R. Kuntzman, *J. Pharmacol. Exp. Ther.*, **154,** 310(1966).
(75) E. C. Gomez, P. Frost, and S. L. Hsia, *J. Invest. Dermatol.*, **64,** 240(1975).
(76) T. Tabei, H. Haga, W. L. Heinrichs, and W. L. Hermann, *Steroids*, **23,** 651(1974).
(77) F. A. Kincl, in "Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents," vol. I, International Encyclopedia of Pharmacology and Therapeutics, sect. 48, M. Tausk, Ed., Pergamon, New York, N.Y., 1971, pp. 13–64.
(78) H. G. Spies, C. J. Mahoney, R. L. Norman, D. K. Clifton, and J. A. Resko, *J. Clin. Endocrinol. Metab.*, **39,** 347(1974).
(79) T. M. Plant, V. H. T. James, and R. P. Michael, *J. Endocrinol.*, **51,** 751(1971).
(80) J. Chamberlain, B. A. Knights, and G. H. Thomas, *ibid.*, **28,** 235(1964).
(81) J. d'A. Jeffery, *ibid.*, **34,** 387(1966).
(82) L. P. Romanoff, M. Grace, E. M. Sugarman, and G. Pincus, *Gen. Comp. Endocrinol.*, **3,** 649(1963).
(83) T. Shinada and K. J. Ryan, *Steroids*, **21,** 233(1973).
(84) J. W. Goldzieher and L. R. Axelrod, *Gen. Comp. Endocrinol.*, **13,** 201(1969).
(85) B. D. Kulkarni, C. S. Kammer, and J. W. Goldzieher, *ibid.*, **14,** 68(1970).
(86) B. W. O'Malley and A. R. Means, *Science*, **183,** 610(1974).
(87) E. V. Jensen and E. R. DeSombre, *ibid.*, **182,** 126(1973).
(88) I. S. Edelman, *J. Steroid Biochem.*, **6,** 147(1975).
(89) R. G. Smith, C. A. Iramain, V. C. Buttram, and B. O'Malley, *Nature*, **253,** 271(1975).
(90) U. Verma and K. R. Laumas, *Biochim. Biophys. Acta*, **317,** 403(1973).
(91) W. T. Schrader, *Methods Enzymol.*, **36,** 187(1975).
(92) D. Philibert and J. P. Raynaud, *Contraception*, **10,** 457(1974).
(93) J. L. McGuire, C. D. Bariso, and B. S. Fuller, *Acta Endocrinol.*, **75,** 579(1974).
(94) P. C. Young and R. E. Cleary, *J. Clin. Endocrinol. Metab.*, **39,** 425(1974).
(95) D. V. Illingworth, G. P. Wood, G. L. Flickinger, and G. Mikhail, *ibid.*, **40,** 1001(1975).
(96) B. R. Rao, W. G. Wiest, and W. M. Allen, *Endocrinology*, **95,** 1275(1974).
(97) J. L. McGuire and C. DeDella, *ibid.*, **88,** 1099(1971).
(98) P. D. Feil, S. R. Glasser, D. O. Toft, and B. W. O'Malley, *ibid.*, **91,** 738(1972).
(99) W. W. Leavitt and C. J. Grossman, *Proc. Nat. Acad. Sci. USA*, **71,** 4341(1974).
(100) W. T. Schrader, S. H. Socher, and R. E. Buller, *Methods Enzymol.*, **36,** 292(1975).
(101) S. J. Segal, R. Ige, and M. Burgos, in "Physiology and Genetics of Reproduction," Part A, E. M. Coutinho and F. Fuchs, Eds., Plenum, New York, N.Y., 1973, pp. 99–112.
(102) E. Milgrom, M. Luu Thi, and E. E. Baulieu, *Acta Endocrinol., Suppl. 180,* **74,** 380(1973).
(103) M. Haukkamaa and T. Luukkainen, *J. Steroid Biochem.*, **5,** 447(1974).
(104) E. Milgrom, M. Atger, M. Perrot, and E. E. Baulieu, *Endocrinology*, **90,** 1071(1972).
(105) W. W. Leavitt, D. O. Toft, C. A. Strott, and B. W. O'Malley, *ibid.*, **94,** 1041(1974).
(106) D. O. Toft and B. W. O'Malley, *ibid.*, **90,** 1041(1972).
(107) E. Milgrom, M. Luu Thi, M. Atger, and E. E. Baulieu, *J. Biol. Chem.*, **248,** 6366(1973).
(108) K. Pollow, H. Luebbert, E. Boquoi, G. Kreuzer, and B. Pollow, *Endocrinology*, **96,** 319(1975).
(109) K. B. Horwitz, W. L. McGuire, O. H. Pearson, and A. Segaloff, *Science*, **189,** 726(1975).
(110) M. A. Yussman, M. L. Taymor, J. Miyara, and C. Phetteplace, *Fertil. Steril.*, **21,** 119(1970).
(111) U. Goebelsmann, A. R. Midgley, Jr., and R. B. Jaffe, *J. Clin. Endocrinol. Metab.*, **29,** 1222(1969).
(112) K. S. Moghissi, F. N. Syner, and T. N. Evans, *Amer. J. Obstet. Gynecol.*, **114,** 405(1972).
(113) E. Johansson and L. Wide, *Acta Endocrinol.*, **62,** 82(1969).
(114) S. M. McCann, *Amer. J. Physiol.*, **202,** 601(1962).
(115) V. C. Stevens and N. Vorys, *Obstet. Gynecol. Surv.*, **22,** 781(1967).
(116) R. V. Short, *Recent Progr. Horm. Res.*, **20,** 303(1964).
(117) F. C. Hagemenas and G. W. Kittinger, *Endocrinology*, **94,** 922(1974).
(118) L. P. Bengtsson and P. M. Ejarque, *Acta Obstet. Gynecol. Scand.*, **43,** 49(1964).
(119) P. M. Ejarque and L. P. Bengtsson, *Acta Endocrinol.*, **44,** 521(1962).
(120) W. M. Allen, *Gynecol. Invest.*, **5,** 142(1974).
(121) J. W. Everett, *Physiol. Rev.*, **44,** 373(1964).
(122) G. H. Zeilmaker, in "Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents," vol. I, International Encyclopedia of Pharmacology and Therapeutics, sect. 48, M. Tausk, Ed., Pergamon, New York, N.Y., 1971, pp. 331–352.
(123) G. Pincus, "The Control of Fertility," Academic, New York, N.Y., 1965.
(124) M. Sar and W. Stumpf, *Science*, **182,** 1266(1973).
(125) W. L. Herrmann, W. L. Heinrichs, and T. Tabei, *Amer. J. Obstet. Gynecol.*, **117,** 679(1973).
(126) A. Wirz-Justice, E. Hackmann, and M. Lichtsteiner, *J. Neurochem.*, **22,** 187(1974).
(127) E. I. Kohorn and R. Tchao, *J. Endocrinol.*, **45,** 401(1969).
(128) H. Schmidt-Matthiesen, "The Normal Human Endometrium," McGraw-Hill, New York, N.Y., 1963.
(129) H. Schmidt-Matthiesen, in "Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents," vol. I, International Encyclopedia of Pharmacology and Therapeutics, sect. 48, M. Tausk, Ed., Pergamon, New York, N.Y., 1971, pp. 457–486.
(130) A. Franceschelli, *Monit. Obstet. Ginecol. Endocrinol. Metab.*, **34,** 330(1963).
(131) W. Lindenschmidt and T. Zeile, *Zentralbl. Gynaekol.*, **84,** 577(1962).
(132) F. V. Lucas, *Amer. J. Obstet. Gynecol.*, **88,** 965(1964).
(133) W. Luh and H. Brandau, *Z. Geburtshilfe Gynaekol.*, **168,** 14(1967).
(134) A. P. Baker, F. Bergman, and K. G. Paul, *Acta Endocrinol.*, **54,** 696(1967).
(135) L. Bjersing and N. E. Borglin, *Acta Pathol. Microbiol. Scand.*, **60,** 27(1964).
(136) T. H. Brinsfield, H. W. Hawk, and H. F. Righter, *J. Reprod. Fert.*, **8,** 293(1964).
(137) H. W. Hawk, G. D. Turner, and T. H. Brinsfield, *Amer. J. Vet. Res.*, **24,** 595(1963).
(138) J. E. Nellor, *Anat. Rec.*, **151,** 171(1965).
(139) L. P. Bengtsson, in "Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents," vol. I, International Encyclopedia of Pharmacology and Therapeutics, sect. 48, M. Tausk, Ed., Pergamon, New York, N.Y., 1971, pp. 487–517.
(140) A. H. Moawad and L. P. Bengtsson, *Amer. J. Obstet. Gynecol.*, **98,** 1057(1967).
(141) L. P. Bengtsson, *Acta Obstet. Gynecol. Scand., Suppl. 6,*

49, 5(1970).
(142) A. I. Csapo, C. E. R. DeMattos, and M. B. DeSousa Filho, *Amer. J. Obstet. Gynecol.*, **87,** 793(1963).
(143) D. G. Porter and H. R. Behrman, *Nature*, **232,** 627(1971).
(144) A. I. Csapo, O. Pohanka, and H. L. Kaihola, *Brit. Med. J.*, **1,** 137(1974).
(145) J. M. Marshall and A. I. Csapo, *Endocrinology*, **68,** 1026(1961).
(146) A. Lanza, *J. Obstet. Gynaecol. Brit. Commonw.*, **81,** 568(1974).
(147) D. Kumar, P. R. Adams, and A. C. Barnes, *Nature*, **205,** 701(1965).
(148) M. Cohen, *Fertil. Steril.*, **21,** 715(1970).
(149) J. Ferin, in "Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents," vol. I, International Encyclopedia of Pharmacology and Therapeutics, sect. 48, M. Tausk, Ed., Pergamon, New York, N.Y., 1971, pp. 441–456.
(150) G. D. London and P. B. Lawrence, *Fertil. Steril.*, **18,** 1(1967).
(151) E. Kesserii, P. Camacho-Ortega, G. Laudahn, and G. Schöpflin, *ibid.*, **26,** 57(1975).
(152) T. Mann and L. C. Prosser, *Biol. Bull. (Woods Hole, Mass.)*, **125,** 384(1963).
(153) M. Freund, *Bibliogr. Reprod.*, **15,** 1(1970).
(154) M. Bygdeman, *Mem. Soc. Endocrinol.*, **14,** 49(1966).
(155) V. R. Pickles and R. J. Fitzpatrick, "Symposium on Endogenous Substances Affecting the Myometrium," vol. 14, Society for Endocrinology, Cambridge University Press, New York, N.Y., 1966.
(156) V. R. Pickles, W. J. Hall, P. C. Clegg, and T. J. Sullivan, in *ibid.*, p. 89.
(157) C. R. Austin, *Int. J. Fertil.*, **12,** 25(1967).
(158) M. C. Chang, *Endocrinology*, **63,** 619(1958).
(159) R. Deanesly, in "Marshall's Physiology of Reproduction," A. Parkes, Ed., Little, Brown, Boston, Mass., 1966.
(160) A. McLaren, *J. Reprod. Fertil., Suppl.*, **18,** 159(1973).
(161) R. Courrier, *Vitam. Horm. (N.Y.)*, **8,** 179(1950).
(162) G. Mayer, in "Delayed Implantation," A. C. Enders, Ed., University of Chicago Press, Chicago, Ill., 1963, pp. 213–228.
(163) B. Seshadri, Y. Gibor, and A. Scommegna, *Amer. J. Obstet. Gynecol.*, **109,** 536(1971).
(164) A. Scommegna, G. N. Pandya, M. Christ, A. W. Lee, and M. R. Cohen, *Fertil. Steril.*, **21,** 201(1970).
(165) A. Scommegna, *Atti Semin. Int. Sui Problemi Med. Sociale Controllo Fecondito*, **1972,** 161.
(166) G. N. Pandya and A. Scommegna, *Excerpta Med. Found. Int. Congr. Ser. No. 246*, **VII,** 103(1972).
(167) Y. Gibor, *Amer. J. Obstet. Gynecol.*, **109,** 542(1971).
(168) S. A. Tillson, B. B. Pharriss, and J. D. Neill, *J. Steroid Biochem.*, **5,** 376(1974).
(169) S. A. Tillson, M. Marian, R. Hudson, P. Wong, B. Pharriss, R. Aznar, and J. Martinez-Manautou, *Contraception*, **11,** 179(1975).
(170) J. Martinez-Manautou, M. Maqueo, R. Aznar, B. Pharriss, and A. Zaffaroni, *Amer. J. Obstet. Gynecol.*, **121,** 175(1975).
(171) M. C. Chang, *Endocrinology*, **81,** 1251(1967).
(172) M. Roland, *Bull. N. Y. Acad. Med.*, **45,** 681(1969).
(173) A. Rosado, J. J. Hicks, R. Aznar, and E. Mercado, *Contraception*, **9,** 39(1974).
(174) International Academy of Gynecological Cytology, *Acta Cytol.*, **3,** 197(1959).
(175) *Ibid.*, **4,** 221(1960).
(176) G. Jones and E. B. Astwood, *Endocrinology*, **30,** 295(1942).
(177) J. Ferin, J. Bonte, and J. Vassilopoulos, *Bull. Soc. R. Belge Gynecol. Obstet.*, **25,** 265(1955).
(178) G. K. Benson, A. T. Cowie, C. P. Cox, and S. A. Goldzveig, *J. Endocrinol.*, **15,** 126(1957).
(179) J. Hilgers, in "Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents," vol. I, International Encyclopedia of Pharmacology and Therapeutics, sect. 48, M. Tausk, Ed., Pergamon, New York, N.Y., 1971, pp. 83–101.
(180) H. Selye, *Proc. Soc. Exp. Biol. Med.*, **43,** 343(1940).
(181) C. G. Hartman and H. Speert, *Endocrinology*, **29,** 639(1941).
(182) D. G. Hall, M. S. Fahim, Z. Fahim, R. Der, and G. Dement, *J. Reprod. Med.*, **6,** 116(1971).
(183) C. S. Song and A. Kappas, *Vitam. Horm. (N.Y.)*, **26,** 147(1968).
(184) A. Kappas and R. H. Palmer, *Pharmacol. Rev.*, **15,** 123(1963).
(185) M. Kramer, L. Damrosch, and G. Klink, in "Die Gestagene, Handbook of Experimental Pharmacology," vol. XXII/I, K. Junkmann, Ed., Springer-Verlag, New York, N.Y., 1968, p. 512.
(186) C. A. De Groot, M. T. van der Lely, and R. Kooij, *Brit. J. Dermatol.*, **77,** 617(1965).
(187) C. H. Sawyer, M. Kawakami, and S. Kanematsu, *Res. Publ., Ass. Nerv. Ment. Dis.*, **43,** 59(1966).
(188) M. Tausk and J. De Visser, in "Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents," vol. I, International Encyclopedia of Pharmacology and Therapeutics, sect. 48, M. Tausk, Ed., Pergamon, New York, N.Y., 1971, pp. 375–387.
(189) D. A. Hamburg, *Res. Publ. Ass. Nerv. Ment. Dis.*, **43,** 251(1966).
(190) B. C. Little, R. J. Matta, and T. Zahn, *J. Nerv. Ment. Dis.*, **159,** 256(1974).
(191) F. T. Melges, *Psychosom. Med.*, **30,** 95(1968).
(192) K. Kyger and B. Webb, *Amer. J. Obstet. Gynecol.*, **113,**759(1972).
(193) M. T. Epstein, J. M. Hockaday, and T. D. R. Hockaday, *Lancet*, **1,** 543(1975).
(194) H. Selye, *J. Pharmacol.*, **73,** 127(1941).
(195) H. Selye, *Endocrinology*, **30,** 437(1942).
(196) F. Navratil-Brunel, thesis, Montpellier, France, 1967.
(197) K. H. Raisinghani, R. I. Dorfman, E. Forchielli, L. Gyermek, and G. Genther, *Acta Endocrinol.*, **57,** 395(1968).
(198) S. K. Figdor, M. J. Kodet, B. M. Bloom, E. J. Agnello, S. Y. Pan, and G. D. Laubach, *J. Pharmacol.*, **119,** 299(1957).
(199) W. Merryman, R. Boiman, L. Barnes, and J. Rothchild, *J. Clin. Endocrinol. Metab.*, **14,** 1567(1954).
(200) D. E. Wooley and P. S. Timiras, *Endocrinology*, **70,** 196(1962).
(201) J. Laidlaw, *Lancet*, **2,** 1235(1956).
(202) F. Morrell, *Neurology*, **9,** 352(1959).
(203) E. D. B. Johansson, U. Larsson-Cohn, and C. Gemzell, *Amer. J. Obstet. Gynecol.*, **113,** 933(1972).
(204) J. Klein, *Geburtshilfe Frauenheilkd.*, **11,** 418(1951).
(205) J. Rothchild and A. Barnes, *Endocrinology*, **50,** 485(1952).
(206) M. E. Freeman, J. K. Crissman, Jr., G. N. Louw, R. L. Butcher, and E. K. Inskeep, *ibid.*, **86,** 717(1970).
(207) J. G. Armstrong, *Proc. Soc. Exp. Biol. Med.*, **102,** 452(1959).
(208) J. Genest, W. Nowaczynski, E. Koiw, T. Sandor, and P. Biron, in "Essential Hypertension," K. D. Block and P. Cottier Eds., Springer-Verlag, Berlin, Germany, 1960 (English Edition, 1962), pp. 126–146.
(209) L. De Soldati, I. E. De Fortega, C. R. Pellegatta, and H. Cammarota, *Cardiologia*, **48,** 489(1966).
(210) D. F. Horrobin, *Lancet*, **1,** 1390(1972).
(211) G. Telegdy and K. Lissák, *Acta Physiol. Acad. Sci. Hung.*, **26,** 313(1965).
(212) R. J. Weir, *Lancet*, **1,** 467(1971).
(213) J. S. Noumoff, T. Schoendorf, W. Theiss, and F. K. Beller, *J. Reprod. Med.*, **9,** 55(1972).
(214) R. Silberberg and M. Silberberg, *Exp. Med. Surg.*, **23,** 157(1965).
(215) K. Masuda, *Nichidai Igaku Zasshi*, **19,** 3813(1960).
(216) S. K. Bhatia, D. Moore, and R. Kalkhoff, *J. Clin. Endocrinol. Metab.*, **35,** 364(1972).
(217) D. W. Bullock and B. Cook, *J. Endocrinol.*, **37,** 382(1967).
(218) A. D. Dewar, *J. Reprod. Fertil., Suppl.*, **9,** 17(1969).
(219) G. Bourdel and R. Jacquot, *Arch. Sci. Physiol.*, **19,** 99(1965).
(220) E. Hervey and G. R. Hervey, *J. Endocrinol.*, **37,** 361(1967).
(221) E. Hervey, G. R. Hervey, and P. M. Zamboanga, "Second International Congress on Hormonal Steroids," Excerpta Medica Foundation, Amsterdam, The Netherlands, 1966, p. 190.
(222) M. Tausk and J. De Visser, in "Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents," vol. I, International Encyclopedia

of Pharmacology and Therapeutics, sect. 48, M. Tausk, Ed., Pergamon, New York, N.Y., 1971, pp. 361–366.
(223) R. L. Landau and K. Lugibihl, in "Recent Progress in Hormone Research," vol. XVII, G. Pincus, Ed., Academic, New York, N.Y., 1961, pp. 249–281.
(224) R. S. Rivlin, *N. Engl. J. Med.*, **292,** 26(1975).
(225) W. Yotis and R. Stanke, *J. Bacteriol.*, **92,** 1285(1966).
(226) S. A. Morse and T. J. Fitzgerald, *Infect. Immunol.*, **10,** 1370(1974).
(227) M. Ciavatti, G. Michel, B. Chataing, and A. Jouvenceux, *Biochem. Med.*, **9,** 293(1974).
(228) M. L. Koch, *Amer. J. Obstet. Gynecol.*, **59,** 168(1950).
(229) M. Kramer, L. Damrosch, and G. Klink, in "Die Gestagene, Handbook of Experimental Pharmacology," vol. XXII/I, K. Junkmann, Ed., Springer-Verlag, New York, N.Y., 1968, pp. 597–679.
(230) A. Lipschütz, *J. Amer. Med. Ass.*, **120,** 171(1942).
(231) A. Segaloff, *Cancer Res.*, **33,** 1136(1973).
(232) K. A. Karande and K. J. Ranadive, *Brit. J. Cancer,* **28,** 299(1973).
(233) S. Reboud and G. Pageaut, *Nature,* **241,** 398(1973).
(234) S. Blanzat-Reboud and A. Russfield, *Amer. J. Obstet. Gynecol.*, **103,** 46(1969).
(235) W. E. Poel and H. Haran-Ghera, *Lancet,* **2,** 970(1963).
(236) W. E. Poel, *Brit. J. Cancer,* **19,** 824(1965).
(237) A. G. Jabara and A. G. Harcourt, *Pathology,* **2,** 115(1970).
(238) A. G. Jabara and J. S. Maritz, *Brit. J. Cancer,* **28,** 161(1973).
(239) G. S. Kledzik, C. J. Bradley, and J. Meites, *Cancer Res.*, **34,** 2953(1974).
(240) A. Jabara, P. H. Toyne, and A. G. Harcourt, *Brit. J. Cancer,* **27,** 63(1973).
(241) W. Wentz, *Obstet. Gynecol.*, **24,** 370(1964).
(242) J. B. Bonte, *Acta Obstet. Gynecol. Scand., Suppl. 19,* **51,** 21(1972).
(243) G. Malkasian, D. G. Decker, E. Mussey, and C. E. Johnson, *Amer. J. Obstet. Gynecol.*, **110,** 15(1971).
(244) J. G. Peck and D. A. Boyes, *ibid.*, **103,** 90(1969).
(245) J. A. Collins and D. M. Jewkes, *ibid.*, **120,** 779(1974).
(246) B. A. Stoll, *Clin. Obstet. Gynecol.*, **16** (4), 130(1973).
(247) M. Roland, "Progestogen Therapy," Charles C Thomas, Springfield, Ill., 1965.
(248) S. L. Israel, "Diagnosis and Treatment of Menstrual Disorders and Sterility," 5th ed., Harper and Row, New York, N.Y., 1967, pp. 214–216.
(249) L. Wilkins, *J. Amer. Med. Ass.*, **172,** 1028(1960).
(250) A. H. Nora and J. J. Nora, *Arch. Environ. Health,* **30,** 17(1975).
(251) L. G. Crowley and S. A. Duwe, *Calif. Med.*, **110,** 139(1969).
(252) S. B. Gusberg, *Obstet. Gynecol.*, **30,** 287(1967).
(253) R. M. Kelley and W. H. Baker, *Cancer Res.*, **25,** 1190(1965).
(254) D. Gordon, B. N. Horwitt, A. Segaloff, P. Murison, and J. V. Schlosser, *Cancer,* **5,** 275(1952).
(255) B. M. Sherman and S. G. Korenman, *ibid.*, **33,** 1306(1974).
(256) R. Hertz, *J. Amer. Med. Ass.*, **154,** 1114(1954).
(257) R. Hertz, J. K. Cramer, J. P. Young, and B. B. Westfall, *J. Nat. Cancer Inst.*, **11,** 867(1951).
(258) A. L. Herbst, S. J. Robboy, G. J. McDonald, and R. E. Scully, *Amer. J. Obstet. Gynecol.*, **118,** 607(1974).
(259) C. H. Hendricks, W. E. Brenner, R. A. Gabel, and T. Kerenyi, in "Brook Lodge Symposium on Progesterone," A. C. Barnes, Ed., Pergamon, New York, N.Y., 1961, pp. 53–64.
(260) S. J. Nillius and E. D. Johansson, *Amer. J. Obstet. Gynecol.*, **110,** 470(1971).
(261) J. E. Seidl, J. A. Epstein, and H. S. Kupperman, *Int. J. Fertil.*, **3,** 349(1958).
(262) P. H. Berczeller, I. S. Young, and H. S. Kupperman, *Clin. Pharmacol. Ther.*, **5,** 216(1964).
(263) G. Pincus, *Vitam. Horm. (N.Y.)*, **17,** 307(1959).
(264) I. Rothchild, *J. Clin. Endocrinol. Metab.*, **17,** 754(1957).
(265) C. A. Paulsen, D. J. Moore, R. T. Roscoe, and C. G. Heller, *Acta Endocrinol., Suppl.*, **51,** 203(1960).
(266) A. Zaffaroni, *Acta Endocrinol., Suppl. 185,* **75,** 423(1974).
(267) B. B. Pharriss, R. Erickson, J. Bashaw, S. Hoff, V. A. Place, and A. Zaffaroni, *Fertil. Steril.*, **25,** 915(1974).
(268) E. I. Kohorn and R. Tchao, *J. Obstet. Gynaecol. Brit. Commonw.*, **75,** 1262(1968).
(269) D. Perlman, N. H. Guiffre, S. A. Brindle, and S. C. Pan, *Proc. Soc. Exp. Biol. Med.*, **111,** 623(1962).
(270) S. Biswas, J. D. Macdougall, and R. P. Cook, *Brit. J. Exp. Pathol.*, **45,** 13(1964).
(271) W. J. Rappoport, B. Goldstein, and A. L. Haskings, *Obstet. Gynecol.*, **9,** 497(1957).
(272) W. S. Spector, "Handbook of Toxicology," vol. I, Saunders, Philadelphia, Pa., 1956, p. 246.
(273) H. W. Rudel and F. A. Kincl, in "Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Agents," vol. I, International Encyclopedia of Pharmacology and Therapeutics, sect. 48, M. Tausk, Ed., Pergamon, New York, N.Y., 1971, pp. 405–409.
(274) Z. Dickmann, *Fertil. Steril.*, **21,** 541(1970).
(275) W. K. Whitten, *J. Endocrinol.*, **16,** 80(1957).
(276) M. C. Allen and R. H. Foote, *Fertil. Steril.*, **24,** 220(1973).
(277) J. C. Daniel and J. D. Levy, *J. Reprod. Fertil.*, **7,** 323(1964).
(278) H. C. Moore, *Acta Endocrinol., Suppl.*, **51,** 911(1960).
(279) H. C. Moore, *J. Obstet. Gynaecol. Brit. Commonw.*, **68,** 570(1961).
(280) H. G. Spies, D. R. Zimmerman, H. L. Self, and L. E. Casida, *J. Anim. Sci.*, **18,** 163(1959).
(281) P. H. Sammelwitz, P. J. Dziuk, and A. V. Nabandov, *ibid.*, **15,** 1211(1956).
(282) G. Carpent and L. Desclin, *Endocrinology,* **84,** 315(1969).
(283) G. Carpent and L. Desclin, *C. R. Acad. Sci., Ser. D,* **264,** 2933(1967).
(284) R. Mey, *Geburtshilfe Frauenheilkd.*, **23,** 615(1963).
(285) G. K. Suchowsky and K. Junkmann, *Endocrinology,* **68,** 341(1961).
(286) L. Wilkins, H. W. Jones, G. H. Holman, and R. S. Stempfel, Jr., *J. Clin. Endocrinol. Metab.*, **18,** 559(1958).
(287) S. Hagler, A. Schultz, H. Hankin, and R. H. Kunstadter, *Amer. J. Dis. Child.*, **106,** 586(1963).
(288) D. Aarskog, *Birth Defects,* **7,** 122(1971).
(289) E. P. Levy, *Lancet,* **1,** 611(1973).
(290) I. Gal, *Nature,* **240,** 241(1972).
(291) L. E. Sever, *ibid.*, **242,** 410(1973).
(292) R. L. Kaufman, *Lancet,* **1,** 1396(1973).
(293) J. J. Nora and A. H. Nora, *ibid.*, **1,** 941(1973).
(294) D. T. Janerich, J. M. Piper, and D. M. Glebatis, *N. Engl. J. Med.*, **291,** 697(1974).
(295) A. Jost, *Clin. Pharmacol. Ther.*, **14,** 714(1973).
(296) J. L. Marx, *Science,* **180,** 174(1973).
(297) F. A. Kincl and M. Maqueo, *Endocrinology,* **77,** 859(1965).
(298) D. A. Karnofsky, P. J. Hamre, and G. Hysom, *Proc. Soc. Exp. Biol. Med.*, **79,** 641(1952).
(299) T. V. Purandare, S. R. Munshi, and S. S. Rao, *J. Reprod. Fertil.*, **38,** 247(1974).

ACKNOWLEDGMENTS AND ADDRESSES

Received from *Alza Corporation, Palo Alto, CA 94304*
The authors thank Dr. V. Place and Dr. B. Pharriss for their careful study of the manuscript, and B. Klompus and C. Record for their valuable assistance.
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