Abstracts

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24th Annual Meeting of the Society for Gynecologic Investigation

Scientific Abstracts

S. Karger · Basel · München · Paris · London · New York · Sydney 1977
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Program of Events
Registration
Wednesday, March 23, 1977, 4 p.m. Hotel Lobby Marriott Hotel
Hospitality Hour Wednesday, March 23, 1977, 6 p.m.
Courtesy of Ross Laboratories Columbus, Ohio Marriott Hotel
Registration
Thursday, March 24, 1977, 7.30 a.m., and Friday, March 25, 1977, 7.30 a.m. Hotel Lobby Marriott Hotel
Scientific Sessions Thursday, March 24,1977, 8 a.m. to 4.30 p.m.
and Friday, March 25, 1977, 8.m. to 12.30 p.m. Mohave and Maricopa Rooms, Greenlee and Graham Rooms, Gila and Coconino Rooms or Cochise and Apache Rooms Marriott Hotel

Introduction and President’s Address First Plenary Session Concurrent Session A Concurrent Session B First Poster Session Concurrent Session C Concurrent Session D Concurrent Session E

Thursday, March 24, 1977
8 a.m.
8.30 a.m. to 10.15 a.m. 10.45 a.m. to 12.15 p.m. 10.45 a.m. to 12.15 p.m. 10.45 a.m. to 12.15 p.m. 1.45 p.m. to 4.30 p.m. 1.45 p.m. to 4.30 p.m. 1.45 p.m. to 4.30 p.m. 1.45 p.m. to 4.30 p.m.
Mohave and Maricopa Rooms Mohave and Maricopa Rooms Mohave and Maricopa Rooms Greenlee and Graham Rooms Cochise and Apache Rooms Mohave and Maricopa Rooms Greenlee and Graham Rooms Gila and Coconino Rooms

Friday, March 25, 1977
Second Plenary Session Guest Lecture Concurrent Session A Concurrent Session B Second Poster Session
8 a.m. to 10.15 a.m. 8 a.m. to 9 a.m. 10.45 a.m. to 12.30 p.m. 10.45 a.m. to 12.30 p.m. 10.45 a.m. to 12.30 p.m.
Mohave and Maricopa Rooms Mohave and Maricopa Rooms Mohave and Maricopa Rooms Greenlee and Graham Rooms Cochise and Apache Rooms

Business Meeting Thursday, March 24, 1977, Mohave and Maricopa Rooms (members only) 4.30 p.m.
Reception and Banquet Thursday, March 24, 1977, 7.00 p.m. Old Tucson
Charter buses will provide transportation from the Marriott Hotel to Old Tucson.
Reception and Banquet are supported, in part, by Ortho Pharmaceutical Corporation, Raritan, N.J., and by G.D. Searle and Company, Chicago, 111.
Coffee and Coke will be served in the Hotel lobby during intermissions on Thursday morning and afternoon and on Friday morning.

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The Inhibition of PMN and Lymphocyte-Mediated RBC Lysis by Promethazine in an in vitro Erythroblastosis Model

John P. Gusdon, jr. and Glenn A. Herbst

Departments of Gynecology, Bowman Gray School of Medicine, Winston-Salem, N.C.

An in vitro method for the measurement of fetal red blood cell (RBC) destruction by FC receptor bearing polymorphonuclear leukocytes (PMNs) and lymphocytes has been developed. Bloods were obtained from infants who were Rh-D positive, and compatible with their mother, as well as infants who were Rh-D positive and incompatible with their Rh-D-sensitized mothers. RBCs, lymphocytes and PMN preparations were individually separated from each cord blood. Rh-D positive cord RBCs from compatible pregnancies were coated with anti-Rh-D. RBCs from babies whose mothers were sensitized to Rh-D and who had a positive direct Coombs were used without the further addition of antibody. All RBCs were labeled with 51Cr, and cultured with autologous lymphocytes or PMNs at a 10:1 effector:RBC ratio. Cultures contained varying amounts of promethazine-HCl (P-HCl). Antibody alone did not cause red cell lysis. Both lymphocytes and PMNs were effective in causing the lysis of RBCs bearing antibody. Lysis of RBCs by PMNs or lymphocytes was inhibited in a linear fashion by increasing concentrations of P-HCl: correcting for spontaneous lysis, 5 µg/ml of P-HCl inhibited RBC lysis 10–20% over a 24-hour period, while 25 µg/ml decreased antibody dependent cell mediated lysis (ADCL) 70%. Low doses of P-HCl decreased spontaneous lysis by 50%. P-HCl was found to have two actions: (1) it inhibited ADCL of autologous RBC coated with antibody, and (2) it stabilized the RBC membranes so that even spontaneous lysis of RBC was significantly decreased. These data help to explain some of the: (1) possible mechanisms of fetal RBC destruction in erythroblastosis and, (2) mechanisms of action of P-HCl in the treatment of the disease.

Society for Gynecologic Investigation

Modulating Effects of Prostaglandins on the Uterine Vascular Bed

Robert Resnik and Gary W. Brink

Department of Reproductive Medicine, University of California, San Diego School of Medicine, La Jolla, Calif.

Recent observations suggest that the prostaglandins (PG) of the E series may play an integral role in mediating estrogen-induced uterine blood flow (UBF), as well as increasing and maintaining UBF in pregnancy. The evidence to support this hypothesis is indirect, however, and data pertaining to the effect of PG on the uterine vascular bed following direct intra-arterial infusion is lacking. Accordingly, the vascular responses to uterine intra-arterial PG infusions were studied in 5 non-pregnant, castrated ewes, chronically equipped with square wave electromagnetic flow probes, and with catheters inserted into branches of the uterine arteries.
PGE\(^\text{\textsuperscript{\textregistered}}\) at arterial concentrations of 0.7 µM, was found to be a potent uterine vasodilator which will rapidly increase UBF to levels achieved by maximal doses of estradiol-17/3. Conversely, PGF\(_2\alpha\) has marked vasopressor properties and will decrease peak estrogen-induced UBF by 50% at uterine arterial concentrations of 0.1 µM. These findings demonstrate the vasoactive effects of prostaglandins in the uterine vascular bed, and support the hypothesis that the prostaglandins are involved in the auto-regulation of UBF.

(Supported by a grant from the National Foundation, March of Dimes.)

9 a.m. 3 Fetal Baboon Pulmonary Developmental Response to Intra-Amniotic Betamethasone R. V. Kotas, O.R. Kling, M.F. Block, J.F. Soodsma and R.D. Harlow University of Oklahoma College of Medicine, Department of Gynecology and Obstetrics, William K. Warren Medical Research Center, Tulsa, Okla.

The baboon pregnancy model was studied to test if intra-amniotic administration of 6 mg betamethasone, at 4 and 3 days prior to premature delivery by cesarean section, effectively accelerated surfactant appearance in the fetal lung. Intra-amniotic betamethasone given to 6 fetal baboons between 147 and 152 days gestation (term =180 days) significantly increased (p < 0.02) the amniotic fluid L/S ratio (control 1.35 ± 0.18; treatment 2.17 ± 0.48; mean ± SE). At delivery, treated animal lungs had a significantly increased deflation stability at 10 cm H2OP (p < 0.001) to 54 ± 3.4% as compared to the 5 controls of 31 ± 1.9%. The minimum surface tension was significantly decreased (p < 0.001) in treated (7.8 ± 1.2 dynes/cm2) versus controls (23 ± 2.2 dynes/cm2). Changes in maximum air distensibility at 40 cm water pressure lagged about 10 days behind changes in deflation stability. The major molecular species of pulmonary phosphatidylcholine were analyzed by GLC as the diacylglycerol derivatives. The proportions of 14:0/16:0, 16:0/16:0 and 16:0/18:0 significantly increased over controls while unsaturated species decreased in animals exposed to intra-amniotic betamethasone. The fetal baboon pulmonary system does respond to intra-amniotic betamethasone with an increase in the L/S ratio, improved pulmonary stability and a more mature pulmonary lecithin composition.

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9.15 a.m. 4 Ovarian Metabolism of Polycyclic Aromatic Hydrocarbons and Associated Ovotoxicity in the Mouse

Donald R. Mattison and Snorri S. Thorgeirsson NIH, Bethesda, Md.

The polycyclic aromatic hydrocarbons (PAH); benzo(a)pyrene (BP) and 3-methyl-cholanthrene (MC) are known initiators of ovarian granulosa cell tumors in mice. We have investigated PAH-induced ovarian aryl hydrocarbon hydroxylase (AHH) activity and primordial oocyte destruction in responsive C57B1/6N(B6), nonresponsive DBA/2N(D2) and (D2xB6) F1XD2 backcross mice. Aromatic hydrocarbon responsiveness is known to segregate as an autosomal dominant trait in these two strains. Basal levels of ovarian AHH are similar in all mice; however, following MC treatment ovarian AHH increases 3-fold in B6 and responsive backcross mice but does not change in D2 and nonresponsible backcross mice. Time-response studies indicate that a single intraperitoneal injection of MC produces a 40% decrease in primordial oocyte number in 48 h in B6 mice and complete destruction in 4 days. In D2 mice however, little change in primordial oocyte number is observed until 5 days after MC treatment, and at 7 days 50% of the primordial oocytes remain. Ovotoxicity in backcross mice is similarly more pronounced in the responsive than nonresponsible pheno-type. The morphological changes in primordial oocytes following PAH treatment such as loss of oocyte nuclear architecture, disruption of nuclear membrane, pyknotic hyperchro-matic nuclei, increased eosinophilia and swollen oocytes are not reflected in
other ovarian cells. These results show that ovarian PAH metabolism and ovotoxicity are expressed as an autosomal dominant trait in these mice. The high and rising incidence of human ovarian cancer in industrialized countries where PAH pollution is common, underscores the necessity of investigating ovarian metabolism of xenobiotics.

9.30 a.m. 5 Hypothalamic-Pituitary Vasculature: Evidence for Retrograde Blood Flow John C. Porter and Charles Oliver

Department of Obstetrics-Gynecology, University of Texas Southwestern Medical School at Dallas, Dallas, Tex.

Does retrograde blood flow occur in the pituitary stalk? Do pituitary hormones reach the hypothalamus by retrograde flow? Does venous blood from the anterior pituitary reach the posterior pituitary? Do posterior pituitary hormones reach the anterior pituitary? Such questions imply that anterior pituitary hormones influence function of the posterior pituitary and vice versa, and that pituitary hormones may influence hypothalamic function. In order to address some of these questions, blood was collected from a long portal vessel of rats; and LH, TSH, prolactin (Pr), ACTH, α-MSH, and vasopressin (Vp) were determined in the plasma. The concentrations (ng/ml) of pituitary hormones in portal plasma from male rats with intact pituitaries were as follows: LH, 2,320 ± 874 (mean ± SE); TSH, 10,180 ± 1,471; Pr, 5,430 ± 1,176; ACTH, 82 ± 17; α-MSH, 103 ± 17.8; and Vp, 2.4 ± 1.0. These values were 70–700 times that seen in arterial plasma from the same animals. After anterior lobectomy, LH, TSH, Pr, and ACTH levels in portal plasma were markedly reduced; α-MSH was reduced to a lesser extent, and Vp was unaffected. Posterior lobectomy had no effect on portal plasma concentrations of LH and TSH, but did suppress Pr, ACTH, αMSH, and Vp. These findings suggest that: (1) LH and TSH enter the retrograde channels in the stalk independent of the posterior pituitary; (2) Pr, ACTH, α-MSH, and Vp enter the retrograde channels via the posterior pituitary vasculature; (3) all pituitary hormones probably reach the hypothalamus in high concentrations and may affect brain function.

9.45 a.m. 6 Function of Progesterone (P) in Pregnancy Maintenance F. Febres, B. Gondos and P.K. Siiteri

Departments of Obstetrics-Gynecology and Pathology, University of California, San Francisco School of Medicine, San Francisco, Calif.

On the basis of recent experiments that demonstrate marked antiinflammatory and immunosuppressive activity of P in vivo we have proposed that high local levels of P may protect the fetus from maternal immune attack. P-filled silastic tubes, previously used, had release rates of ca. 170 µg/cm/day. More recent results show that the granuloma response to cotton thread is blocked by using P-capsules with release rates of 10 or 2 µg/cm/day. Granuloma inhibition with the latter was observed in adrenalectomized rats suggesting that P effect is independent of corticosteroids. Other experiments have shown that: (1) Human trophoblasts from 15–20 week placentas survive for at least 28 days in the lungs of rats treated with silastic implants containing pregnenolone (PE) to increase trophoblastic P production. Marked inflammation of lungs observed at 8 and 13 days in controls was not found in Pe-treated animals. Survival of trophoblasts beyond 13 days has not been observed in untreated rats or those with subcutaneous implants of P. (2) Decidua obtained from pregnant (day 16) Sprague-Dawley rats implanted in the abdominal muscle of nonpregnant Long-Evans female rats remained histologically normal for 16 days if the recipients were treated with P implants (n = 5) whereas
control implants (n = 5) were virtually destroyed. Peripheral progesterone levels were similar to those at mid pregnancy (140–180 ng/ml) in treated animals. These results indicate that P production by trophoblasts and/or P accumulation by the decidua may play an important role in prevention of fetal allograft rejection during pregnancy.

(Supported by NIH grant HD 8692.)

10 a.m. 7 The Membrane-Dependent Cleavage of the Human Placental Lactogen Precursor
Irving Boime, Donna Smith and Elzbieta Szczesna
Washington University School of Medicine, Department of Obstetrics-Gynecology, St. Louis, Mo.

In placenta, human placental lactogen (HPL, mol wt 22,000) is synthesized on the endoplasmic reticulum as a precursor (preHPL, mol wt 25,000). Since the processing of preHPL is a possible control point for the in vivo expression of HPL, this reaction was investigated in vitro. MRNA derived from term placenta directs the synthesis of preHPL in an ascites tumor system containing cytosol and ribosomes. The processing of preHPL to HPL required the addition of microsomal membranes to this system. Cleavage occurred only during synthesis of preHPL; completed chains of preHPL released from the ribosome were not cleaved. This accounts for the absence of preHPL in the circulation. Cleavage activity was inhibited 100% by 0.04% Triton, while protein synthesis was inhibited only 30%. Using Triton to block cleavage at intervals after mRNA and membrane additions, it was shown that cleavage required about 15 min. This lag period probably reflects the synthesis of the chain to the appropriate length, the binding of the nascent chain ribosomal complex to the membrane and cleavage.

When the ascites system was incubated with charged initiator (35S) methionine-tRNA, labeled preHPL was formed. It was processed when membranes were added during the first few minutes of incubation, but no cleavage occurred when membranes were added after the complete protein was synthesized. Since only the primary gene product can be labeled with the initiator methionine, the data show that preHPL is the initial translation product from the placental genome and that it is not a cleavage product of a still larger protein.

10.15 to 10.45 a.m. Intermission
Concurrent Session A
Thursday, March 24, 1977
Mohave and Maricopa Rooms – Marriott Hotel
10.45 a.m. to 12.15 p.m.
Moderators: Girgis Mikhail and Norman F. Gant
10.45 a.m. 8 Androgen Insensitivity – a Cause of Oligospermia and Infertility in a Phenotypic Male
E. James Aiman, James E. Griffin, Jean D. Wilson and Paul C. MacDonald Department of Obstetrics-Gynecology, University of Texas Southwestern Medical School at Dallas, Dallas, Tex.

We have previously described the hormonal milieu and the magnitude of high-affinity specific binding of dihydrotestosterone (DHT) in genital skin fibroblasts in normal men and in genetic males with various androgen insensitivity syndromes. We have now studied a heretofore undescribed form of androgen resistance in a phenotypic male with severe oligospermia (≤ 106/ml) who had no somatic stigmata of androgen insensitivity. The plasma production rate of
testosterone (PR-T) in this man was 11.9 mg/day, a value twice that of normal men but similar to that of two men with Reifenstein’s syndrome. Specific metabolic events, expected as a consequence of this increased PR-T, were not present; namely the plasma concentration of LH (mean = 49.5 ng/ml) was significantly increased despite the increased PR-T and despite significant increases in the plasma concentration of testosterone (mean = 11.5 ng/ml), the metabolic clearance rate of T (1,043 L/D) was not low as expected with increased PR-T and binding capacity of the androgen binding plasma protein (396 fmol T/mg protein) was not low. No testicular secretion of estradiol occurred although LH concentrations were increased. The high affinity specific binding of DHT (B max) in genital skin fibroblasts was 7.8 fmol DHT/mg protein in this oligospermic man, compared to 18–45 in control subjects and 4–9 in males with Reifenstein’s syndrome. Finally, the occurrence of oligospermia and infertility may also constitute evidence for androgen insensitivity in view of testosterone action on the seminiferous epithelium to initiate and/or maintain spermatogenesis.

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11 a.m. 9 Ovarian Failure Consistent with Aromatase Deficiency
Uwe Goebelsmann, Val Davajan, Jorge H. Mestman, Frank Z. Stanczyk and Miriam G. Wilson
Departments of Obstetrics-Gynecology and Pediatrics, University of Southern California School of Medicine and Los Angeles County-USC Medical Center, Los Angeles, Calif.
A 24-year-old female presented with 1° amenorrhea, hirsutism and clitoromegaly. Androgen excess became evident at puberty. Menstruation occurred only after oral contraceptives. This normotensive, 157-cm tall, genetic female (46, XX) had elevated serum progesterone (P), 17-hydroxyprogesterone (170HP), androstenedione (A), testosterone (T), urinary 17-ketosteroids (17KS), normal serum cortisol (F) and dehydroepiandrosterone sulfate (DHEAS), and highly increased serum LH and FSH. Serum estrone (E^ and estradiol (E2) were only 13 and 21 pg/ml, respectively. Dexamethasone suppressed F and DHEAS, lowered 17KS partially and failed to decrease serum P, 170HP, A and T. Enovid-E, however, suppressed serum LH, FSH, P, 170PH, A and T. ACTH caused appropriate rises in F, DHEAS, P, 170HP, A and T. Two-third wedge resection of both 6 X 4 cm multicystic ovaries revealed multiple small follicle cysts, very few follicles and coUagenous or myxoid stroma with corpora albicantia-like structures. Ovarian chromosome analysis: right: 46, XX; left: 45, X (6%)/46, XX (79%)/47, XXX (15%). No Y chromosome was detected. Incubation of 14C-pregnenolone with tissue from both ovaries resulted in extensive metabolism to neutral metabolites. T propionate intramuscularly raised serum T to 16 ng/ml, but failed to increase serum E2 ( &lt; 3 pg/ml) and Ei ( &lt; 5 pg/ml) and to suppress serum LH and FSH. These findings are consistent with deficient aromatization. They supported the assumption that ovarian androgen excess and deficient E2 production prevented normal follicle maturation and caused premature follicle depletion. The unilateral ovarian mosaicism may or may not be causally related.
(Supported by NICHD grant 05932.)

11.15 a.m. 10 True Agonadism: a Variant of Testicular Dysgenesis
Robert E. Cleary, Robert L. Rosenfield and Peter CM. Young
Departments of Obstetrics-Gynecology, Indiana University School of Medicine, Indianapolis, Ind.
A 23-year-old phenotypic female with XY genotype presented with primary amenorrhea, minimal breast development, sparse pubic hair, fusion of the labia, and no clitoromegaly. Her vagina ended in a short blind pouch. Plasma FSH and LH were markedly elevated with FSH
level being higher than LH. Plasma values of cortisol (F), progesterone (P), and dehydroepiandrosterone sulfate (DHA-SO4) were in the normal range for females. Plasma testosterone was 25 ng/100 ml, increased to 42 ng/100 ml after ACTH, fell to 6 ng/100 ml after dexamethasone, but did not change after administration of human chorionic gonadotropin. Following ACTH infusion, F increased from 20 to 48 µg/100 mg, estrone increased from 40 to 67 pg/ml, P increased from 140 to 880 ng/100 ml, DHA-SO4 from 216 to 395 µg/100 mg, 17-OHCS from 5.9 to 17.3 mg/day, and 17-KS from 3.3 to 4.3 mg/day. At laparotomy, no uterus, only vestigial remnants of fallopian tube, and a very small ‘steak’ gonad was seen. Microscopic examination showed loose cellular gonadal stroma and no germinal elements. On the basis of the clinical, genotypic, and endocrine features of patients with ‘true agonadism’, a unified nomenclature is proposed in which ‘true agonadism’ is referred to as ‘intersexual testicular dysgenesis’ to distinguish it from Swyer syndrome and the syndrome of bilateral anorchia, both being variants of testicular dysgenesis.

11.30 a.m. 11 The Effect of an Oral Contraceptive on Plasma Concentrations of Dehydroisoandrosterone Sulfate and ACTH

James D. Madden, Leon Milewich, Celso Gomez-Sanchez, Bruce R. Carr, C. Richard Parker, jr., Norman F. Gant, John C. Porter and Paul C. MacDonald Department of Obstetrics and Gynecology, University of Texas Southwestern Medical School, Dallas, Tex.

Dehydroisoandrosterone sulfate (DS), the major C-19 steroid found in the human peripheral circulation, was measured daily (08.00–10.00 h) throughout the menstrual cycles of eight normal ovulatory women and four women on oral contraception (Norethindrone 1 mg and mestranol 80 µg). The concentrations of DS in the ovulatory women ranged from 1,025 to 4,200 ng/ml with a mean of 2,062 ± 137 (mean ± SEM). DS concentrations during the follicular and luteal phases of the cycle were not different. In women taking the oral contraceptive, the DS concentration ranged from 475 to 1,400 ng/ml with a mean of 895 ± 83. The decrease in the plasma concentration of DS is likely a result of a reduction in DS secretion since comparable differences in the urinary production rates of DS were found in one ovulatory women (13.2 mg/day) and one women on the oral contraceptive (7.2 mg/day). Since DS secretion by the normal human ovary is negligible and ovarian dehydroisoandrosterone secretion is small, it is likely that the reduced plasma DS levels in women on this oral contraceptive is the consequence of reduced ACTH secretion. In studies of four normal ovulatory women whose plasma was sampled at 08.00–10.00 h the mean concentration of ACTH was 88 ± 2 pg/ml whereas in four women on this oral contraceptive the concentration was 54 ± 5 pg/ml.

11.45 a.m. 12 The Use of a Rapid Corticosteroid-Binding Globulin Assay to Quantitate Potency of Exogenous and Endogenous Estrogens

Donald E. Moore, Shinnosuke Kawagoe, Daniel R. Mishell, jr., Val Davajan and Robert M. Nakamura

Department of Obstetrics-Gynecology, University of Southern California School of Medicine, Los Angeles County Medical Center, Los Angeles, Calif.

A simple, precise and accurate charcoal adsorption method has been developed to assay the binding capacity of human corticosteroid-binding globulin (CBG-BC). 40 duplicate serum samples, each with a heat-inactivated blank, can be assayed per day. The interassay coefficient of variation is less than 6%. CBG-BC levels remained constant throughout the cycle in 5 normal women despite fluctuating E2 levels which reached peaks of 190–430 pg/ml. CBG-BC did not
fall in postmenopausal women. In pregnancy there is a steady increase in CBG-BC beginning when E2 levels are greater than 1 ng/ml and E, greater than 500 pg/ml (8–9 gestational weeks). This increase correlates well with both the increase in E2 (rs = 0.85, p < 0.001) and E, (rs = 0.88, p < 0.001). Exogenous estrogens of various types, alone, or in combination with progestins also cause increases in CBG-BC. Oral conjugated estrogens

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in dosages of 0.625 mg/day or more are associated with a dose-response increase in CBG-BC (rs = 0.80, p < 0.005). This easily performed assay is of use in comparing the effects of various dosages of different exogenous estrogens upon one important metabolic parameter, the alteration of hepatic production of a serum protein.

12 a.m. 13 Variability as a Source of Sampling Error of Steroid Plasma Concentrations in Late Pregnancy

Paul J. Meis, John E. Buster, Calvin J. Hobel and John R. Marshall UCLA School of Medicine, Harbor General Hospital, Department of Obstetrics-Gynecology, Torrance, Calif.

Plasma from 5 normal 3rd trimester pregnant women drawn every 5 min × 7 and every 15 min X 7 at similar times on 2 days, 2 days apart, was assayed in duplicate for estradiol (E2), estriol (E,), progesterone (P), 16α-OH-progesterone (16P), and 17α-OH-progesterone (17P). Data were analyzed using two-way analysis of variance. Single sampling carries a maximum error of ± 100% and mean errors for the individual steroids ranging from ± 36% to ± 60%. Although all pregnancies were uncomplicated and all mean values were within the normal range, variability differed between patients significantly (p < 0.01) for E2, 17P, and P. Variability of 5-min sampling was not different from 15-min sampling.

Mean inter- Mean 5-min Mean 15-min Percent error at 95% CI for N samples assay CV variance

<table>
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| E2 | 5.62% ± 0.28 | 15.6% ± 5.7 | 14.6% ± 5.3 | ± 36 | ± 20 | ± 16 | ± 14 | ± 12 | ± 8
| E3 | 4.80% ± 0.59 | 18.9% ± 3.2 | 19.8% ± 2.3 | ± 42 | ± 24 | ± 19 | ± 15 | ± 12 | ± 9.4
| P  | 5.54% ± 0.21 | 13.4% ± 6.2 | 16.5% ± 5.6 | ± 38 | ± 22 | ± 17 | ± 14 | ± 12 | ± 8.5
| 16P| 5.36% ± 0.08 | 17.9% ± 2.5 | 17.4% ± 3.8 | ± 42 | ± 24 | ± 19 | ± 16 | ± 13 | ± 9.4
| 17P| 6.62% ± 0.50 | 25.2% ± 3.1 | 21.3% ± 3.6 | ± 60 | ± 35 | ± 27 | ± 23 | ± 19 | ± 13

Percent error at 95% confidence interval (CI) is determined by number of samples. Analysis of pooled aliquots of 5 samples obtained every 5 min by indwelling needle provides error at the 95% CI of from ± 16% to ± 27%, a 55% reduction in error. Multiple sampling is required for the accurate study of steroid levels in individual subjects in late pregnancy.

12.15 to 1.45 p.m. Luncheon

Concurrent Session B
Thursday, March 24, 1977

Greenlee and Graham Rooms – Marriott Hotel

10.45 a.m. to 12.15 p.m. Moderator: Edward E. Wallach
10.45 a.m. 14 Enhancement of Growth of Herpes Virus by Crude Human Chorionic Gonadotropin (HCG)

G.E. Knox, D. W. Reynolds and C.A. Alford
Departments of Obstetrics and Pediatrics, University of Alabama School of Medicine, Birmingham, Ala.
Epidemiological studies establishing suppression of cervical CMV excretion during early gestation led to recently reported experiments demonstrating in vitro suppression of growth of cytomegalovirus by crude human chorionic gonadotropin (HCG). The effect was shown to: (1) require cellular protein synthesis; (2) occur early in the replicative cycle; (3) be accompanied by increased cell growth and number; (4) be caused by substances found in crude HCG other than immunochemically pure HCG. The experiments currently reported demonstrate: (1) enhancement of the growth of Herpes Simplex (HSV) by crude HCG, and (2) separation of the active molecule from HCG by physiochemical techniques. Using human fibroblasts grown to confluency followed by pretreatment with crude HCG or separated fractions of crude HCG, the growth of HSV was shown to be significantly enhanced in both plaque production and growth curve assays. Enhancement of rate of growth as well as absolute titer was shown to be dose-dependent in both systems using a range of multiplicities of input. Fractionation of the crude HCG was accomplished stepwise by G-100 sephadex gel filtration followed by discontinuous polyacrylamide gel electrophoresis with demonstrated coelution of the protein (mol wt a, 30,000) responsible for suppression of CMV and enhancement of HSV. Pure HCG has no effect on HSV growth. These results suggest that first trimester pregnancy urine contains a substance capable of altering human fibroblasts such that suppression or enhancement of growth of members of the herpes virus family occur in vitro, the role of this naturally occurring protein with regard to other facets of growth and differentiation in normal pregnancy remains to be defined.

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11 a.m. 15 Biochemical Characterization of the Vaginal Microenvironment and Its Relationship to Vaginal Bacterial Colonization
Bryan Larsen, Allen J. Markovetz and Rudolph P. Galask
Departments of Obstetrics-Gynecology and Microbiology, University of Iowa College of Medicine, Iowa City, Iowa
Using the rat as a model of vaginal colonization we have demonstrated that the bacterial content of the vagina is influenced by estrogenic stimulation. Ultrastructural observations indicate that following estrogen treatment cytoproliferative changes occur and result in keratinization of the vaginal epithelium. Concomitant to this process, bacterial colonization of the epithelium is significantly increased. The increase is also demonstrable micro-biologically. It appears that changes in the vaginal tissue are stimulated by estrogen, and the estrogen-stimulated tissue contains a bacterial growth promoting substrate sufficient to cause the proliferation of the vaginal microflora. Ovariectomized rats were treated with α-estradiol, ß-estradiol or the suspending vehicle. On each of the following 5 days, vaginal lavage was performed on each rat and the material recovered was used for plate count determination of bacteria, and measurement of protein, carbohydrates, RNA, DNA, and amino acids. By the second estrogen post-treatment day increases were seen in the concentration of protein, amino acid and carbohydrates present in the vaginal washings from rats treated with ß-estradiol. Rats treated with α-estradiol showed increases in protein and carbohydrate but not amino acids. Bacterial counts increased in rats treated with β- but not α-estradiol and correlated with the amino acid content of the vaginal washings.
11.15 a.m. 16 Adhesiveness of Mouse Trophoblast to L1210 Cells and to Inert Particles
The object of the current study was to identify areas of the implantation stage mouse embryo which have adhesive characteristics, and to determine the specificity or nonspecificity of this property. Blastocysts were cultured in vitro in Eagle’s basal medium modified to contain the amino acids optimal for blastocyst attachment and trophoblast outgrowth. The following cells or particles were added separately to the culture 24 h later: LI 210 leukemia cells; latex particles, diameter 5.6 µm; microspheres coated with a polymeric resin, diameter 10 µm. When the culture was terminated 6 days later all three were found to be adherent to trophoblast cells. The binding was so strong that it was not disrupted by vigorous washing, while the washing did dislodge the inner cell mass from the trophoblast. The adherence of cells and particles occurred over the entire exposed surface of the trophoblast, which indicates that the adhesive properties are not localized. In contrast, there was no adherence of cells or particles to the inner cell mass. Incubation of blastocysts in 0.1 M β-galactose which inhibits aggregation in the cellular slime mold did not prevent adherence of trophoblast to the plastic dish nor did it prevent adherence of LI210 cells to trophoblast.

The trophoblast of mouse embryos has the ability to attach not only to uterine epithelium, but also to ectopic sites in vivo and to glass or plastic in vitro. Our results demonstrate that the adhesive properties are expressed on the entire surface of the trophoblast cells when they are grown in vitro.

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11.30 a.m. 17 In vitro Suppression of Human Lymphocyte Transformation by Progesterone L.E. Clemens, D. Stites and P.K. Siiteri

Departments of Obstetrics-Gynecology, Medicine and Laboratory of Medicine, University of California at San Francisco, School of Medicine, San Francisco, Calif.

Our recent studies have shown that locally administered progesterone (P) blocks antigenically stimulated inflammatory and/or immune responses. Characteristic of these reactions is the cellular division of activated lymphocytes. To elucidate the mechanism(s) of P action on these responses we compared its effect with that of other steroids on DNA synthesis in human mixed lymphocyte cultures (MLC). The hormones were added to the MLC at various times of the 5-day incubation period in order to determine which phase(s) of the activation sequence are inhibited. When present at 1–20 µg/ml throughout the 5-day period, P, estradiol (E), testosterone (T), and cortisol (C) inhibited MLC response in a dose-related fashion; percent-inhibition at 20 µg/ml was 88, 86, 83, and 78%, respectively. The response to C was, however, highly variable, with an ID50 range of 0.05–20 µg/ml. Preincubation of responding cells with P, E, or C for 12 h followed by washing prior to the addition of allogeneic cells, inhibited DNA synthesis by: P = 20%, E = 0% and C = 93%. However, when P, E, or C was added together with thymidine to activated cells (i.e. on day 5) inhibition was 92, 70, and 58%, respectively. Furthermore P, but not C, inhibited the increase in 3H-thymidine uptake by stimulated cells. The inhibition could be reversed by increasing 3H-thymidine in the media. These results indicate that inhibition of MLC by C occurs at a specific early stage of transformation, whereas P blocks precursor uptake. Nevertheless, our data suggest that maternal T-lymphocyte function may be suppressed during placental transit by the high concentration of P produced by their potential target cells, i.e. the trophoblast.

(Supported by NIH grants HD08692 and HD03939.)

11.45 a.m. 18 T and B Lymphocytes in the Early Human Fetus
The order of appearance of lymphocytes exhibiting typical T and B surface characteristics was studied in a series of aborted human fetus of 8 to 18 weeks gestation age. T cells were identified by E (sheep erythrocyte) rosette formation, and B cells by EAC (sheep erythrocyte + antibody + complement) rosette, and by surface immunoglobulins. Typical T cells were found in the thymus as early as 8 weeks gestation and reached a peak proportion of 93–94% at 12–13 weeks gestation and declined slightly toward 28 weeks gestation. A few B cells (2%) appeared in the fetal thymus at 9 weeks gestation and gradually increased in proportion and in absolute numbers throughout the period of observation. Small numbers of T and B cells were observed in the 12–13 week spleen but did not reach significant numbers until 18 weeks gestational age.

We have demonstrated the presence of typical T lymphocytes in the human fetal thymus as early as 8 weeks gestation and have documented the appearance of T and B lymphocytes in the thymus prior to this appearance in the spleen.

Morphologic studies have shown that thrombotic occlusion of uteroplacental arteries leading to a decreased maternal placental circulation and infarction is a frequent finding in pregnancies resulting in small-for-date babies. Increased platelet consumption due to platelet-mediated thrombotic disorders can be clinically diagnosed by measurement of 51Cr platelet survival time, a method which for obvious reasons has not been employed in pregnant women. Recently a nonisotope technique for determination of platelet life-span was developed (New Engl. J. Med. 292: 1310, 1975), based on the complete inhibition of platelet lipid peroxidation and formation of malonaldehyde in vivo by a single dose of acetylsalicylic acid. Platelet life span was determined by means of this technique between the 35–40th week of pregnancy in 17 women with clinically normal gestation (group I) and in 9 women with small-for-date babies (group II). Nine nonpregnant women were used as controls (group III). It was found that (1) platelet life span (days) in group I (mean = 9.2 ± 0.30 SEM) was not different from that in group III (mean = 9.7 ± 0.48 SEM); (2) life span in group II (mean = 7.3 ± 0.43 SEM) was significantly (p = 0.001) shortened as compared with that in group I. These data support the morphologic evidence that platelet-mediated arterial thrombosis contributes to placental insufficiency leading to intrauterine growth retardation. Determination of platelet life span might be a useful clinical procedure to distinguish between circulatory and other causes of placental insufficiency.

First Poster Session
Thursday, March 24, 1977
Cochise and Apache Rooms – Marriott Hotel
10.45 a.m. to 12.15 p.m.
20 Presence of Biologically Active ACTH in Normal Human Trophoblasts.
Rapin Osathanondh, Dorothy T. Krieger, Kenneth J. Ryan, Anthony S. Liotta and Dan Tulchinsky
Extracts of extensively washed placental tissue and dispersed viable trophoblasts contained high ACTH activity as determined by radioimmunoassay (I) and bioassay (B). Serial dilutions of placental homogenate gave inhibition parallel to that of standard pACTH in I and B. I-ACTH content in mid-trimester placental tissue (3.4 ± SE 0.1 ng/g) obtained vaginally following intra-amniotic prostaglandin infusion was significantly greater than that obtained via elective cesarean section at term (1.7 ± SE 0.1 ng/g) (n = 4). The ratios of B-ACTH over I-ACTH in placental extracts obtained at 12, 15, 18, and 39 weeks of gestation ranged from 0.31 to 0.40. Sephadex G-50 filtration of placental homogenate obtained at term pregnancy revealed 29% of the total immunoreactivity to be in the void volume and 54% in the authentic 125I ACTH peak.

Dexamethasone given orally (8–16 mg) in divided doses 10–48 h prior to elective cesarean section did not significantly alter placental ACTH content.

21 Amino Acid Transfer through the Human Placenta Studied by in vitro Perfusion
Henning Schneider, Karlheinz Möhlen, Jean-Claude Challier and Joseph Dancis
Universitäts-Frauenklinik, Marburg, BRD, Universitäts-Frauenklinik, Münster, BRD, Université de Paris, Biologie de la Reproduction, Paris, New York University School of Medicine, New York, N.Y.

Amino acid transport in human term placenta has been studied with an in vitro perfusion technique in which separate maternal (MC) and fetal (FC) circulations are established. 12 of 15 amino acids were transferred from MC to FC at approximately the same rate, which was about one third the rate of antipyrine transfer. Glutamate, aspartate and cysteine were transferred at approximately half the rate of the other amino acids, consistent with the slow transfer rates reported in vivo, L-leucine and L-alanine are transferred considerably more rapidly than their respective Z-isomers, the difference being attributed to an active transport mechanism. However, D-glutamate is transferred more rapidly than its L-isomer. Studies were undertaken in which the fetal perfusate was recirculated permitting the establishment of gradients across the placenta. Of several amino acids studied, all except glutamate and aspartate developed higher concentrations in the FC; the levels of aspartate and glutamate in the FC fell progressively, reaching concentrations below those in MC. The Z-dicarboxylic acids are rapidly metabolized by placenta explaining the preferential transfer of the Z-isomer and the establishment of a transplacental gradient directed towards MC.

22 Lipid Transport and Metabolism in the Post-Term Rabbit
Martin I. Shapiro, Jacques F. Roux, Alice Harlow and Denise Masse
Department of Obstetrics-Gynecology, Hôtel-Dieu/St. Justine Hospitals, Pediatric Research Center, St. Justine Hospital, University of Montreal, Montreal, P.Q.

APL-injected pregnant rabbits were delivered by cesarean section 27 and 30 days (d) near term (NT) and 3 and 4 days post-term (PT). Lipid metabolism of the PT fetus, NT fetus, and 3- and 4-day-old newborns (NB) was compared. Pre and postnatal body and organ weights as well as lipid concentration in brain, liver, lung, brown adipose tissue and placenta were determined. The half-time (t1/2) of FFA in mother and fetus was calculated following a single maternal injection of 1-14C-palmitate (50µCi). Placental weight remains unchanged after 30NT. However, a significant positive correlation exists between fetal body weight (BW) and placental weight. The brain is spared – its weight increasing in a manner proportional to BW. Brain lipid concentration remains...
constant throughout the study period. Dramatic changes (greater than 50% drop) in fetal lipid concentration occur in the liver when extending the PT period beyond 34 days (between 3PT and 4PT). The rate and time of peak appearance of radioactivity in fetal circulation indicate a peak shift in 4PT (peak appearance is at about 4 min [30NT] increasing to 8 min in the 4PT fetus) as well as a slower rate of entry, 4PT vs. 30NT. These changes imply some breakdown in placental transport (‘placental insufficiency’). The concentration and t\textsubscript{V2} of FFA in fetal plasma is maintained in spite of significantly slower placental transfer of FFA. Maternal ‘attempts’ at compensation include a diminished t\textsuperscript{1/2}; this is evidently inadequate requiring in addition dramatic increases in fetal liver lipid mobilization.

(Supported by MRC grant No. DG111 and the University of Montreal.)

23 Stimulatory Effect of Soluble Supernatant on Hydroxylase Activity of Rat Testis Microsomes
G. Betz, P. Tsai and G. Olson
Departments of Obstetrics and Gynecology and Biochemistry. University Colorado School of Medicine, Denver, Colo.
The stimulatory effect of 105,000 g supernatant (S) on the particulate enzymes which mediate cholesterol synthesis and further conversion to steroid hormones appears to be established as a unique and specific phenomenon. It has been proposed that the participation of steroid-carrier protein found in S may be a general case when enzymes interact with these insoluble substrates. These studies report the effect of S on the activities of 17\textsubscript{a}\textendash hydroxylase (17-H) and 17,20-lyase (17,20-L) of rat testis microsomes. When S is added to the 17-H assay, initial velocity increases to a maximum of 170% of the control. Exposure of S to 100° × 3 min diminishes the enhancement to 135% of control but this effect is less resistant to heat (enhancement reduced to 110% of control). Exhaustive dialysis of S does not alter its effect. The possibility of NADPH generation is excluded by adding this nucleotide to ten times saturation in the presence of a generating system. No alteration in the products of the reaction was detected after addition of S. Purification of the stimulating factor of S has been undertaken by salt fractionation with 4-fold purification. A plot of vi of 17-H or 17,20-L vs. micrograms of purified S added to the assay yields a hyperbolic curve, indicating that the stimulating factor is non-catalytic. The stimulatory activity of testis supernatant appears to be distinct from that involved in cholesterol synthesis (where S is requisite for activity) and in drug metabolism (S prevents P-450 degradation). The effect of S on the kinetic parameters of both enzymes is being studied.

24 Stereoselective Activities of Aminoglutethimide Enantiomers
Hilton A. Salhanick, Carmen A lonso Whipple, Vytautas I. Uzgiris, Penelope E. Graves, E. Noel McIntosh and Hugh R. Holtrop
Departments of Obstetrics-Gynecology and Popular Sciences, Harvard University, Boston, Mass.
Aminoglutethimide is an important drug under investigation for the treatment of breast carcinoma, adrenal carcinoma and adenoma, and fertility control. Its therapeutic effectiveness is limited by its sedative side effects. The enantiomers have been individually examined in the following systems: affinity for the cytochrome P-450 associated with cholesterol side chain cleavage, enzymatic inhibition of cholesterol side chain cleavage in corpus luteum and adrenal mitochondria, inhibition of aromatization in placental microsomes and luteolytic activity in the rat, rabbit and human. In these systems, the dextrorotatory form is 2 to 25 times more active than...
its levo-enantiomer. Toxicity data in the rat and mouse indicate approximately equivalent neurological activity for the two isomers. In view of the enhanced therapeutic ratio, the clinical use of the dextroisomer appears to be indicated.

25 Effect of Cumene Hydroperoxide (CHP) on Placental Aromatase W. G. Kelly and Ann Stolee Departments of Obstetrics-Gynecology and Biochemistry, University of Minnesota Medical School, Minneapolis, Minn.

Hydroxylation of drugs by hepatic microsomes and aromatization of androstenedione (Δ) by placental microsomes are catalyzed by mixed function oxidases employing cytochrome P-450. Recently, several laboratories have reported that CHP and IO; support hydroxylation of drugs and steroids by hepatic microsomes in the absence of TPNH. To determine whether CHP and IO; also support aromatization of Δ, lyophillized microsomes from human term placentae were incubated in 0.05 M Tris-maleate buffer (1.5 mg/l0 ml) at 37 °C with 1,2–3H-Δ (0.3 µM) in the presence of CHP, IO; or TPNH. The rate of aromatization was determined by filtering aliquots taken at various times through charcoal and counting 3H»20 in the filtrate. Placental microsomes aromatized Δ rapidly at a constant rate for 30 min in the presence of TPNH. No reaction was observed in the presence of CHP (0.1

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to 9 mM) or 10; (0.01 to 80 mM). In the presence of both TPNH and CHP (2 mM) the rate of aromatization was constant for only a few minutes and decreased thereafter. Dithio-threitol (10 mM) and EDTA (20 µM) together afforded protection against the effect of CHP. Neither CHP nor IO; support aromatization of Δ in placental microsomes and CHP destroys the activity of aromatase. In this respect, placental aromatase differs from the hepatic hydroxylases. It has been previously noted that CO inhibits hepatic hydroxylases but not aromatase. These differences suggest fundamental differences in the nature and operation of the respective cytochrome P-450.

26 Synthesis and Studies of the Human Placental Lactogen Gene
Irving Boime and Diana McWilliams
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.

For examining the control of human placental lactogen (HPL) gene expression during pregnancy, it is necessary to have a sensitive assay for both HPL mRNA synthesis and its structural genes. To achieve this goal we have synthesized a radioactive complementary DNA (cDNA) from a purified fraction of HPL mRNA using reverse transcriptase. Based on the size of the cDNA it contains at least 80% of the HPL genome and there is evidence for a significant amount of complete gene transcripts in the cDNA population. Previously it was shown that 5 times more HPL was synthesized in cell-free extracts derived from term as compared to first trimester placentae. Employing hybridization techniques, the cDNA was used for assaying the levels of HPL mRNA in equivalent amounts of first trimester and term placenta. These studies showed that there was about a 4-fold greater population of HPL sequences in total RNA from term placenta than in a comparable quantity of total first trimester RNA. Only background hybridization was observed between the cDNA and total RNA derived from human kidney. Hybridization of the labeled cDNA with nuclear placental DNA revealed that the number of HPL genes (ca. 2) per haploid genome is the same in term and first trimester placenta. Thus, the enhanced synthesis of HPL mRNA per gram of placenta appears to be the result of a transcriptional activation rather than amplification of the HPL genes. The increase likely reflects placental differentiation in which the proportion of syncytium increases at term.
27 Establishment of Two New Tissue Culture Lines from Human Squamous Cell Carcinoma of the Cervix and Vagina R.H. Nalick, P.C. MacDonald, F. Vellios and J.C. Porter
Department of Obstetrics-Gynecology, University of Texas Southwestern Medical School at Dallas, Dallas, Tex.

This report describes the successful establishment in culture and characterization of two lines of squamous cell carcinoma derived from two patients, one with recurrent carcinoma of the cervix and the other with primary carcinoma of the vagina. Cells obtained from malignant ascitic fluid (cervical carcinoma) and tissue obtained by biopsy (vaginal carcinoma) were placed in primary culture, utilizing Weymouth’s MB-7531/1 enriched medium containing 15% fetal calf serum (heat inactivated). After 13th passage of the cervical cell line and 17th passage of the vaginal cell line, tumor cells were inoculated into cortisone-immunosuppressed hamsters. Examination of the resultant tumor nodules revealed histological patterns identical with the original human tumors. After the 70th and 72nd passage in culture of the vaginal and cervical cell lines, respectively, the cells were injected into nude (athymic) mice; and solid tumor masses developed rapidly. Chromosomal analysis revealed 65–70 and 83–87 chromosomes for the cervical and vaginal tumor cell lines, respectively. Doubling time during the rapid growth phase in culture was 24 h for both lines. The vaginal cell line produced 40 fg of HCG/day/cell. Tumor cells which maintain neoplastic potential in vivo, should facilitate investigation in such areas of research as sensitivity to radiation and chemotherapeutic agents, immunotherapy and immunodiagnosis, ectopic hormone production, specific cell receptors, and tumor-specific antigens.

28 Lysosomes and Corpus Luteum Function
George L. Flickinger and Jerome F. Strauss, III
Department of Obstetrics-Gynecology, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Alterations in properties of ovarian lysosomes from superovulated rats were studied in relation to stages of luteal function – days 1, 4, 8 and 14 post HCG; 7 rats/group. Activity of N-acetyl-O-glucosaminidase (NAGase) in ovarian homogenates on day 1 was 2.8 ± SE 0.3 mU/ovary and 0.24 ± 0.03 mU/mg protein. A 1.8-fold increase (p < 0.01) in total and specific activity (SA) of NAGase was associated with a 2.8-fold rise in plasma progesterone (P) on day 4. On day 8 NAGase activity was 2.5 times greater than the levels of day 1, but on day 14, when plasma P had declined to values similar to those on day 1 (102 ± 15 ng/ ml), NAGase remained at day 8 levels. Total and SA of NAGase in lysosome-enriched fractions prepared by differential centrifugation followed a similar temporal pattern between days 1–14. Furthermore, changes in \( \beta \)-galactosidase, acid phosphatase and acid phospholipase A, and A2 activities in both ovarian homogenates and lysosome-enriched fractions paralleled the pattern described for NAGase. Significant changes in latency of NAGase were not observed at any time. Lysosomal fractions, suspended in 47% sucrose, were layered between 42 and 52% sucrose and centrifuged; 76 ± 6% of membrane-bound NAGase in homogenates from day 1 ovariies sedimented to the heavier interface while 11 ± 3% rose to the lighter zone. However, only 30 ± 10% of the NAGase from day 8 ovariies sedimented while 43 ± 1% appeared at the lighter interface. This finding suggests increased buoyancy of the lysosomes at this time which could have resulted from accumulation of lipids. Our data indicate that lysosomes may be involved in regulation of cell functions during the period of luteal development and increased steroidogenesis.
29 Studies on the Activation of Sperm Proacrosin to Acrosin; a Process Required for Fertilization
Kenneth L. Polakoski and Richard F. Parrish
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.
Proacrosin is activated to acrosin (EC 3.4.21.10 – a sperm proteinase utilized by sperm to penetrate the ovum’s zona pellucida) during the capacitation process. Since active acrosin is an absolute requirement for fertilization and the control of the activation process has contraceptive potential, we have recently isolated two forms of boar proacrosin to homo-

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geneity and have used sodium dodecyl sulfate disc gel electrophoresis to characterize a mechanism of activation. The proacrosins are autoactivated sequentially to three different active species of acrosin (α, β, and γ):
Proacrosin I → Proacrosin II → α Acrosin → β Acrosin → 7 Acrosin
(55,000 MW (53,000 MW (49,000 MW (34,000 MW (25,000 MW inactive) inactive)
active) active) active)
The autoactivation is concentration-dependent and can be proteolytically induced with either α or β acrosin and trypsin. These results indicate that activation of proacrosin can occur via a bimolecular mechanism. The process is stimulated by liposomes and is inhibited by physiological concentrations of spermine and spermidine, implicating intriguing possibilities for the regulation of this key enzyme system.

12.15 to 1.45 p.m.
Concurrent Session C
Thursday, March 24, 1977
Mohave and Maricopa Rooms – Marriott Hotel
1.45 to 4.30 p.m.
Moderators: Samuel Solomon and Raphael Jewelewicz
1.45 p.m. 30 Differential Feedback Regulation by 17/3-Estradiol of LH Release, Cellular LH Content, and LHRH-Responsiveness in Pituitary Monolayer Cultures Loretta K. Tang
University of Rochester School of Medicine and Dentistry, Department of Obstetrics and Gynecology, Rochester, N.Y.
To evaluate the direct effects of 17/3-estradiol (E2) on pituitary LH release into medium, cellular LH content, and LHRH responsiveness, physiological doses of the steroid (10^-9-10^-8 M E2) were tested in 4-hour incubation with pituitary monolayer cultures of female rats. The effects of E2 were dose-dependent: 10^-9 ME2 stimulated LH release to 176% of the control level; 10^-8 M E2 stimulated cellular LH content to 127% of the control level; 10^-9 M or 10^-8 M E2 stimulated LH accumulation (sum of LH contents in medium and cells). Contrary to its stimulatory effect when given alone, 10^-8 ME2 inhibited cellular LH content to 76% of the control level in the presence of 10^-8 M LHRH. Furthermore, preincubation with 10^-8 M E2 (for 48 h or longer) decreased the subsequent LH release in response to 10^-8 M LHRH stimulation with a coincident increase in cellular LH content. These data indicate that the initial effect after short-term exposure to E2 was stimulatory to the LH-producing cells. However, the latent effect after sustained exposure to E2 was inhibitory to the LHRH responsiveness of the LH-producing cells. The evidence of multiple levels of E2 feedback, which may be regulated indepen
dently by E2, provides the means for biphasic E2 actions in LH secretion.
Assessment of Progesterone-Induced LH-Release at a Test for the Hypothalamic-Gonadotropin Function

Department of Reproductive Medicine, UCSD, School of Medicine, La Jolla, Calif.

It is well known that under estrogen (E) primed conditions, progesterone (P) induces a prompt release of LH. Our recent studies indicate that this P effect is due to a combined event of amplification of E-augmented pituitary sensitivity and an LRF-dependent LH release.

Administration of P (10 mg, intramuscularly), in subjects with high endogenous E (late follicular phase) or through enhancement by daily injection of incremental doses of EB for 5 days in early follicular phase, a mean of 4- to 5-fold increase in LH release within a mean time of 9 h was observed. In 12 hypothalamic amenorrhea (HA) patients with lower basal LH levels (p < 0.05) and the absence of pulsatile pattern, EB treatment alone induced at 200% increase in pituitary sensitivity to 10 µg LRF stimulation without change in the basal levels (11 ± 1.4 vs. 9.1 ± 2.4 mIU/ml). Thus, the functional capacity of the gonado-troph in HA is responsive to E augmentation but with no discernible increase in endogenous LRF. In another 15 patients with HA, following 5–7 days of EB priming, P induced a small but significant (p < 0.05) increase in LH release in only 3 and no response in 12. In contrast, all patients with hyperprolactinemic amenorrhea showed a small (185 ± 27%) but definite response to this EB-P stimulation.

Analyses of the relationship between basal LH and peak response to P revealed a significant positive logarithmic correlation (r = 0.81), indicating a critical basal LH level at which the expression of P-induced LH release is manifested. Our findings implicate that: (1) the gonadotroph in HA patients is fully operational as evidenced by the functional augmentation by E; (2) HA is associated with a dysfunction of P-mediated LRF release, and (3) although present, the P-mediated LH release is impaired in hyperprolactinemic amenorrhea patients.

Changes in Response to Gonadotrophin-Releasing Hormone (GnRH) in Male Fetal and Infant Rhesus Monkeys

Tu T. Huhtaniemi, Carol C. Korenbrot, Maria Seron-Ferre, Julian T. Parer, Dallas B. Foster and Robert B. Jaffe
Department of Obstetrics-Gynecology and Reproductive Sciences, University of California, San Francisco, Calif.

17 fetal and infant male monkeys were challenged with GnRH between 130 days’ gestation and 1 year postnatally, and pituitary and testicular responses measured. Responses of circulating LH and testosterone (T) were observed at all ages; clear differences in response were seen between fetal, neonatal and infant stages of development. Intravenous administration of GnRH to the chronically catheterized fetus in utero resulted in a mean T increase of 110% in lh during the last third of gestation; doses of 50 µg GnRH, but not 10 µg, consistently resulted in stimulation. In contrast, during the 4 days following delivery, 3–5 µg GnRH stimulated T increases of similar magnitude. From 18–89 days of age, an increased mean response (300%) to 10 µg GnRH was seen. After this neonatal period, T responses following GnRH declined, and no effect of 10 µg GnRH was seen by 1 year. Similarly, subcutaneous injections of GnRH in slow-release form (500 µg/2 weeks) maintained high T levels (6–10 ng/ml) until 65–80 days of age. No stimulation
was seen after this time. Circulating LH responses to GnRH, determined by Leydig cell in vitro bioassay, changed in a parallel fashion to T responses between fetal, neonatal and infant stages. It is concluded that the male monkey perinatal pituitary-gonadal axis responds to GnRH. An increase in the sensitivity and magnitude occurs after birth and is maintained until about 90 days of age after which responsiveness gradually decreases during the first year of life. These findings correlate well with changes seen in pituitary-gonadal function in the human male infant.

### 2.30 p.m.

33 Delineation of the Significance of Falling E2 on Pituitary LH Sensitivity Prior to the Mid-Cycle Surge

J.D. Hoff, B.L. Lasley and S.S.C. Yen

Department of Reproductive Medicine, UCSD, School of Medicine, La Jolla, Calif.

It has been observed that prior to the onset of mid-cycle surge of LH, E2 often exhibits a decline and that controversy exists concerning the role of this fall in E2 in the initiation of the midcycle surge. To resolve this question, the following experiment was performed. Increasing circulating E2 to late follicular levels was achieved by daily incremental estradiol benzoate (EB) injection over a period of 5–7 days during the early follicular (EF) phase of the menstrual cycle. Pituitary sensitivity (S) and reserve (R) were assessed by 10 µg pulses of LRF and 2-hour intervals × 3, given either immediately after the last dose of EB when E2 levels were highest (EB0) or at 36 h after discontinuation of EB when E2 levels had fallen significantly (EB36). LRF responses in six women in the EF phase without EB treatment served as controls. EB induced an increase in pituitary S and R in the EB0 group, and a further amplification of this increase for the S and R was observed after the fall in E2 (EB36). From EB0 to EB36, while basal levels are unchanged, the ΔLH increased more than 2-fold (78.8 ± 31.9 vs. 171 ± 38 mIU/ml) and the percent rise increased 1.9-fold (380 ± 56% vs. 726 ± 59%, p < 0.01). Pituitary R (integrated Δresponse X 6 h) increased 2.7-fold (31.2 ± 4.7 vs. 86.5 ± 22.4 IU-min/6 h, p < 0.04). Thus, the pituitary S and R are further augmented in the face of falling levels of E2; this may be related either to the continuous tissue action of E2 despite the fall in circulating levels or to the loss of E2 inhibition. The fall of circulating E2 at the late follicular phase is not temporally related to the timing of mid-cycle surge but it may contribute to the excursion and duration of the surge.

### 2.45 p.m.

34 Correlation of Hypothalamic LRF and Pituitary LH and FSH in the Human Fetus throughout Gestation

Theresa M. Siler-Khodr and Gabriel S. Khodr

Department of Obstetrics-Gynecology, American University of Beirut, Beirut

Hypothalamic and pituitary tissues were obtained from 50 human fetuses with no apparent endocrinopathies. These tissues were stored at – 20 °C in acetone until extracted and analyzed for LRF, LH and FSH by RIA.

The hormonal patterns throughout gestation were distinctly different for male and female fetuses. In the female, hypothalamic LRF and pituitary LH and FSH attained peak content at 23 weeks’ fetal age and thereafter declined. A second, lesser rise in LH and FSH occurred late in gestation (34 week fetal age to term); however, a concomitant increase in hypothalamic LRF was not observed. In the male, LRF, LH and FSH increased with progressing gestational age.

Hypothalamic LRF was significantly greater (p < 0.001) at 34 week fetal age to term than
earlier in gestation. Pituitary LH increased exponentially with gestation and at a rate greater than the increase in pituitary size, while the increase of FSH paralleled the pituitary growth rate.

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The ratio of LRF:LH and LRF:FSH in both male and female fetuses varied throughout gestation, suggesting that other factors in the fetus may also modulate gonadotrophin production and/or the effect of LRF on LH and FSH production. However, the finding that peak pituitary LH and FSH content correlated with the peak hypothalamic LRF content in both male and female fetuses indicates that fetal hypothalamic LRF is most likely an important factor in regulating fetal gonadotrophin production and thus normal reproductive development.

3 to 3.15 p.m. Intermission

3.15 p.m. 35 Serial Determination of Maternal and Fetal C19 Steroids in Ovine Plasma during the Days Preceding Parturition
Antonio E. Colas and Luis B. Curet
Department of Obstetrics-Gynecology, University of Wisconsin Medical School, Madison, Wis.

Cortisol-induced increases in placental aromatizing activity or in the supply of 4-androstene-3,17-dione (A) synthesized from C21 steroids in the placenta have been proposed as possible explanations for the estrogen surge which occurs in the few hours before ovine parturition. Another possibility is that the supply of extraplacental C19 precursors, perhaps from the fetal adrenal, increases concomitantly with the production of fetal cortisol. To investigate this possibility, we have repeatedly measured A, dehydroepiandrosterone (D) and testosterone (T) by RIA in plasma from blood drawn through catheters implanted in the maternal femoral artery (FA), uterine vein (UV), and umbilical vein and artery (UmV and UmA) of 12 ewes. For D there was a significant difference UV-FA, 1.35 ± SE 0.51 ng/ml, which disappeared as parturition approached. There was a significant increase of A in UmV in the last day of gestation to 550 ± 108 (pg/ml ± SE) compared to a mean of 288 ± 21 for the 6 preceding days. The levels of D were greater in UmA or UmV than in FA; the concentration of T in UmV was higher than in UmA or FA, and the levels of A were about the same in FA and UmV and significantly greater than in UmA. These results suggest that the conversion of extraplacental D to A and T (and presumably estrogens) increases during the last few days of pregnancy.

(Supported by NIH grants No. 1-RO1-HD-05387–05 and No. 5-TO1-HD-00104–10 and Ford Foundation grant No. 630–0505B.C.)

3.30 p.m. 36 Increased Metabolic Clearance (MCR) and Production (PR) of Cortisol (F) by Baboon Neonates (Papio papio) is Associated with Spontaneous Delivery Gerald J. Pepe and John D. Townsley Pregnancy Research Branch, NICHD, NIH, Bethesda, Md.

MCR, interconversion (p), PR, and secretion (SR) of F and cortisone (E) were determined in 9 newboms, 5 (4 ¥ 1 ♀) delivered by cesarean section (group 1, 164–179 days), and 4 (3 ♀, 1♂) spontaneously (group 2, 166–180 days, term = 184 days). 25 µCi (3H)F and 50 mCi (14C)E in 0.9% NaCl were constantly infused (0.1 ml/min) via an antecubital vein. Saphenous vein blood was obtained at 0, 70, 80 and 90 min. F and E were extracted from serum and purified chromatographically. Serum levels (jug/100 ml) were determined by radioimmunoassay. Results (mean ± SE):

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MCR-E exceeded (p < 0.001) that of F. Percent F → E was greater (p < 0.001) than % E→F, therefore, F–E interconversion favors E formation. PR-E exceeded (p < 0.001) PR-F with 83% E secreted. Since MCR-E was greater (p < 0.05) in group 2 than in group 1 but serum E was lower (p < 0.05) in group 2 (26 ± 4) than in group 1 (36 ± 2), PR-E was similar in both groups. MCR-F in group 2 was twice (p < 0.001) that in group 1 and since serum F was similar in groups 1 (32 ± 7) and 2 (34 ± 8), PR-F was greater (p < 0.05) in spontaneously delivered newborns. About 65% F was secreted in both groups. The greater F synthesis associated with spontaneous delivery is compatible with the 4-fold greater adrenal 3(3-hydroxysteroid dehydrogenase-isomerase activity in such animals (G.J.P., J.D.T., Soc. Study Reprod. Abstract 155,1976).

3.45 p.m. 37 Fetal ACTH Stimulation of Steroidogenesis and its Implications for Parturition in Chronically Prepared Rhesus Monkeys
Scott W. Walsh and Miles J. Novy
Perinatal Physiology, Oregon Regional Primate Research Center, Beaverton, Oreg.
Fetal carotid and jugular, maternal femoral and amniotic fluid catheters were placed in 5 rhesus monkeys at 125 days’ gestation. The following experiments were performed: (1) Two animals received short-term (3–4 h) fetal ACTH infusions (5 IU injection plus 1 IU/h infusion) in conjunction with maternal dexamethasone infusion. Mean fetal plasma estrone (E1) increased 425% (55 to 289 pg/ml) and fetal estradiol (E2) increased 216% (9.8 to 31 pg/ml) after 30 min of ACTH. Mean fetal progesterone (P) rose 39% (8.2 to 11.4 ng/ml) and cortisol increased from 5.0 to 12.0µg/100 ml after 2 h. Maternal plasma steroids increased similarly but maximum levels were reached later and percent changes were not as great. (2) Three animals received short-term fetal ACTH without concurrent dexamethasone. Fetal and maternal plasma P and cortisol increased but plasma estrogens were not substantially altered when endogenous ACTH was not first suppressed by dexamethasone. (3) Three animals received long-term (1–9 days) fetal ACTH infusions which resulted in the onset of labor preceded by gradual increases of E1 in fetal plasma and of E1 and E2 in maternal plasma. Neither fetal nor maternal plasma P decreased prior to parturition. Amniotic fluid E1, prostaglandin E and F also increased during ACTH treatment. These data suggest that the fetal adrenals play an important role in steroidogenesis and that increased release of fetal ACTH with subsequent increases of fetal and maternal plasma estrogens and amniotic fluid E, and prostaglandins may normally precede the onset of labor in primates.

4 p.m. 38 Dehydroepiandrosterone and not Dehydroepiandrosterone Sulfate is the Major Circulating Estrogen Precursor in Pregnant Baboons John D. Townsley, Herman A.J. Schut and Gerald J. Pepe Pregnancy Research Branch, NICHD, NIH, Bethesda, Md.
To examine whether Dehydroepiandrosterone (D) is quantitatively more important than dehydroepiandrosterone sulfate (DS) as an estrogen precursor in baboon pregnancy, the serum concentrations, metabolic clearance (MCR), conversion ratios (CR), intercon-version (p), production rates (PR), secretion rates (SR) and contributions of D and DS to serum estradiol-[3H] (E2) were determined. At 11.00–12.00 h, 3 animals (154–167 days gestation, term = 184) weighing 18.4 ± 0.6 kg were sedated with ketamine intravenously and 150 µCi 14C-D and 1 mCi 3H-DS were infused constantly for 2 h via an antecubital vein. Saphenous vein blood was withdrawn after 100, 110 and 120 min. Radio chemically pure serum D, DS and E2 were isolated by chromatography and crystallization. D and DS levels (µg/100 ml) were determined by
radioimmunoassay. Results (mean ± SE): Serum D (2.5 ± 1.4) was < serum DS (18.9 ± 5.7) but MCR-D, 1/day/kg (35.0 ± 2.5) was > MCR-DS (2.6 ± 0.4) making mean PR-D, µg/h/kg (36.0) > MCR-DS (2.6 ± 0.4). Since CR-D → DS (5.66 ± 0.83) was > CR-DS → D (0.005 ± 0.001), p-D → DS (42.7 ± 4.5%) was > p-DS → D (6.9 ± 0.6%). Therefore, mean SR-D was > mean SR-DS, 35 vs. 5 µg/h/kg, indicating that 95% D but only 25% DS was secreted. CR-D → E2 (0.263 ± 0.029) was > CR-DS → E2 (0.002 ± 0). Using these serum concentrations and conversion ratios, it was calculated that 91% serum E2 was derived from D directly and 4% from D via circulating DS, while only 1% E2 was derived directly from DS and 4% from DS via circulating D. Thus, despite the low serum D concentration resulting from a high MCR, the large SR-D and efficient conversion of D to E2 makes D the major circulating estrogen precursor in late baboon pregnancy.

4.15 p.m. 39 Fetal Contribution of Oxytocin in Human Parturition
M. Yusoff Dawood, Chun F. Wang, Rommel Gupta, and Fritz Fuchs Department of Obstetrics-Gynecology, Cornell University Medical College, New York, N.Y.
Recent evidence suggested that the fetus might contribute oxytocin to the mother during spontaneous labor. Oxytocin (OT) was measured by a specific and sensitive radio-immunoassay, requiring preliminary extraction with Fuller’s earth and using oxytocin antibody raised in rabbits and rabbit anti-γ-globulin from goats to separate bound from free hormone. In 26 subjects with spontaneous labor and vaginal delivery (group I) and 18 subjects with cesarean section after labor (group II), umbilical arterial plasma (UA) levels were significantly higher than umbilical venous plasma (UV) (116 ± 17.2 and 118.4 ± 18.1 pg/ml, respectively) were significantly higher than umbilical venous plasma (UV) (38.0 ± 5–6 and 34.9 ± 6.6 pg/ml; p = &lt; 0.001 and p = &lt; 0.001, respectively). With elective cesarean section (group III), UA OT was 29.8 ± 7.5 pg/ml and UV OT was 16.1 ± 5.9 pg/ml (n = 14). In contrast, UV levels (69.9 ± 18.6 pg/ml) were higher than UA levels (24.6 ± 9.0 pg/ml) (n = 7), when pitocin was given to the mother (group IV). The arteriovenous (A-V) difference in OT levels which were 73.3 ± 13.3 pg/ml and 81.0 ± 12.4 pg/ml in groups I and II were significantly higher than in group III (13.8 ± 5.1 pg/ml; p = &lt; 0.005 and p = &lt; 0.005, respectively). Amniotic fluid OT levels, which were 110.8 ± 19.7 pg/ml in group I (n = 3) and 48.1 ± 12.4 pg/ml in group II (n = 11), were higher than in group HI (13.6 ± 6.7 pg/ml, n = 11). OT was also present in fetal urine. The findings indicate that during spontaneous labor, a substantial amount of oxytocin is produced by the fetus and transferred to the maternal circulation. (Supported by Ford Foundation grant No. 670–0455.)

4.30 p.m. Business Meeting (members only)
Mohave and Maricopa Rooms – Marriott Hotel
7 p.m.
Reception, Banquet and Entertainment
Old Tucson
Charter buses are available for transportation from the Marriott Hotel to Old Tucson. Reception and Banquet are supported, in part, by the Ortho Pharmaceutical Corporation and the G.D. Searle Company.
Concurrent Session D
Thursday, March 24, 1977
Greenlee and Graham Rooms – Marriott Hotel
1.45 to 4.30 p.m.
1.45 p.m. 40 In vivo Measurement of Regional Cerebral Metabolic Rate in Fetal Sheep in utero
R.M. Abrams, J.F. Clapp, III and M. Notelovitz
Department of Obstetrics-Gynecology, University of Florida, School of Medicine, Gainesville, Fla.
Healthy fetal brain continually metabolizes energy, most of which is converted to heat and lost to the circulating blood. In preliminary studies in 5 fetal sheep in utero, brief total occlusion of the brachiocephalic artery (BC) prevented loss of fetal brain metabolic heat and led to a rise in brain temperature \( \frac{\circ}{\circ} \). As the ischemia needed for the accurate estimation of fetal brain metabolic heat production may have been incomplete, the effect of simultaneous occlusion of the pulmonary artery and aorta (PA-A) on brain temperature was investigated in 10 near-term fetal sheep and the results compared with the alternate method of occlusion of the BC. Thermocouples (36 gauge) were implanted to a minimum depth of 1 cm in brain tissue, but their exact position was not verified. Rate of \( T_{FBR} \) rise (\( T_{FBR} \)) following PA-A occlusion (0.144 ± 0.018 SEM \( \circ/\circ \)/min) was significantly greater than \( T_{FBR} \) following BC occlusion (0.130 ± 0.014 SEM \( \circ/\circ \)/min). Brain specific heat (c) of 3 other fetal brains measured by the method of mixtures averaged 0.873 cal/g/\( \circ \). On this basis the fetal brain heat production (\( \dot{q}_{GR} \times c \)) was 0.126 cal/g/\( \circ \)/min. Assuming brain metabolism to be completely aerobic and glucose to be the sole energy substrate, this estimated rate of fetal brain heat production was equivalent to a cerebral oxygen consumption of 2.5 cm\(^3\)/100 g/\( \circ \)/min or about 4 times the oxygen uptake (per 100 g) of the fetal body as studied in comparable acute experiments.

Society for Gynecologic Investigation
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2 p.m. 41 Effect of Atropine on Fetal Cardiac Output during Hypoxemia
James R. Green, Robert K. Creasy, Michael A. Heymann and Abraham M. Rudolph
Cardiovascular Research Institute, University of California, School of Medicine, San Francisco, Calif.
It has been suggested by Cohn et al, that the decrease in fetal cardiac output during hypoxia is aggravated by atropine blockade. We have investigated this question by continuous measurement of left cardiac output (LCO) or right cardiac output (RCO) during induced hypoxia with atropine blockade. An electromagnetic flow transducer was placed on the ascending aorta or the main pulmonary trunk of fetal lambs from 122 to 127 days’ gestation. 2–7 days after operation fetal hypoxemia was induced by administration of a low \( \rho_{O2} \) mixture (\( \rho_{O2} 53 \)) to the standing ewe. The mean fetal \( pO2 \) decreased from 22.5 mm Hg to 13.4 mm Hg. In 5 studies on 3 fetuses with aortic flow transducers the fetal heart rate (FHR) decreased to 86% of control after 5 min and the mean LCO decreased to 84% of control. Administration of 0.2 mg/kg atropine was followed by an increase in the FHR to 133% of control and a return of LCO to 98% of control. In 3 studies on 2 fetuses with main pulmonary trunk flow transducers the FHR decreased to 91% of control after 5 min of hypoxemia, but RCO decreased minimally to 98% of control. Administration of atropine caused a rise in the FHR to 160% of control and an increase in RCO to 15% above control values. The results indicate that atropine administration during moderate hypoxemia results in an increase in both left and right cardiac output and suggest that right cardiac output may be relatively maintained during moderate hypoxemia.
2.15 p.m. 42 Effects of 2-\( \alpha \)-Br-Ergocryptine on Prolactin Concentration and Mammary Blood Flow during Parturition in the Ewe
Laurence I. Burd
Division of Fetal and Maternal Medicine, Michael Reese Hospital and Medical Center, Chicago, Ill.

Previous studies in chronic sheep preparations with uterine vein sampling catheters and electromagnetic flow probes implanted around the mammary arteries, demonstrated that an increase in mammary blood flow (MBF), a rise in prolactin concentration and a decrease in progesterone concentration were early physiologic events during spontaneous and induced parturition, while an increase in estradiol-17β and onset of uterine contractions occurred later. This study was designed to examine the role of prolactin as a cause of the increase in MBF during parturition. In 3 ewes 1 mg of 2-α-Br-ergocryptine was injected every 6 h to lower prolactin concentration. A control group of 3 animals received injections of the vehicle alone. In both groups, dexamethasone (1 mg/24 h) was infused into the fetus to initiate parturition. Prolactin concentration increased from 69 ± SEM 19 ng/ml to 279 ± SEM 90 ng/ml in the control group while it fell from 33 ± SEM 4 ng/ml to 2 ± SEM 0.1 ng/ml in the group receiving 2-α-Br-ergocryptine. Although prolactin concentration rose in the control group and decreased in the experimental group, a similar increase in MBF occurred in both groups (control, 61 ± SEM 12 ml/min to 243 ± SEM 8 ml/min; experimental, 68 ± SEM 16 ml/min to 265 ± SEM 59 ml/min). This study seems to indicate that the increase in prolactin concentration and MBF which occur at the time of parturition in the ewe are not causally related.

Scientific Abstracts

2.30 p.m. 43 Cardiac Output and Uterine Blood Flow in the Pregnant Ewe
James F. Clapp, III
Department of Obstetrics-Gynecology, University of Vermont College of Medicine, Burlington, Vt.
15 chronically instrumented ewes were studied using the direct Fick technique for measurement of cardiac output and the diffusion equilibrium technique to measure uterine blood flow. The mean weight of the uterus and its tissue contents at term was 6.2 ± 0.5 kg with mean rates of uterine blood flow and oxygen consumption of 1.62 ± 0.15 1/min and 57 ± 4 cm³/min, respectively. These data indicate that the uterus and its tissue contents at term utilize 24% of maternal oxygen consumption while accounting for only 13% of maternal weight. In 8 animals studied at term and again 3 months thereafter, uterine blood flow at term represented 79% of the increase in maternal cardiac output above the nonpregnant level. Likewise, uterine oxygen consumption at term represented 84% of the increase in maternal oxygen consumption above the nonpregnant level. The same relationship was noted throughout pregnancy in 4 animals studied repetitively from 60 days to term. When uterine blood flow and oxygen consumption at term were subtracted from maternal values there was no significant difference between maternal cardiac output and oxygen consumption at term and that found in the non-pregnant state. (Supported by Vt. Heart Association grant No. 88.)

2.45 p.m. 44 The Effect of Systemic Infusions of Dehydroisoandrosterone on the Distribution of Uterine Blood Flow in the Ovine Pregnancy Charles R. Rosenfeld, Richard J. Worley and Norman F. Gant
Departments of Obstetrics-Gynecology and Pediatrics, Southwestern Medical School at Dallas, Dallas, Tex.
Although estrogen is a potent vasodilator of the vascular beds of the ovine uterus, precursors of ovine estrogen remain unknown. Studies in our laboratories have shown significant increases in UBF and plasma estrone (E1) and estradiol (E2) after a systemic infusion of
dehydroisoandrosterone (D) in the pregnant ewe. To investigate the distribution of uterine blood flow (UBF), 4 pregnant ewes, 105 to 128 days of gestation, were studied with microspheres before and after a systemic infusion of 6 mg D. Serial blood samples obtained from 3 ewes showed increases at 15 min in E1 from 27.3 ± 2.23 (mean ± SE) to 117 ± 13.2 pg/ml and in E2 from 34.3 ± 4.91 to 71.7 ± 5.21 pg/ml (p < 0.05). At 140 min neither UBF nor placental blood flow was significantly changed. Endometrial blood flow increased from 176 ± 24 to 242 ± 32 ml/min (39%, p < 0.005) and myometrial blood flow rose from 35 ± 6.1 to 51 ± 8.4 ml/min (45%, p < 0.01). Of interest were the responses in cervical blood flow, increasing from 3.18 ± 0.6 to 15.6 ± 2.0 ml/min (441%, p < 0.005), and vaginal blood flow, increasing from 0.175 ± 0.03 to 0.992 ± 0.15 ml/min·gm (476%, p < 0.01). These studies suggest that D may be an important precursor of E, and E2 and that the ovine estrogen surge at term may prepare the uterus, cervix and vagina for the process of parturition. Furthermore, they reveal that the increase in UBF following an infusion of D reflects increased perfusion of nonplacental tissues, supporting earlier observations that exogenous estrogens might have no beneficial effects for the fetus.

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3.15 p.m. 45 A Pharmacokinetic Model Describing the Distribution and Elimination of Meperidine in the Maternal-Fetal Unit
Hazel H. Szeto, Charles E. Inturrisi, Amrutha Bhakthavathsalan, Maida Liu and Leon I. Mann
Department of Pharmacology, Cornell University Medical College, New York, N.Y., and Department of Obstetrics-Gynecology, University of Vermont College of Medicine, Burlington, Vt.

Meperidine (M) pharmacokinetics were evaluated in the chronic pregnant ewe preparation. Plasma levels of M were measured (J. Chromat. 125: 503, 1976) in mother (MA) and fetus (FA) following intravenous bolus and continuous infusion of M to MA. After an intravenous bolus (2.5 mg/kg), M appears in FA within 2 min at levels approaching MA. Thereafter, FA and MA levels fall at approximately the same rate in a biexponential fashion. Pharmacokinetic analysis reveals that the fetus may be considered as part of the maternal central compartment, implying that there is rapid equilibration of M between mother and fetus. When M is infused at a rate of 0.06 mg/kg/min, steady state (SS) is achieved in MA in 30 min and in FA in 60 min. At SS, the plasma M concentration ratio of FA/MA is equal to 0.3. Plasma protein binding of M averaged 54% for MA, and 28% for FA. When differences between MA and FA in plasma binding and degree of ionization are taken into account the recalculated SS concentration ratio is still significantly less than 1 (approx. 0.26). These data suggest that there is either active transport of M from fetus to mother, or fetal elimination of M. Data from the intravenous bolus study does not support active transport. Therefore we propose that M confers on the maternal-fetal unit the characteristics of a two-compartment open model with elimination from both maternal and fetal compartments. This model suggests that the elimination by the fetus makes an important contribution to the disposition of M.

(Supported in part by DA-01457, UCP 237-71 and Hoffmann-La Roche.)

3.30 p.m. 46 Cardiovascular Reactivity of Sheep to Autonomic Stimuli during Adrenergic Depletion
Department of Obstetrics-Gynecology, UCLA School of Medicine, Los Angeles, Calif.
Previous studies have shown that autonomic controls of cardiovascular functions change continuously throughout the perinatal period assuming adult pattern at 8 weeks of age. To further characterize intrinsic cardiovascular sensitivity to neurohumoral mediators, responses of chronically instrumented neonate and adult sheep to autonomic agonists and antagonists were investigated during neuronal adrenergic depletion. Effects on heart rate (HR) and arterial pressure (AP) of cholinergic stimulation (acetylcholine) and inhibition (atropine), α-adrenergic stimulation (norepinephrine) and inhibition (phenoxybenzamine), β-stimulation (isoproterenol) and inhibition (propranolol) and ganglionic stimulation (DMPP) and inhibition (Arfonad) were monitored in control periods and after adrenergic depletion with reserpine (20 µg/kg intramuscularly daily for 5–7 days) using the same animals as its own control. Complete depletion was ascertained by abolition of response to tyramine. Adrenergic depletion produced:

1. marked bradycardia with insignificant AP changes;
2. increased reactivity of HR and AP to cholinergic receptor blockade and stimulation;
3. reversal of effects of α-blockade and increased reactivity to α- and β-stimulation;
4. reversal of ganglionic blocking action and diminished response to ganglionic stimulation.

Conclusions: (a) neuronal adrenergic depletion with reserpine renders heart and blood vessels supersensitive to action of neurotransmitters and to atropine, and reverses action of ganglionic blockade; (b) neonate supersensitivity was not different from adult sheep.

3.45 p.m.

47 Vascular Compliance in the Fetal Sheep Placenta
Gordon G. Power and Raymond D. Gilbert
Loma Linda University School of Medicine, Loma Linda, Calif.

To explore the mechanical properties of umbilical vessels and to test the interaction between maternal and fetal vessels in the placenta we recorded pressure-volume curves from isolated in situ placentas of 17 sheep. We measured compliance at 3 rates of volume change and estimated true compliance by extrapolating to infinitely slow rates of volume change. We found control umbilical compliance averaged 0.218 (± 0.020 SEM) ml/mm Hg/kg fetal weight, a value that increased 28%, a significant rise (p &lt; 0.001), when maternal arterial pressure was lowered 85 mm Hg (clamping aorta), but did not change significantly when venous pressure was raised 35 mm Hg (clamping IVC). After replacing blood with kerosene which does not penetrate small vessels, we found arteries accounted for 22% and veins for 40% of total compliance, leaving 38% attributable to the placental unit. We conclude that umbilical vessels are about one half as compliant as adult vessels per body weight, but comparable to vessels elsewhere in the fetal body. We compared the observed interaction with predictions of mechanical and mathematical models, assuming that expanding fetal vessels would tend to stretch surrounding placental tissue and displace maternal blood. The observed interaction could be explained if maternal vessels operate on the linear part of their pressure-volume curve at normal and high pressures but become more compliant when maternal pressure falls. Thus, expanding fetal vessels could more easily displace maternal blood, and a higher umbilical compliance would be measured.

4 p.m.

48 Vasoreactivity to Angiotensin-II Infusion during Gestational Age 29–32 Weeks
John P. O’Grady, Cynthia J. Hamilton and John A. Morris
Department of Obstetrics-Gynecology, Charles R. Drew Postgraduate Medical School, Los Angeles, Calif.
Reportedly (Gant N.F. et al, J. clin Invest. 52: 2682, 1973), healthy young primi-gravid patients at risk of developing pregnancy-induced hypertension (PIH) demonstrate an enhanced diastolic pressor response (\(\geq 20\) torr) to \(\leq 8.0\) ng/kg maternal body weight/min infused A-II. We tested 26 such patients serially during a 4-week interval (29–32 weeks), maintained in the left lateral recumbency, with progressive increments in A-II dose \((2.0–15.0\) ng/kg/min). Blood pressure was obtained with an ultrasound device. All patients were followed through delivery. 3 patients (12%) developed PIH; only 1 of 3 demonstrated enhanced vasoreactivity. Conversely, 13 patients who did not develop PIH demonstrated enhanced vasoreactivity at least once during the testing interval. Comparison of results obtained from 1 week to the next was evaluated in 58 test pairs: discordant data, i.e. reactive to \(\leq 8\) ng/kg/min one week and unreactive the next, was observed in 18 pairs (45%).

We conclude that assessment of PIH risk, utilizing the diastolic pressor response to infused A-II as reported, is unreliable.

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4.15 p.m. 49 Hemodynamic Changes in Pregnant Rabbits
Bahij Nuwayhid
Department of Obstetrics-Gynecology, Washington University, School of Medicine, St. Louis, Mo.

The hemodynamic changes during pregnancy have been controversial. Present data were obtained from 3 groups of rabbits: control nonpregnant (Gl), 10–20 day pregnancy (Gil) and 20–30 day pregnancy (GUI). Under light pentobarbital anesthesia, jugular, carotid and femoral vessels were catheterized. Evans blue dye was used to measure plasma volume and 85Sr microspheres \(15 \pm 5\) m\(\mu\) were used to measure organ flow and cardiac output (CO). Parameters recorded were: arterial pressure (AP); heart rate (HR); plasma volume (PV); red blood cell volume (RBCV); reproductive flow (RF), including myometrial, tubal, ovarian, vaginal and placental flow; organ flow, including liver, lung, kidney, spleen and heart. Results showed: (1) HR increased 6 and 10% in Gil and GUI, AP dropped 11 and 19%; (2) total PV and RBCV increased by 45 and 28%, CO increased 40% when these values were related to body weight; there was no difference between Gil and GUI; (3) systemic resistance dropped 18 and 27% in GI and GUI; (4) RP increased progressively but when measured per gram of tissue, there was a drop in myometrial and vaginal flow and an increase in placental and ovarian flows; (5) liver and spleen flows dropped, coronary flow increased. Conclusions: (1) the placenta is a low resistance structure implanted in parallel with the systemic circulation; (2) the BV and CO changes in pregnant rabbits reach a peak in mid-pregnancy; (3) pregnancy induces decreased vascularity in the vagina and myometrium but, in contrast, placental vascularity increases; (4) the liver and splenic flows decrease which may suggest increased sympathetic activity and venous return.

4.30 p.m.
Business Meeting (members only)
Mohave and Maricopa Rooms – Marriott Hotel
7.00 p.m.
Reception, Banquet and Entertainment
Old Tucson
Charter buses are available for transportation from the Marriott Hotel to Old Tucson. Reception and Banquet are supported, in part, by the Ortho Pharmaceutical Corporation and the G.D. Searle Company.
1.45 p.m.  50 ADH and Oxytocin Content of Prolactin (PR) Powder

Helmuth W. Vorherr, Ute F. Vorherr and Sidney Solomon
Departments of Obstetrics-Gynecology, Pharmacology, and Physiology, University of New Mexico, School of Medicine, Albuquerque, N. Mex.

Possible renal salt and water retaining effect of Pr in laboratory animals and humans has been linked to premenstrual edema and to excessive water and salt retention in pregnant women. Since other pituitary hormones may be responsible for some renal effects attributed to Pr, rat (NIH-RP-1), ovine (NIH-P-S-10, S-12), and bovine (NIH-P-B4), Pr preparations were examined for their content of ADH and oxytocin using rat antidiuresis, milk-ejection, and blood pressure assays.

Blood pressure, antidiuretic, and milk-ejection activities were measured and identified as ADH or oxytocin or both by incubation of Pr solutions (0.001 to 2.0 mg/ml) with ADH antiserum, oxytocin antiserum or pregnancy plasma.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>RP-1 P-S-10 P-S-12 P-B4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH: µU/mgPr powder</td>
<td>100,700 ± 700  2,540 ± 207  1,582 ± 94  1,578 ± 450</td>
</tr>
<tr>
<td>Oxytocin: µU/mg Pr powder</td>
<td>155,250 ± 3,500  795 ± 95  510 ± 56  784 ± 41</td>
</tr>
</tbody>
</table>

(1) = mean ± SE;  
(2) = number of assay animals.

ADH (mainly) and oxytocin impurities of Pr powder exert renal effects falsely attributed to Pr. Pregnancy plasma or ADH and oxytocin antisera can inactivate Pr impurities of ADH and oxytocin allowing determination of the true renal effect of the Pr molecule.

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2 p.m. 51 Further Evidence for the Specificity of Amnionic Osmoregulation by Prolactin

Emilio A. Leontic, Barbara Andreassen, Beverly Smith and John E. Tyson
Department of Obstetrics-Gynecology, The Johns Hopkins University School of Medicine, Baltimore, Md.

Studies in this laboratory have shown that ovine prolactin (OPRL) significantly decreases fetal to maternal transport of tritiated water (THO) across human term amnion in vitro (Am. J. Physiol., in press). Since extracts of OPRL are known to be contaminated with vasopressin, studies were performed where vasopressin (20–200 µU/ml) was added to the fetal side of the membrane suspended in an Ussing chamber. No influence of vasopressin was observed on membrane permeability. When equimolar concentrations of HPL or HGH were substituted for OPRL (10 µg/ml), no changes in permeability constants were observed. That is, these substances failed to decrease permeability. Furthermore, the addition of an excess of antibody to OPRL abolished the OPRL effect on membrane permeability, yet it had no effect in control preparations which did not contain OPRL. Further substantiation of OPRL effect on amnion permeability was obtained when amniotic membranes were pre-incubated with a specific antiprolactin receptor antibody. The antireceptor sera added in a concentration of 200 µl (1:50 dilution) nullified the OPRL effect. Others have shown that a 1:100 dilution of a similar antiserum causes 50% of inhibition in the binding of radiolabeled prolactin to specific tissue receptors. These results add to the growing
body of evidence suggesting that prolactin plays a specific role in the regulation of water transport across the human amnion at term.

2.15 p.m. 52 The Influence of Gonadotropins on Ovulation in vitro
Yasuo Hamada, Karen H. Wright and Edward E. Wallach
Department of Obstetrics-Gynecology, Pennsylvania Hospital, and University of Pennsylvania School of Medicine, Philadelphia, Pa.
The purpose of the present investigation was to determine both temporal and qualitative requirements for gonadotropins to bring about ovulation in the isolated in vitro perfused rabbit ovary. Three experimental approaches were used: (1) administration of an ovulation-inducing dose of HCG (50 IU) to the intact rabbit and initiation of ovarian perfusion at various time intervals thereafter (1, 2, and 4 h, post HCG administration); (2) addition of HCG (100 IU) to the perfusion fluid following ovarian removal from the untreated, isolated rabbit; (3) removal and perfusion of both ovaries from the rabbit which has received PMS alone for follicular maturation to determine the effects on ovulation of PGF2α added to the perfusate. A significant reduction in numbers of ovulations occurred in vitro when the ovary for perfusion was removed 2 h or less after HCG administration to the intact animal. Addition of HCG to the perfusate achieved ovulation in vitro with the same frequency as in perfused ovaries from animals which had received systemic HCG prior to ovarian removal and perfusion. In rabbits treated with PMS alone (100 IU intramuscularly, 80 h before beginning perfusion), addition of PGF2α (1 mg) to the perfusion system resulted in an increase in ovaries ovulating as compared to the contralateral perfused ovaries without added PGF2α.

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2.30 p.m. 53 Effect of Ampullary Isthmic Junction Resection on Estrogen-Induced Tube Locking of Ova in the Rabbit
Canton A. Eddy, Jose P. Balmaceda and Carl J. Pauerstein
Department of Obstetrics and Gynecology, The University of Texas Health Science Center, San Antonio, Tex.
The pattern of tubal ovum transport in most mammalian species is dominated by a pause at the ampullary isthmic junction (AIJ) prior to entrance of ova into the uterus. In the rabbit the administration of 250 µg estradiol cypionate (EC) on the day of ovulation significantly prolongs retention of ova in the oviduct. Recent findings (Pauerstein et al.: Gynecol. Investig. 5: 121, 1974) suggest that estrogen in ‘tube locking’ doses causes constriction of the AIJ and that after this junction is negotiated, progress through the isthmus is probably normal. Advances in tuboplastic microsurgery allow us to examine tubal function by altering tubal anatomy (Eddy et al.: Experientia 32: 1194, 1976). The present experiment examines the mechanism of estrogen-induced retardation of tubal ovum transport. Rabbits underwent unilateral microsurgical excision or transection of the AIJ prior to end-to-end tubal anastomosis. Following recovery, animals were given an ovulatory dose of 100 U HCG followed by 250 µg EC. 72 h post HCG animals were killed. Oviducts were excised, dehydrated and cleared (Orsini: J. Reprod. Fert. 3: 283, 1962) and the location of ova determined. Only those oviducts demonstrating patency of the anastomosis site were retained. Resection of the AIJ did not prevent estrogen-induced retardation of ovum transport. These results indicate that estrogen retards transport by acting upon the tubal isthmus rather than through selective action upon the AIJ.

2.45 p.m. 54 Qualitative transition in the Luteotropic Mechanism of Early Pregnancy
David H. Wu and Walter G. Wiest
Ergocarnine blockade of prolactin secretion induces abortion in rats prior to day 7 of pregnancy but is ineffective thereafter. Assuming that changes in gonadotropic requirements for support of the corpus luteum are responsible, we have perfused dispersed luteal cells with luteinizing hormone (LH) and prolactin (PRL) alone and in combination. Progesterone secretion by luteal cells gradually declined during 5 h perfusion under conditions simulating tonic in vivo PRL-LH levels. Initial rates of progesterone secretion from cells obtained from days 5 and 8 of pregnancy were double that from day 2. Using day 5 cells, supplementation of tonic gonadotropin levels with a simulated PRL surge maintained initial progesterone secretion, and PRL withdrawal markedly reduced progesterone secretion while supplemental LH was ineffective. Conversely, using day 8 cells, progesterone secretion could be maintained undiminished with supplemental LH, but PRL was ineffectual. Total deprivation of LH from day 8 cells resulted in acute decline of progesterone secretion. Thus, the dispersed cell model successfully visualizes and more completely defines the qualitative transition in the luteotropic mechanism occurring between days 5–8 of pregnancy and parallels observations in vivo.

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3.15 p.m. Intermission

3.15 p.m. 55 Regulation of Placental Growth and Choriaonic Somatomammotropin (MCS) in the Rhesus Monkey: Effects of Protein Deprivation, Fetal Anencephaly and Placental Ligation

Miles J. Novy, Michel L. Aubert and Melvin M. Grumbach
Perinatal Physiology, Oregon Regional Primate Research Center, Beaverton, Oreg., and Department of Pediatrics, University of California School of Medicine, San Francisco, Calif.

A protein deficient diet (50% of estimated requirements) was administered prior to conception and throughout pregnancy (group I, n = 11). Experimental fetal anencephaly (group II, n = 7) and ligation of the interplacental bridging vessels (group III, n = 6) were performed at 75–80 days’ gestation. MCS was measured serially in maternal plasma and in fetal plasma at cesarean section. Fetal weight, stripped placental weight and placental DNA content were also determined near term in the three experimental groups and in appropriately timed controls.

MCS levels were not affected by protein deprivation, fetal anencephaly or placental ligation. MCS rose steadily until term paralleling the increase in placental weight (MCS at term = 16.5 ± 0.90 µg/ml in maternal and 24 ± 1.2 ng/ml in fetal plasma). At term MCS correlated with placental DNA (r = 0.71, p < 0.01) but not placental or fetal weight. Moderate protein deprivation had a negative effect on maternal weight gain but no effect on placental DNA, placental or fetal weight. Fetal anencephaly resulted in a 25% reduction in placental weight (p < 0.05) and a proportionately greater reduction in fetal carcass weight. Ligation of bridging vessels resulted in atrophy of the secondary placenta, an increase in weight and DNA content of the primary placenta (compensatory hypertrophy) and normal fetal weight. We conclude that placental growth is regulated by vascular and fetal pituitary trophic factors.

3.30 p.m. 56 Glucagon Response to Oral Alanine in Normal and Diabetic Pregnancies

John L. Kitzmiller, Robert Tanenberg, Thomas T. Aoki and John Hare
Harvard Medical School, Boston Hospital for Women, Joslin Clinic and Research Laboratory, Boston, Mass.

The role of glucagon in metabolic homeostasis of pregnancy and hyperglycemia of diabetes is uncertain. The concentration of glucagon was determined in the basal state and after the stimulus
of alanine in late pregnancy and the puerperium. Seven nonobese normo-glycemic pregnant women and 16 insulin-dependent diabetic women were studied at 32–34 weeks’ gestation and at 6–8 weeks’ postpartum. After a 10-hour fast, blood samples were drawn at baseline and 30, 60, 90, and 120 min after ingestion of 10 g L-alanine. In the

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normal subjects basal glucagon levels tended to be higher during pregnancy as compared to postpartum, and showed a significantly greater response to alanine. The rise in glucagon after alanine was

<table>
<thead>
<tr>
<th>Glucagon, pg/ml Mean ± SEM</th>
<th>Basal 30 min 60 min 90 min 120 min</th>
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</thead>
<tbody>
<tr>
<td>7 Controls 34 weeks</td>
<td>41 ± 4</td>
</tr>
<tr>
<td>6 weeks postpartum</td>
<td>22 ± 5</td>
</tr>
<tr>
<td>16 Diabetics 34 weeks</td>
<td>31 ± 4  63 ± 9  84+11  60 ± 7  48 + 7</td>
</tr>
<tr>
<td>6 weeks postpartum</td>
<td>35 ± 3  68 ± 9  66 ± 8  51 ± 7  41 ± 5</td>
</tr>
</tbody>
</table>

similar in diabetics and controls during pregnancy. Diabetic subjects showed no evidence of fasting hyperglucagonemia and basal glucagon concentration was not related to the fasting blood glucose level. Blood glucose did not change significantly during the tests in controls but rose 28 mg/dl at 60 min (antepartum) and 36 mg/dl at 90 min (postpartum) in the diabetics. Seven diabetic patients were also studied before and 3–5 days after delivery, and the glucagon response to alanine was the same or greater than the response approximately 1 week prior to the delivery.

3.45 p.m. 57 Studies of Glucagon Secretion in Normal and Insulin-Dependent Diabetic Pregnant Women

William N. Spellacy, William C. Buhi and Sharon A. Birk
Department of Obstetrics-Gynecology, University of Florida School of Medicine, Gainesville, Fla.

An assessment of glucagon secretion during basal and oral glucose (100 g) induced hyperglycemic periods was made in normal women and in women whose pregnancy was complicated by insulin-dependent diabetes mellitus (White’s Classes B-D). The glucagon was measured by a radioimmunoassay method using a nearly specific α-cell antibody (Unger K30). Measurements of glucose, insulin and human placental lactogen were also made. The results show that basal glucagon levels are elevated in all pregnant women, but the rise is not correlated with the concentration of HPL. Normally, hyperglycemia suppresses the plasma glucagon levels. In the diabetic patients (31.8 ± 2.1 weeks’ gestation) the glucagon was not suppressed with hyperglycemia as is shown in the table (n = 8):

<table>
<thead>
<tr>
<th>Time, h</th>
<th>Fasting</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/100 ml</td>
<td>mean ± SEM</td>
<td>111.5 ± 11.1 173.0 ± 18.9 207.4 ± 12.4 222.3 ± 18.6 230.9 ± 22.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagon, pg/ml</td>
<td>mean ± SEM</td>
<td>242.3 ± 38.2 263.1 ± 35.4 320.6 ± 41.3 272.5 ± 28.3 227.7 ± 34.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t</td>
<td>0.4</td>
<td>1.5</td>
<td>0.9</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

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The failure of glucagon to suppress in the pregnant diabetic may contribute to the difficulty in controlling their blood glucose levels during the gestational period and may partially explain the increased insulin requirement of the pregnant diabetic.

4 p.m. 58 Placental Transfer and Fetal Toxicity of Sodium Nitroprusside
Sodium nitroprusside has been used in preeclampsia for the treatment of severe arterial hypertension. We studied maternal and fetal nitroprusside and cyanide levels in 8 near-term normotensive ewe preparations under intravenous ketamine anesthesia and controlled ventilation. Electromagnetic flow meters were applied to the umbilical and uterine circulations. Baseline maternal and fetal blood pressures, respiratory gases, blood cyanide and nitroprusside levels were obtained during the 30-min postoperative stabilization period. A maternal intravenous infusion of 0.005% solution of nitroprusside was maintained at a rate sufficient to decrease the mean blood pressure by 20% for a period of 1 h. Maternal and fetal levels of nitroprusside were at equilibrium at the 20-min sample. Fetal cyanide levels were not significantly elevated in 4 animals which required only a low rate of nitroprusside infusion to maintain the desired decrease in maternal blood pressure. In 4 animals who required a steadily increasing dose of nitroprusside to maintain the decreased blood pressure there was a marked accumulation of maternal and fetal cyanide with fetal levels significantly higher than the maternal level. These 4 fetuses expired in utero. In this preparation the placenta appears to be readily permeable to the nitroprusside molecule and increasing fetal cyanide levels appeared to be dose-related to maternal nitroprusside levels. The significantly higher fetal cyanide levels may be due to rapid formation of cyanide or a slower rate of detoxification and/or excretion. No significant changes were noted in umbilical or uterine flow.

4.15 p.m. 59 Cadmium Uptake in the Rat Embryo as a Function of Gestational Age
Robert A. Ahokas and P. V. Dilts, jr.
Department of Obstetrics-Gynecology, University of Tennessee Center for the Health Sciences, Memphis, Tenn.
Maternal tissue distribution, placental transfer and fetal accumulation of cadmium (Cd), a known embryotoxic trace element, was investigated following a single oral dose of 100 µg Cd/rat as Cd Cl2-containing 109Cd at days 6, 10, 14 and 17 of gestation. At 24 and 96 h post Cd administration the rats were killed and the fetuses or embryos, placentas, and maternal tissues removed for determination of 109Cd activity. Maternal liver and kidneys were the main target organs of Cd accumulation at all stages of gestation. At 24 h, livers had accumulated 0.039–0.386% dose/g tissue and kidney 0.053–0.203% dose/g tissue. A gradual redistribution occurs after the initial 24 h since 96-hour levels of Cd in liver were slightly decreased and kidney levels were slightly increased. Maternal blood concentrations were low (0.0001–0.0026% dose/g whole blood) at all stages of gestation. Embryo levels of Cd were highest prior to formation of the functional placenta (0.0081 and 0.0043% dose/g at days 6 and 10, respectively). The embryo to maternal blood Cd ratios were 51.6 and 42.3, respectively, indicating that the embryo accumulates Cd. After formation of the functional placenta, fetal Cd levels were decreased (0.00034 and 0.00019% dose/g at days 14 and 17, respectively) while the placenta accumulated Cd (0.033 and 0.092% dose/g at days 14 and 17, respectively). The placenta apparently protects the fetus from exposure to this element during the last third of gestation. The results indicate that the embryotoxic manifestations of large amounts of Cd administered to pregnant rats on days 14–17 may not result from direct action on the fetus but from maternal and/or placental effects.
Business Meeting (members only)
Mohave and Maricopa Rooms – Marriott Hotel
7 p.m.
Reception, Banquet and Entertainment
Old Tucson
Charter buses are available for transportation from the Marriott Hotel to Old Tucson. Reception and Banquet are supported, in part, by the Ortho Pharmaceutical Corporation and the G.D. Searle Company.

Second Plenary Session
Friday, March 25, 1977
Mohave and Maricopa Rooms – Marriott Hotel
8 a.m. to 9 a.m.
Distinguished Guest Lecture (made possible by a continuing grant from Ross Laboratories, Columbus, Ohio). ‘New Aspects of Mechanisms of Steroid Hormone Action: Somatic vs. Germ Cell’, Etienne-Emile Baulieu, MD, PhD, Professor of Biochemistry, Université de Paris Sud, Bicêtre, France
9 a.m. to 10.15 a.m.
Moderators: W. Ann Reynolds and Pentti K. Siiteri
9 a.m. 60 The Isolation from Human Amniotic Fluid and Characterization of Lamellated Structures Derived from Fetal Lungs
Sergio Fabro, Linda B. Gilmore, Mark J. Reasor, Diane Y. Bell and Gary E.R. Hook NIEHS, Pharmacology and Toxicology Branch, N.C., and Department of Obstetrics-Gynecology, George Washington University, Washington, D.C.
Synthesis and storage of fetal lung surfactant is initiated in cytoplasmic inclusion bodies of alveolar type II cells in the latter part of pregnancy. In this paper we wish to report the presence, at term, in human amniotic fluid of lamellated structures resembling lamellar inclusion bodies of the pulmonary alveolar type II cell. These structures were isolated by differential centrifugation at 10,000 g per 10 min and morphologically identified by electron microscopy. This fraction contained 2.8 and 47.8% of the total protein and phospholipids of the amniotic fluid, respectively. The limiting membrane of the intracellular organelle was absent, however, from these lamellated structures. Tubular myelin structures, which are normally found only within the airways of the lung, were also found in amniotic fluid. The lamellated structures were associated with high concentrations of acid hydrolases (e.g. (3-N-acetylglucosaminidase, α-mannosidase, β-glucuronidase, and acid phosphatase) and alkaline phosphatase. Isopycnic centrifugation on continuous density sucrose gradient showed the acid hydrolases were not a contaminant from lysosomes. Although secretion of pulmonary surfactant in the form of lamellated structures by the type II cells has been observed morphologically in fetal animals near birth, this is the first report describing the presence of lamellar bodies free in the human amniotic fluid. Furthermore, the results indicate the lamellar bodies secreted by pulmonary type II cells are carried into the amniotic fluid along with associated hydrolytic enzymes.

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9.15 a.m. 61 Factors Affecting Biologic Action of Progestins in Human Endometrium
William J. Mann, Peter D. Feil, Laurence Demers, Rodrigue Mortel and C. Wayne Bardin
Departments of Obstetrics-Gynecology, Biological Chemistry, Medicine and Pathology,
The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, Pa.

Several studies suggested that the greater potency of medroxyprogesterone acetate (MPA) vs. progesterone could depend upon either differential whole body metabolism of progestins, or factors enhancing the local activity of MPA on the endometrium. In order to distinguish between these two possibilities, we first studied MPA and progesterone metabolic clearance rates (MCR), and binding to serum proteins. When 3H-progesterone and 3H-MPA binding to plasma proteins were analyzed by polyacrylamide gel electrophoresis, only progesterone bound to cortisol binding globulin. The MCR of MPA (2,100 liter/day) was high but still less than progesterone (2,500 liter/day), even though MPA did not bind to serum proteins. We next examined the direct cellular action of progestins. Using an organ culture of human endometrium, MPA stimulated glycogen synthesis to a greater extent than progesterone. The kinetics of progesterone and MPA binding to endometrial progestin receptors was also investigated. The dissociation rate (t1/2) for MPA (24 h) was much slower than progesterone (2 h). Summary: (1) MPA is not bound by serum proteins; (2) MPA clearance rate is high but less than progesterone; (3) MPA has a more potent direct action on endometrium than progesterone, and (4) MPA dissociates slower than progesterone from the cytoplasmic receptor. Conclusion: in women, the increased biologic activity of MPA over progesterone is determined primarily at end organ rather than by differential rates of steroid clearance.

9.30 a.m. 62 The Biosynthesis of the Phosphatidylglycerol Component of Lung Surfactant
John M. Johnston, Gary E. Reynolds and Mary B. Wylie
Departments of Obstetrics-Gynecology and Biochemistry, University of Texas Southwestern Medical School at Dallas, Dallas, Tex.
The type II alveolar cell is the site of synthesis of surfactant, the lipoprotein that lines the alveolar spaces and prevents their collapse. The phospholipids of surfactant are characterized by high concentrations of dipalmitoylphosphatidylcholine (DP-PC) and phosphatidylglycerol (PG). It has been suggested that PG functions to stabilize the surfactant lipoprotein complex. We have shown that the lamellar bodies (LB) of the type II cells are the site of PC biosynthesis and that the increase in DP-PC biosynthesis during fetal development may be the result of an increase in phosphatidic acid phosphohydrolase (PAPase) activity. In this study we have demonstrated the formation of PG from its precursor, phosphatidylglycerol-phosphate (PGP) in LB. The hydrolytic release of P04 from phosphatidic acid (PA) and PGP was shown to be catalyzed by the same enzyme in LB by demonstrating that: (1) the substrates are competitive; (2) an identical inactivation for the hydrolysis of the two substrates is obtained by the addition of Hg2+, and (3) heat inactivation profiles are similar for both substrates. The Km and Vmax for PA and PGP hydrolysis are similar. These findings are consistent with the observed increase in DP-PC and PG in surfactant, the decrease in phosphatidylinositol concentration found in surfactant obtained during the latter stages of gestation, and the increased incidence of hyaline membrane disease of the newborn when the PG concentration in surfactant is relatively low.
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9.45 a.m. 63 Extraglandular Aromatization – Primarily an Extrahepatic Metabolic Process
Clare D. Edman and Paul C. MacDonald
Department of Obstetrics-Gynecology, University of Texas Southwestern Medical School at Dallas, Dallas, Tex.
Extraglandular aromatization increases with aging, obesity, and liver disease. It has also been shown that extraglandular aromatization increases during postoperative recovery, in
hyperthyroidism, compensated congestive heart failure and acute starvation. A common finding in these metabolic disorders is a relative increase in extrahepatic metabolism of plasma androstenedione (A). For this reason, we sought to ascertain if the extent of extraglandular aromatization was inversely related to the hepatic clearance of A. First, we found that only 5% of total extraglandular aromatization could be accounted for by trans-splanchnic-transhepatic metabolism. Second, an inverse relationship exists between hepatic extraction of plasma androstenedione and the transfer constant of conversion of A to estrone (EI) $k_{p^1}$. When the hepatic extraction of A is 90%, the conversion of A to EI is 0.015; but when the hepatic extraction is 10%, the $k_{p^1}$ is 0.16. Modest reductions in hepatic clearance of A (e.g. 65%) are associated with an increase of the $k_{p^1}$ to 0.06. We envision that a decreased hepatic extraction of plasma A results in relatively greater extrahepatic metabolism favoring aromatization. Reduced hepatic clearance of A may occur in early hepatocellular damage, before extensive scarring and fibrosis, and thus account for the increased extraglandular aromatization observed with aging, obesity, congestive heart failure, postoperative convalescence, starvation, and liver disease.

10 a.m. 64 Effect of Atropine on Heart Rate and Oxygen Consumption of the Hypoxic Fetus
Julian T. Parer
Department of Obstetrics-Gynecology and Reproductive Science and Cardiovascular Research Institute, University of California, San Francisco, Calif.
To determine if vagal blockade during hypoxic bradycardia improves fetal oxygenation (Vq), 10 studies were carried out on 5 chronically instrumented sheep, after 0.8 of gestation, with mean fetal weight of 2,674 g. Catheters were placed in the maternal and fetal distal aorta, common umbilical vein, and amniotic cavity. An electromagnetic flow probe was placed around the common portion of the umbilical artery. After control sampling, hypoxic gas mixtures were administered by face mask to achieve a mean maternal arterial pO2 of 32.5 ± 3.7 mm Hg but no change in maternal arterial pCO2 or pH. This produced a 20% decrease in FHR (171 ± 30 bpm, $p < 0.001$) and fetal Vq decreased from 7.9 ± 1.9 to 4.6 ± 1.5 ml/min/kg fetus ($p < 0.001$) 27 min after institution of hypoxia. The umbilical blood flow (mean 219 ± 57 ml/min/kg fetus) was unchanged but the Cy0-Ca0 decreased from 3.5 ± 0.9 to 2.1 ± 0.5 ml O2/100 ml ($p < 0.01$).

There was an immediate increase in FHR to 249 ± 26 bpm after atropine (mean dose 190 µg) was infused rapidly into the umbilical vein. At sampling, 8 min after atropine, FHR was 209 ± 44 bpm ($p < 0.001$), but umbilical blood flow and fetal Vq were not significantly changed. Atropine caused only a 25 bpm increase in fetal heart rate in the normoxic fetus.

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It is concluded that during hypoxia there is a substantial increase in vagal activity. Other studies have shown that there is also an augmented sympathetic chronotropic effect, unmasked by atropine blockade. These investigations show that atropine is of no benefit to fetal oxygenation during hypoxic bradycardia.
(Supported by NIH grant No. HD 09980.)
Moderators: Hilton A. Salhanick and Eric Block

10.45 a.m. 65 Isolation of αHCG Subunit mRNA
Thomas Landefeld and Irving Boime
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.

To examine the factors controlling the synthesis of human chorionic gonadotropin (HCG) during pregnancy it is important to isolate the mRNAs encoding the hormone. Purified first trimester placental mRNA, when translated in wheat germ, or ascites tumor extracts directed the synthesis of a major protein with a molecular weight of about 14,000. A similar protein was synthesized in partially purified placental extracts. Both proteins contained tryptic peptides corresponding to those of the αHCG subunit. Since the molecular weight of the protein portion of native α-subunit is 11,000, the data suggest that the cell-free product is a precursor.

No detectable synthesis of the Ø-subunit was observed. When first trimester RNA was translated in the presence of a variety of labeled amino acids only the α-subunit was detected. Similar results were obtained when mRNA was isolated from the whole placenta, post-nuclear, or post-mitochondrial supernates, and translated in the wheat germ cell-free system.

These results suggest that (a) the α-subunit is synthesized as a precursor protein and (b) the mRNA encoding the Ø-subunit turns over very rapidly and thus is under stringent control; its levels perhaps constituting a rate-limiting step in the expression of HCG in vivo.

11 a.m. 66 Study of the Steroid Binding Site of Human Placental Estradiol 17ß-Dehydrogenase with 12ß-Bromoacetoxy-4-estrene-3,17-dione
James C. Warren and Chang-Chen Chin
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.

We have recently crystallized human placental estradiol 17ß-dehydrogenase and identified a histidine residue in the catalytic region of the active site by affinity labeling with 16α-bromoacetoxyestradiol 3-methyl ether. Presuming that this histidine might actually proximate the steroid 17α-hydrogen (which is removed during dehydrogenation) and thus be directly involved in the catalytic step, we sought to further pinpoint its location. Examination of molecular models reveals that if a 12ß-bromoacetoxyestroid also affinity labels this residue, it must be so located, as the rototmers of the two reagent arms (12ß-bromo-acetoxy and 16α-bromoacetoxy) overlap only in the region of the 17α-H. Accordingly, 4-estrene-3,17-dione was incubated with Colletotrichum derridis and the resulting 120-hydroxy-4-estrene-3,17-dione was reacted with (2–3H)bromoacetic acid and dicyclohexyl-carbodiimide in pyridine. The product was recrystallized from ethanol and structure assured by IR spectroscopy and elemental analysis as 12ß-bromo(3H)acetoxy-4-estrene-3,17-dione (12ß-BAE). This steroid is a substrate, proving that it binds at the active site. Enzyme incubated with a 150-fold molar excess of 12ß-BAE in 0.5 M potassium phosphate buffer at pH 7.0, is inactivated in a time dependent, irreversible manner. Inactivation follows pseudo first order kinetics with t/2 = 18 h. Amino acid analysis of a hydrolysate of the 12ß-BAE enzyme inactivated revealed tritiated 1,3-dicarboxymethylhistidine. Affinity labeling of the histidine residue by both 16α- and 12ß-bromoacetoxy steroids localizes it at the point of catalysis and identifies it as a catalytic residue.

11.15 a.m. 67 Biological Testing and Receptor Binding of Medroxyprogesterone 17ß-Bromoacetate
Previously we reported that intrauterine release of 1–2 mg of 16α-bromoacetoxy-progesterone (16α-BAP) or 16α-bromoacetoxymedroxyprogesterone (16α-BAMP) in 7-day pregnant rats causes resorption of over 50% of the fetuses by day 14. The present work was undertaken to further investigate the relationships among the position of the bromoacetoxy reagent group on the steroid, interceptive activity, and progesterone receptor binding. For this purpose we synthesized medroxyprogesterone 17-bromoacetate (MPBA), an affinity labeling analog of Provera. Treatment of 7-day pregnant rats with 2–3 mg of MPBA caused no observable interruption of pregnancy. The biological activities of 16α-BAP, 16α-BAMP and MPBA were correlated with competitive binding against 3H-progesterone of the steroids for crude rabbit uterine progesterone receptor. 16α-BAP and 16α-BAMP had relative affinity constants (RAC) of 0.5, while MPBA had an RAC value of over 100, similar to medroxyprogesterone acetate. These results suggest that the position of the bromoacetoxy reagent group on the progesterone D-ring critically determines antiprogestational and thus interceptive activity, and also the degree of progesterone receptor binding.

11.30 a.m. 68 Danazol – 17α-Preg-4-en-20-yno-(2,3-d) isoxazol-17-ol – Inhibits Gonadal Steroidogenesis
Robert L. Barbieri, Jacob A. Canick and Kenneth J. Ryan
Harvard Medical School, Laboratory of Human Reproduction and Reproductive Biology, Department of Obstetrics-Gynecology, Boston, Mass.
Danazol is being used in the management of endometriosis, chronic cystic mastitis, and precocious puberty. Parenteral administration of danazol to castrated immature rats can suppress their high levels of serum LH and FSH (Biol. Reprod. 10: 438, 1974). Based on these findings it has been repeatedly stated that danazol exerts its pharmacologic effects by acting as an antigonadotropin. However, oral administration of danazol to humans significantly suppresses serum gonadal steroids without significantly altering serum LH or FSH levels (J. clin. Endocr. Metab. 32: 522, 1971; Obstet. Gynec N.Y. 45: 302, 1975; Johns Hopkins med. J. 137: 265, 1975). These clinical observations suggest that danazol exerts its pharmacologic effects by directly inhibiting gonadal steroidogenesis. Concentrations of danazol as low as 1 µM significantly inhibit LH stimulated testosterone and androstenedione production in cultured rat Leydig cells. Danazol binds to rat testis microsomal cytochrome P-450, eliciting a type I binding spectrum (Kg = 3.0 µM), which implies that danazol binds to the active enzymatic site. Danazol competitively inhibits rat testis 17α-hydroxylase with an inhibition constant (Ki) of 2.5 µM and 17/3-hydroxysteroid dehydrogenase with a Ki of 2.8 µM. These inhibition constants are similar to the concentration of danazol in the serum of human females taking 800 mg/day of danazol for two days. Given these experimental findings and the clinical observations cited above, it is likely that danazol exerts its primary pharmacologic effect by directly inhibiting gonadal steroidogenesis.

11.45 a.m.
69 Leucine-3H Incorporation into the Proteins of Hypothalamus and Pituitary and LH Release following Estrogen Treatment
Satya P. Kalra and Eugene O. Mitchell
Single injections of estradiol benzoate (EB, 10 µg/rat) to ovariectomized rats significantly suppressed serum LH levels 2, 4, 8 and 24 h later; serum LH-RH (methanol extracted) levels were unaltered but the LH-RH content in the medial basal hypothalamus (MBH) was significantly elevated at 24 h. This treatment also has been shown to modify the sensitivity of the pituitary to LH-RH administration: a rapid decrease (up to 4 h) followed by an augmentation in LH release. To study whether new protein synthesis is the common underlying mechanism in the estrogen feedback action at the hypothalmo-pituitary axis, the incorporation of leucine-3H (80 µc/rat s.c.) into proteins of the preoptic area, MBH, cortex and the pituitary was examined at intervals after EB injection. Leucine-3H incorporation was unaffected in these tissues for 4 h following EB treatment at the time when serum LH and the responsiveness of the pituitary to LH-RH were clearly depressed. However, a marked increase in leucine-3H incorporation into the proteins of the pituitary only occurred at 8, 16 and 24 h after EB administration, coincident with the enhanced pituitary sensitivity to LH-RH. These studies show that estrogen promotes storage of LH-RH in the MBH and that new protein synthesis may be an important initial step in the estrogen-induced augmentation of the pituitary responsiveness to LH-RH.

(Supported by NIH grant HD-08364.)

12 p.m.

70 Prostaglandins – Calcium Ionophores?
Mary E. Carsten and Jordan D. Miller
Department of Obstetrics-Gynecology and Anesthesiology, University of California School of Medicine, Los Angeles, Calif.

The concentration of free calcium in the myometrial cell determines contraction and relaxation of the uterus with an increase in free calcium causing contraction. Previous studies have demonstrated that prostaglandins (PG) and oxytocin are able to regulate calcium accumulation in a microsomal fraction derived from bovine myometrium. In this in vitro model, the change in calcium accumulation can be brought about by inhibition of ATP-dependent calcium binding or by enhancing calcium release.

Experiments were designed to separate these two processes. Microsomal preparations were allowed to take up calcium in the presence of limited amounts of ATP. When the ATP was exhausted, a steady level of calcium was attained. Addition of PGE2, PGFα, but not PGFβ, partially released the calcium previously taken up. Calcium release was measured by the 45Ca Millipore filtration method. Exchange of 45Ca with intrinsic calcium was determined in separate experiments and corrected for. The antibiotic ionophores X537A and A23183, as well as oxytocin, also released calcium previously accumulated under ATP stimulation. None of these agents with the exception of oxytocin released intrinsic calcium. Thus, the effect of the PGs resembles that of the ionophores, suggesting an ionophoretic action of these prostaglandins. The release of calcium conforms with the in vivo smooth muscle contracting action of these agents.

12.15 p.m. 71 Human Placental Lactogen (HPL) Concentration and Pools in the Placenta
Clifford Ernshar and David Gusseck
Departments of Perinatal Research and Biochemistry, Loma Linda University School of Medicine, Loma Linda, Calif.
Other studies of the regulation of HPL synthesis by the placenta require that we know the placental content of HPL, the fraction of HPL in readily secretable storage granules and the rate of HPL turnover within the placenta. Changes in these parameters as a function of gestational age or trophoblastic disease could, in themselves, serve as regulatory mechanisms. Conflicting reports of placental HPL levels in the literature probably stem from the rapid loss of HPL from tissue into extracellular fluid as a function of time after delivery or into wash medium during rinsing of the tissue. We have optimized the rapid extraction of HPL from placental tissue with a process utilizing detergents. Over 93% of total tissue HPL is obtained in one extraction to yield an average term placental content of 660 (± 67 SEM) µg HPL/g tissue. In a flow-through apparatus utilizing placental fragments, we have resolved the rate of extracellular fluid washout from the secretion rate and the rate of synthesis. We have found that 87% of placental HPL appears to be packaged for secretion and can be readily washed from the tissue. When this readily secreted fraction is depleted, a steady state level (86 µg/g) is reached which appears to be limited by the rate of synthesis. This steady state level can be maintained for over 13 h, reflects an initial rate of HPL synthesis of 10–12 µg HPL/g tissue, is slowly decreased by tissue death (t'/2 = 8 h), and is interrupted by the addition of inhibitors of protein synthesis. HPL turnover rate measurements are in progress and will be reported.

(Supported by NIH grant No. HD 09440.)

12.30 p.m. Adjournment
Concurrent Session B
Friday, March 25, 1977
Greenlee and Graham Rooms – Marriott Hotel
10.45 a.m. to 12.30 p.m.
Moderators: Guy M. Harbert, Jr. and Frank C. Greiss, jr.
10.45 a.m. 72 The Effect of Progesterone (P) and/or Estradiol (E) on Uterine Contractility and (3-Adrenergic Receptor (/3-AR) Number
James M. Roberts, P.A. Insel, R. Goldfien and Alan Goldfien
Department of Obstetrics-Gynecology and Reproductive Sciences, Medicine and Cardiovascular Research Institute, University of California, San Francisco, Calif.
In some species adrenergic stimulation causes contraction (α-AR) or relaxation (Ø-AR) depending on the hormonal milieu. We examined the contractile response to norepinephrine and (3-AR in uteri of immature rabbits treated with P and/or E to determine the relationship between changes in contractility and (3-AR sites. Norepinephrine (5 × 10^{-6} M) increased uterine contractility in E treated rabbits and the increase was blocked by phentolamine. After E + P, spontaneous uterine activity was inhibited by the same concentration of norepinephrine. The effect was blocked by propranolol. Particulate fractions of myo-metrium with isoproterenol responsive adenylate cyclase (with added guanyl nucleotide) were assayed for Ø-AR activity with 12SI-hydroxybenzylpindolol (I-HYP). We have shown that I-HYP, a potent /3-adrenergic antagonist, binds specifically, rapidly, reversibly and stereoselectively to uterus with high affinity (Krj = 70–360 pM) and low capacity (5–20 fm/mg protein) and competes with /3-agonists in a rank order characteristic of the /3j-AR. We found 20 ± 5 fm of sites/uterus in E treated animals and 16 ± 3 fm/uterus in those receiving E + P. We conclude that the P induced predominance of Ø-AR activity is not associated with an increase in number of /3j-AR/uterus.
11 a.m. 73 Reactivity of Uterine Vasculature to Dopamine
Karen Blanchard, Charles R. Brinkman, HI, Adrien Dandavino, Kenneth E. Clark and Nicholas S. Assali
The use of dopamine in the management of various forms of circulatory shock has received increasing attention in recent years; very little is known about its effects on the uterine circulation. The present report deals with data on uterine hemodynamic response to i.v. dopamine in pregnant and nonpregnant sheep. Pregnant and nonpregnant sheep were chronically instrumented for measurement of heart rate (HR), arterial pressure (AP), central venous pressure (CVP) and uterine blood flow (QU). Uterine vascular resistance (UVR) was calculated from the ratio of AP and QU. Dose response curves were developed to both bolus injections and constant infusions in doses ranging from 2–80 µg/kg. Results show: (a) AP progressively increased with doses above 10 µg/kg to a maximal increase of 90% in both groups of animals; (b) progressive and sustained increases in CVP were noted above doses of 10 µg/kg; (c) HR progressively increased in the nonpregnant animals while it decreased in the pregnant; these responses were present at 5 µg/kg; (d) QU increased linearly with increasing doses reaching a maximal increase of 25% in both groups of animals; the QU response was also noted at a lower dose level than the AP response. Conclusions: (1) dopamine has a paradoxical effect upon the heart rate of pregnant sheep; (2) pregnant and nonpregnant animals are equally sensitive to the vasopressor effects of dopamine; (3) UVR increases less than other regional vascular resistances, and (4) increased QU may be related to increased cardiac output.

11.15 a.m.

74 Biorythms in the Dynamics of a Pregnant Uterus
Guy M. Harbert
Department of Obstetrics-Gynecology, University of Virginia School of Medicine, Charlottesville, Va.
Rhesus monkeys were used in chronic experiments to delineate the existence and influencing factors of biorythms in the dynamics of the uterus during pregnancy. Part 1 of the study established the biorythms of spontaneous uterine activity, uterine artery blood flow, and aortic blood pressure. During a 24-hour period, all measured functions varied in patterns conforming to significant Fourier curves. Amplitude of variation was as great as 59% for intraamniotic pressure and 63% for uterine blood flow. These patterns were compounded by labor. Parturition produced inversely related exponential changes in uterine pressure and blood flow values and a linear increase in mean blood pressure. In part 2, the effect of adrenergic blockade and prostaglandin inhibition on the biorythms was investigated. α-Blockade (phentolamine) abolished the circadian rhythm of uterine pressure but not the exponential pattern of labor. Uterine blood flow increased. β-Blockade (propranolol) decreased uterine blood flow without significantly altering the basic rhythms. Inhibition of prostaglandin synthesis (indomethacin) decreased the amplitude but did not abolish the circadian pattern of uterine activity. Uterine blood flow exhibited disproportionate changes. Labor was inhibited. Differences in chronology and amplitude of the curves suggest adrenergic factors may act independently on the myometrium and uterine vascular bed to modulate these rhythms.
(Supported in part by USPHS grant HD 02798.)

11.30 a.m.

75 A Uterine Vasoactive Property of Glucosamine
Frank C. Greiss, jr. and J. Gordon Still
Department of Obstetrics-Gynecology, Bowman Gray School of Medicine, Wake Forest
Barcroft described a relatively constant concentration of glucosamine in the ovine cotyledon after 50 days of gestation which he associated with the ingrowth of Wharton’s jelly. The present experiment was designed to evaluate possible vasoactive properties of this amino sugar. Ewes were oophorectomized, an electromagnetic flow-probe was implanted on one uterine artery and its first branch was cannulated for drug infusions as described by Killam et al. (Am. J. Obstet. Gynec. 115: 1045, 1973). When daily intravenous estradiol-17β (E2), 1 µg/kg, produced consistent increases in uterine blood flow (UBF), 5-min uterine arterial infusions of a 1-mol solution of glucosamine-HCl (pH 2.9) were given prior to E2 stimulation. These infusions produced control arterial glucosamine concentrations from 2.6 to 77 mg/ml. Above 2 mg/ml, an immediate sustained increase in UBF occurred which generally decreased rapidly to control levels when the infusion was discontinued. UBF responses were expressed as a percentage of the subsequent response induced by E2 on the same day. Within the doses tested, the dose-response curves were linear attaining 75–95% of the E2 response at doses between 40 and 77 mg/ml. In a few experiments where the glucosamine solution was buffered to pH 7.0, comparable vascular responses occurred.

We believe this observation of a vasoactive property of an amino sugar is unique and may explain, in part at least, the marked distributional shift of UBF to the ovine cotyledon during definitive placentation.

(Supported by USPHS grant No. HL-03941 from the National Heart and Lung Institute.)

76 Changes in Cervical Compliance at Parturition Independent of Uterine Activity
Stanley J. Stys, William H. Clewell and Giacomo Meschia
Division of Perinatal Medicine, University of Colorado Medical Center, Denver, Colo.
Cervical compliance changes at spontaneous and dexamethasone-induced parturition were studied in 6 pregnant ewes. At 111–124 days of gestation, small balloons were placed within the cervical os and amniotic cavity to measure cervical compliance and intracervical and intrauterine pressures. The internal os was purse-stringed to mechanically isolate the cervix from the uterus; a catheter was placed into the fetal femoral vein for dexamethasone infusion. Continuous recordings of intracervical and intrauterine pressures and daily intermittent measurements of cervical compliance were made for at least 2 weeks prior to parturition. Up to fivefold increases in cervical compliance were noted in several animals 48 h following surgery, with a gradual return to baseline values.

Cervical compliance changed abruptly at parturition, increasing tenfold or more within 12 h. The abruptness and magnitude of the compliance change was similar in spontaneous and dexamethasone-induced parturition, and occurred before the onset of uterine activity. In the 3 dexamethasone-induced (1 mg/24 h) ewes, cervical compliance remained unchanged for approximately 48 h after the dexamethasone infusion was begun. In all 6 animals, the abrupt increase in cervical compliance was followed within hours by uterine activity characteristic of early labor. We conclude that uterine contractions dilate the cervix only after it has become compliant by another mechanism.

12 p.m.

77 Stimulus Summation and Tachyphylaxis in Estrogen Response
William H. Clewell, Stanley J. Stys and Giacomo Meschia
Division of Perinatal Medicine, University of Colorado Medical Center, Denver, Colo.
Previous studies in ovariectomized, nonpregnant ewes have shown that the injection of 1 µg of estradiol-17β (E2) over 1 min into the lumen of the uterine artery causes a maximal local increase in uterine blood flow and that this response can be reproduced daily for 1 month or more. We now report that by dividing the dose, temporal summation of the stimulus can be demonstrated. Five 1-min doses of 0.2 µg injected at 5-min intervals, or 0.04 µg/min infused over 25 min, have an effect virtually identical to that of a 1-µg bolus. However, a comparison of submaximal doses shows that there is a threshold for temporal summation of the stimulus and that above this threshold there is a dose range in which temporal summation is incomplete; i.e., the bolus causes greater response than divided doses. Tachyphylaxis to estrogens was induced by continuous infusion of 8 µg/h of E2 into one uterine artery. Following the initial response, the flow returned to baseline and was refractory to stimulation by a systemic dose of E2 (which caused the expected maximal vasodilatation in the contralateral uterine horn). The tachyphylaxis to E2 did not prevent vasodilatation by bradykinin and adenosine. Following discontinuation of the E2 infusion, responsiveness to the vasodilatory effect of estrogen returned to normal in approximately 24 h.

12.15 p.m. 78 Isolation of Human Placental Myosin

Gabor Huszar
Department of Obstetrics-Gynecology, Yale University School of Medicine, New Haven, Conn.

As a part of our study on the contractile proteins of the utero-placental unit the isolation and characterization of myosin in human placenta was carried out. Human placentas were previously shown to contain an actomyosin like protein with ATPase activity and the amounts of this actomyosin increase with the gestational age. The actomyosin is thought to arise from the anchoring villi which are composed substantially of smooth muscle and bridge the fetal and maternal surface of the placenta (Michael, C: J. Obstet. Gynec. Br. Commonw. 81: 307, 1974 and ref. herein). In the present work the placentas were subjected to high salt extraction and purification and the placental myosin was further studied by Sepharose-column chromatography, SDS-gel electrophoresis, amino acid analysis, and ATPase enzymatic assays. High salt extracts yield about 0.2% of myosin of the wet placental tissue. The myosin has an apparent molec. wt of 480,000, with heavy chains of about 200,000 and light chains of about 24,000 and 20,000 molec. wt which are present in equal ratios. The ATPase of myosin is activated by K-EDTA and calcium (80–100 µmol Pi/mg myosin/min) and it is inhibited by magnesium. Magnesium activates the placental myosin ATPase in presence of actin. Amino acid composition of placental myosin is not remarkably different from that of myosins of other sources, only the amounts of methylated amino acids are lower than in skeletal or cardiac muscle myosin (Huszar, G.: J. molec. Biol. 94: 311, 1975). The study of placental contractile proteins seems to be important because contraction-relaxation of the anchoring villi is implicated in the regulation of placental hemodynamics by changing the volume of the intervillous space.

12.30 p.m. Adjournment

Second Poster Session
Friday, March 25, 1977
Cochise and Apache Rooms – Marriott Hotel
10.45 a.m. to 12.30 p.m.
79 Calcium Metabolism during the Human Menstrual Cycle
Roy M. Pitkin, W. Ann Reynolds, Gerald A. Williams, Gary K. Hargis and Wanda Kawahara
Department of Obstetrics-Gynecology, University of Iowa College of Medicine, Iowa City, Iowa, and Departments of Anatomy and Medicine, University of Illinois College of Medicine and West Side VA Hospital, Chicago, 111.
Fasting blood samples were obtained at 0800 every day or every other day throughout ovulatory menstrual cycles (as indicated by plasma progesterone > 2 ng/ml) in 6 women. Total calcium (Ca) and magnesium (Mg) were measured by atomic absorption spectrometry, ionic calcium (Ca++) by flow-through electrode and phosphorus (P) by a colori-metric method. Parathyroid hormone (PTH) and calcitonin (CT) were determined by radio-immunoassay. The most striking finding was a consistent cyclicity of PTH with progressive increase during the follicular phase to a peak slightly after mid-cycle and then a decrease during the luteal phase. The peak PTH level, which followed the LH ‘surge’ by 1–3 days, was 20–55% above the early follicular level and 20–68% above the late luteal value. CT exhibited a similar, though somewhat more attenuated and less precise cyclic pattern with peak levels reaching values 15–70% above early follicular levels and 22–59% above luteal levels. In each subject, PTH and CT correlated significantly, as did CT and Ca++. This represents the first reported variation with the menstrual cycle in calcium-regulating hormones. These findings suggest an effect (presumably of estrogen) on Ca++ levels in extracellular fluid with a resultant stimulation of PTH and CT which regulate calcium metabolism. On the other hand, a direct response to other hormones regulating ovulation and menstruation cannot be ruled out.

Scientific Abstracts

61
80 Secretion of Progesterone and Relaxin by the Human Pregnancy Corpus luteum
Gerson Weiss, E. Milikin O’Byrne, Joseph A. Hochman, Laura T. Goldsmith and Bernard G. Steinnetz
Department of Obstetrics-Gynecology, New York University School of Medicine, New York, N.Y., and Ciba-Geigy Corp., Ardsley, N.Y.
The function of the corpus luteum at midtrimester and at term was studied in 19 pregnant women. Six women had their pregnancies terminated by hysterotomy at 14–18 weeks. The remaining 13 women were delivered by cesarean section at term. Luteectomies were also performed on six women at the time of cesarean section. Progesterone and relaxin levels in peripheral blood serum were used as indices of luteal activity. Relaxin is a product of the human pregnancy corpus luteum. Relaxin secretion correlates well with luteal progesterone secretion (Science, N.Y. 194: in press).
After cesarean section at term the decline in serum progesterone was parallel to that observed after hysterotomy at midtrimester, although the absolute levels were much higher at term. On the other hand, the actual relaxin concentrations, as well as the decrease in relaxin levels seen after evacuation of the uterus, were similar at midtrimester and at term. After luteectomy there was a more precipitous decrease in serum levels of both progesterone and relaxin than seen in non-luteectomized patients.
Thus, in contrast to previous findings in lower primates, the corpus luteum of human beings does not regress in midpregnancy but instead, remains functional throughout pregnancy. There is continued secretion of luteal progesterone and relaxin in the puerperium. The corpus luteum appears to be the only source of these hormones in the puerperium.
81 Polyamines in Amniotic Fluid as Potential Indicators of Fetal Growth
Polyamines are a group of small, low molecular weight cations that are ubiquitous in nature. Although originally relegated to a role in putrefaction, polyamines have become integrally associated with normal and abnormal RNA and DNA replication in vitro and in vivo. Recent work has raised the possibility that polyamines may be valuable markers for tumor cell depletion and replication in patients undergoing therapy for malignancies.

Concentrations of four polyamines – putrescine, cadaverine, spermidine, and spermine – were determined by amino acid analysis of amniotic fluid samples. Control values were obtained from patients undergoing elective termination of pregnancy, from Rh sensitized mothers who subsequently delivered Rh negative infants, or from elective repeat cesarean sections. Eleven patients with intrauterine fetal demise (IUFD) were noted to have significant elevations of cadaverine (p < 0.001) in amniotic fluid when compared to controls matched for gestational age. Eight patients with intrauterine growth retardation (IUGR) exhibited similar elevations in cadaverine and a less marked, but statistically significant increase in amniotic fluid spermidine. Eight other patients with significant pregnancy complications but without growth retardation exhibited amniotic fluid polyamine profiles which were not significantly different from the normal controls. The question is thus raised as to whether amniotic fluid concentration of certain polyamines, notably cadaverine and spermidine may be clinically useful as an indicator of fetal growth.

Society for Gynecologic Investigation

62 Effects of Fasting on Ovine Uterine Blood Flow and Substrate Uptake
Frank H. Morriss, Eugene W. Adcock, Arlyn H. Hartfiel and Sharon S. Crandell Departments of Pediatrics and Obstetrics-Gynecology, University of Texas Medical School at Houston, Houston, Tex.

To determine the effect of maternal nutrition during pregnancy on uterine blood flow (UBF) and uptake (Q) of O2, glucose (glu) and 21 amino acids (aa), 7 ewes 92–126 days gestation (GA) were prepared with uterine artery flow transducers; 4 of these received catheters in uterine veins and femoral artery. After recovery and during adequate nutritional intake, control studies of UBF and substrate uptake were made. Each ewe was then fasted, but allowed water, and restudied after 3–4 days and after 5–7 days. Whole blood glucose was determined by the glucose oxidase method, O2 with a Lex02Con analyzer, and aa by ion-exchange column chromatography.

During fasting maternal arterial whole blood glucose and 7 aa decreased while lysine and 1-methyl histidine increased. When all fasting studies are compared with 27 studies of Q aa in 5 additional well-fed ewes at similar GA, Q ornithine and Q lysine were decreased (p < 0.025).

Conclusions: (1) fasting is accompanied by significant decreases in uterine consumption of O2, glucose and 3 aa which are major fetal sources of N2; (2) both a 25% decrease in UBF and decreased (substrate) contribute to decreased Q; (3) whole blood lysine increases with GA in well-fed ewes as well as during fasting, suggesting that a maternal aa metabolic alteration similar to fasting develops during pregnancy.

(Aided by a Basil O’Connor Starter Research grant from The National Foundation-March of Dimes.)

83 The Control of Vascular Reactivity to Angiotensin II (A-II) in Human Pregnancy
Gravidas destined to develop pregnancy-induced hypertension (PIH) lose resistance to the pressor effects of A-II several weeks before the onset of hypertension. Moreover, this loss of resistance to A-II is apparently unrelated to plasma renin activity or A-II levels. The present study was designed to ascertain if prostaglandin(s) or related substances are involved in the control of vascular reactivity during human pregnancy. In six normal gravidas beyond the 28th week of gestation, the administration of 25 mg of indomethacin on two occasions 6 h apart was associated with a marked loss in A-II resistance. The dose of A-II required to evoke a pressor response of a 20 mm of rise in diastolic pressure before treatment in these six women was 25.84 ± 6.04 (mean ± SEM) whereas the dose required after treatment was 9.71 ± 1.77 (p < 0.025). Resistance to A-II is regained by 24 h after discontinuation of indomethacin administration. These findings are consistent with the view that a generalized inhibition of the synthesis of prostaglandin(s) or related substances is associated with a loss in the pregnancy acquired resistance to the pressor effects of infused angiotensin II.

Failure of Glucocorticoid Administration in Inducing the Production of a Mature L/S Ratio

F. Arias and J. Pineda
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.

It has been reported that antepartum glucocorticoid administration is useful in the prevention of neonatal respiratory distress syndrome but estimations of the amniotic fluid L/S ratio (as an objective index of fetal pulmonary surfactant production) after corticoid administration have produced discrepant findings. In an attempt to reconcile the controversy, the effect of glucocorticoids (α-methasone phosphate 6 mg and Ø-methasone acetate 6 mg, given together intramuscularly on each of two consecutive days) on amniotic fluid L/S ratio was measured in 15 patients, all between 28 and 32 weeks of gestation (as determined by clinical estimation and serial ultrasonic cephalometry) where induction of fetal pulmonary surfactant was considered desirable in view of fetal or maternal complications. Determination of amniotic fluid L/S ratio was carried out before, and 3–5 days after as well as 7^14 days after corticoid administration. There was a trend toward increased L/S ratios, but in no single case were corticoids capable of inducing the production of a mature L/S ratio within 1 week and only one patient responded with L/S maturation within 2 weeks after administration of the medication. These findings suggest that glucocorticoids lack any immediate effect on the biochemical indicator of fetal lung maturation and generate doubts about the advantages of their widespread use for the purpose of accelerating fetal surfactant production.

Failure of Severe Distress to Stimulate Aspiration of Amnionic Fluid by the Immature Human Fetus

Johann H. Duenhoelter and Jack A. Pritchard
Department of Obstetrics-Gynecology, University of Texas Southwestern Medical School at Dallas, Dallas, Tex.

Studies have been previously presented before this Society which were interpreted to indicate that even the very young fetus normally inspires appreciable volumes of amnionic fluid. An
alternative explanation raised was that the aspiration was the consequence of the severe distress induced by the termination of the pregnancy rather than a physiologic event. Observations summarized below preclude severe fetal distress as the major stimulus for aspirating amnionic fluid.

Amnionic fluid was labeled as in previous studies with radiochromium (51·Cr) tagged red cells shortly before spontaneous fetal death in 2 cases of severe hypertension, the injection of prostaglandin F2α and subsequent fetal death in 3 cases, shortly before hysterectomy in 3 cases, and immediately after hysterectomy but with the fetal heart beat persisting for more than 1 h after so labeling in 1 case. 51·Cr accumulated in the lungs equivalent to amnionic fluid volumes no greater than % of those found in lungs of fetuses of comparable weights in which the label had been introduced 19–48 h before terminating the pregnancy by hysterectomy.

Conclusions: (1) even the very immature human fetus normally inspires amnionic fluid, and (2) fetal distress, at least under the conditions of these studies, does not markedly intensify the aspiration of amnionic fluid.

86 Effects of PGF2α and PGE2 on Sheep Umbilical and Uterine Circulation
Margaret K. McLaughlin, Susan C. Brennan, Lewis A. Hamilton and Ronald A. Chez
Pregnancy Research Branch, NICHD, NIH, Bethesda, Md.
We studied changes in calculated vascular resistance (VR = arterial – venous pressure/flow) after intraaortic injection of PGE2 or PGF2α, to the fetus (0.1–100 µg/kg estimated body weight, n = 5), and of PGF2α to the ewe (0.5–50 µg/kg body weight, n = 4). Uterine and umbilical blood flow (UtBF, UmBF), maternal and fetal arterial pressures (MAP, FAP), and maternal and fetal heart rates (MHR, FHR) were measured in chronically instrumented sheep at 120–132 days. All responses were dose related and peaked by 3 min postinjection. Statistically significant maximal changes (p at least < 0.02) from control levels were:

Conclusions: (1) Acute vascular changes induced on one side of the sheep placenta by exogenous PGE2 and PGF2α are associated with acute changes on the other side of the placenta. Whether these changes are or are not in the same direction is a function of the agent injected. (2) Thus, the resultant umbilical/uterine perfusion ratio is variably altered. (3) We do not know whether similar changes occur when endogenous prostaglandin levels increase physiologically.

87 Role of HCG in the Regulation of the Fetal Zone of the Human Fetal Adrenal Gland
Maria Seron-Ferre, Christina C. Lawrence and Robert B. Jaffe
Department of Obstetrics-Gynecology and Reproductive Sciences, University of California at San Francisco, San Francisco, Calif.
It has been suggested that human chorionic gonadotropin (HCG) is a trophic hormone for the fetal zone of the human fetal adrenal gland. To test this hypothesis, the isolated fetal zone of adrenals from 5 fetuses 12–17 weeks gestational age were superfused in the presence or absence of HCG (250 ng/ml). Dehydroepiandrosterone sulfate (DHAS) was measured in the superfusion effluent. No difference was observed between control and experimental superfusions during the first 60 min, 65 ± 7.8 vs 72 ± 8.0 ng/ml (mean ± SE) respectively. In the presence of HCG, DHAS secretion rose significantly to 122 ± 7.6 ng/ml, while in the control secretion remained at 76.0 ± 5.32 ng/ml. This difference was main-
tained for the duration of the experiment. These results support the hypothesis that HCG regulates DHAS production by the human fetal adrenal gland early in gestation. As we have found that ACTH stimulated DHAS secretion in some experiments in a previous study, and as there is indirect evidence for a role of ACTH in DHAS regulation late in pregnancy, these observations suggest that a transition from HCG to ACTH regulation of the fetal zone of the human fetal adrenal occurs after midgestation.

(Supported by NIH grant HD 08478 and the Rockefeller Foundation.)

88 Androgen Dynamics in Normal and Castrate Male Rhesus Monkeys
Torn Tabei, Kenneth Burry, Pearl Namkung, Robert A. Steiner, Philip Petra, Harvey Schiller, John Resko and W. LeRoy Heinrichs
Departments of Obstetrics-Gynecology, Physiology, Biochemistry and Laboratory Medicine, University of Washington, Seattle, Wash., and Washington and Oregon Regional Primate Research Center, Seattle, Wash., and Beaverton, Oreg.

To assess the regulatory roles of adrenal and testicular hormones on androgen dynamics in adulthood we measured the metabolic clearance rate (MCR) and production rate (PR) of dehydroepiandrosterone (DHA) and of testosterone (T) in four normal adult male rhesus monkeys and six castrates. The MCR of intact males, 165 ± 23 liter/day (x ± SD) was significantly less than that of the castrates, 334 ± 58, but this difference seemed to be related to body weight. Since the plasma concentration of DHA was similar in both groups (15.6 ± 3.4 vs. 13.4 ± 8.5 ng/ml), the mean PR of intact males (5–7 ± 3.4 mg/day) was greater than that of castrates (2.7 ± 1.0). The MCR of intact males, 55 ± 14 liter/ day was similar in the castrate group, 68 ± 7, and no weight relationship was apparent. Despite great differences in plasma concentrations of T (6.0 ± 3.7 vs. 0.3 ± 0.1 ng/ml) and PR (1,082 ± 932 vs. 25 ± 20 µg/day), the plasma binding capacities of dihydrotestosterone and corticosterone were similar in both groups; plasma estradiol levels were also similar. 5α-Reduction of T by abdominal skin was the same in both groups, but this transformation in scrotal skin of the castrates exceeded by twofold the rate observed in skin from normal animals.

These data indicate that testosterone produced by the testis is not essential for regulating androgen clearance in adulthood.

(Supported by PHS grants No. HD 08736, and HD 00272.)

12.30 p.m. Adjournment

Abstracts

89 Amino Acid Concentration in the Sheep Placenta
Luis B. Curet
Department of Obstetrics-Gynecology, University of Wisconsin Center for Health Sciences, Madison, Wise.

Previous work in our laboratory suggested that amino acids are transported across the sheep placenta in three stages. Amino acids would leave the uterine circulation in the first stage to be concentrated in the placenta during the second stage and eventually appear in the umbilical circulation during the third stage. The concentration gradients shown in figure 1 are consistent with a step-wise transport.

The present study was designed to study the tissue stage of transport. Six ewes were studied at 50, 80 and 140 days of gestation. Three ewes in each group received an intravenous infusion of α-amino isobutyric acid. All animals were sacrificed and fetal and maternal cotyledons were analyzed for amino acid concentration.
Figure 2 summarizes the regression over the three periods studied of each amino acid concentration in maternal and fetal cotyledons. The concentration of amino acids decreases in the maternal cotyledons while that in the fetal cotyledons increases. Figures 3 and 4 show the regression of the difference in concentration between fetal and maternal cotyledon for all amino acids. As expected the regressions have a positive slope. It would appear from these observations that the fetal cotyledon is capable of concentrating amino acids during the course of gestation and provide some degree of safety for the fetus. Current studies underway in our laboratory are aimed at determining how quickly these amino acids become depleted upon reducing the maternal intake of protein.

Scientific Abstracts

90 Behavior of Cardiac Output and Systemic Vascular Resistance during Neonatal Growth
James R. Woods, Jr., Adrien Dandavino, Charles R. Brinkman, HI and Nicholas S. Assali
Department of Obstetrics-Gynecology, UCLA School of Medicine, Los Angeles, Calif.
We have previously shown in sheep that: (a) resting heart rate (HR) decreases progressively during neonatal growth and the changes are independent of autonomic nervous activities; (b) parasympathetic tone rises considerably after birth while sympathetic tone decreases; ratio of both remains constant throughout neonatal period and similar to adult. Present studies deal with behavior of cardiac output (CO), stroke volume (SV) and systemic resistance (SR) during neonatal growth. Two groups of newborn lambs were chronically instrumented for measurements of arterial pressure (AP), SV and CO; in one group CO was monitored with electromagnetic flow transducer around pulmonary artery while in the other, indicator dilution was used. Same lamb was studied from 1–5 weeks and its response to cholinergic and ß-adrenergic stimulation and blockade was tested weekly. Results show: (1) during neonatal growth, changes in HR, AP, SV, CO and SR were comparable in both groups, indicating pulmonary artery instrumentation had no deleterious effects on cardiovascular functions; (2) CO/kg declined 34%, SV remained unchanged and SR increased 50% during first 5 weeks of life; (3) cholinergic blockade resulted in 7–12% increase in CO, whereas ß-adrenergic blockade had minimal effects; (4) ß-adrenergic stimulation produced 30% increase in CO. Conclusions: (1) CO decreases, SR increases and SV remains unaltered during neonatal growth; (2) neonatal heart is capable of exhibiting adult-like inotropic effects in response to autonomic stimuli.

91 In vitro Quanitation of Uterine Inhibitors
Harold Schulman
Department of Obstetrics-Gynecology, Albert Einstein College of Medicine, Bronx, New York, N.Y.
Currently there is not an in vitro or in vivo method of quantititating the potency of uterine inhibiting drugs. Electric field stimulation (EFS) of pregnant and parturient rabbit myometrial strips has been effectively used to assay oxytocic potency of prostaglandins and it is shown in this study to be useful in assaying potency of ß-sympathomimetic compounds. Decreasing electric field stimulation (DEFS) provides 3 measurable endpoints: tension, excitability, and threshold voltage. Three compounds were tested for these parameters; isoproterenol, ritodrine and isoxsuprine.

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<td>Isoproterenol</td>
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Ritodrine  68.3 + 5.1  2.0  \(\lt; 3\)
Isoxsuprine  42.2 + 3.8  2.3  \(\lt; 3\)

It is concluded that in this system isoxsuprine is the more potent inhibitor of uterine tension evoked by EFS. It is also revealed that so-called uterine inhibition by these compounds represents the creation of a chaotic fibrillating muscle which is unable to respond in a synchronous way to produce a contraction of maximal tension.

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92 The Changes in Fetal Red Cell Oxygen Affinity in Relation to Gestational Age: the Role of 2,3-Diphosphoglycerate and Adult Hemoglobin
Harry Bard, Ann Comet and Francois Teasdale

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To reflect the in utero changes in fetal oxygen affinity in relation to gestational age along with the factors that control oxygen affinity, fresh heparinized cord blood obtained at delivery from nonstressed normal fetuses ranging from 28 to 42 weeks of gestation had the following parameters determined simultaneously; P50 by gas mixing tonometry, 2,3-diphosphoglycerate (2,3-DPG) according to the method of Keitt, and the proportions of adult (HbA) and fetal hemoglobin (HbF) by eluting HbF and HbA from DEAE Sephadex A-50. There was a significant positive correlation between Ps0 and gestational age \((r = 0.62, p \lt; 0.001)\). The linear regression increased from 17.8 to 22.5 mm Hg. There was a significant positive correlation between Ps0 and the percentage to HbA \((r = 0.56, p \lt; 0.01)\). Gestational age had no effect on fetal 2,3-DPG levels. The mean and SD was 15.1874 ± 2.1786 µmol/g Hb. Contrary to what is expected during postnatal life, there was no significant correlation found between the percentage of HbA and 2,3-DPG nor between Ps0 and 2,3-DPG. The fetus gradually decreases red cell oxygen affinity during the last trimester of gestation by increasing HbA, while the 2,3-DPG levels remain stable.

93 Predictability of Gestational Hypertension
Shailaja M. Didolkar, Milo B. Sampson, Patrick J. Carmody, Wayne L. Johnson and Loren P. Petersen

Department of Obstetrics-Gynecology, State University of New York at Buffalo, Buffalo, N.Y.

To assess the predictability of various factors for gestational hypertension, 85 patients were studied prospectively. Gestational ages ranged from 28 to 37 weeks. 60% were primigravidas. Patients were admitted to a Clinical Research Center and put on a balanced diet and bedrest the evening before studies began. Next day they were studied for 1 h in the left lateral position and 1 h supine. Blood pressure measurements were done every 10 min and fetal heart rate was monitored continuously. Sodium balance, creatinine clearance, hematocrit HPL, E3 and urine output were measured. Seventeen (20%) developed gestational hypertension, 15 of the 17 were primigravidas. Patients were grouped according to mean diastolic blood pressure (BP) change from left lateral to recumbent position.

Mean diastolic BP ↓ \(\lt; 4\) mm No ↑ 5- til † \(\gt; 20\) mm Total change 10 mm 19 mm ± 4
No. patients 12 23 14 27 9 85
Gestational hypertension 5 0 6 1 17
(41.6%) (21.7%) (0%) (22.2%) (11.1%)
† Rollover (Gant) 0 0 2 12 6 20
Gestational hypertension patient were scattered in all four groups, 41% being in the group where blood pressure actually decreased. Only 3 of the 20 patients (15%) who had a positive rollover test developed gestational hypertension. There was no correlation between creatinine clearance, sodium balance, serum creatinine, hematocrit, urine output and development of gestational hypertension.

94 Nicotine and Breathing Movements in the Fetal Lamb
Frank A. Manning and David Walker
Department of Obstetrics-Gynecology, University of Southern California School of Medicine, LAC/USC Medical Center, Los Angeles, Calif.
Nicotine is responsible for the decrease in fetal breathing movements (FBM) associated with smoking; the mechanism of action is unclear. The effect of nicotine on maternal and fetal heart rate (MHR, FHR), blood pressure (MBP, FBP), blood gas and acid-base status, intrauterine pressure (IUP), and FBM was studied in six chronically catheterized pregnant ewes. In nine experiments, nicotine (10–20 mg) was given by maternal intravascular injection. Nicotine injection produced maternal hypertension maximal at 1 min (130 ± 7.3% of control, p < 0.05). MHR changes were biphasic, an initial bradycardia followed by sustained tachycardia (126 ± 4% of control at 10 min, p < 0.05). Changes in FBP and FHR were similar but delayed in onset and of lesser magnitude. The maximal rise in FBP occurred at 2 min (117 ± 9% of control). FHR fell (83 ± 2.1% of control at 2 min, p < 0.05), then rose to a maximum at 40 min (118 ± 9.5% of control). IUP remained unchanged. No significant changes in maternal PaO2, PaCO2, or pH were observed. In contrast, fetal PaO2 fell within 5 min (Δ = 5.11 ± 1.03 mm Hg, p < 0.01), and the decrease persisted for up to 30 min. No significant changes were observed in PaCO2 or pH. FBM were present for 31.2 ± 6.75% of the time during the control period (1 h). Nicotine injection caused a fall in FBM evident by 15 min (17 ± 11% of the time, p < 0.05) and persistent for up to 45 min. The fall in FBM was related to the fall in fetal PAO2 (r = 0.58, p < 0.001).

These observations suggest that fetal hypoxemia is the mechanism by which nicotine causes a reduction in the incidence of FBM.

95 Effect of Progesterone on the Pituitary’s Response to LHRH
Virendra B. Mahesh and James C. McPherson
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In a previous study it was shown that 26-day-old castrated female rats treated with 0.1 µg/kg body wt. of estradiol and various doses of progesterone for 5 days starting with the day of castration, showed stimulation or suppression of tonic FSH and LH secretion, depending on the dose of progesterone used (Endocrinology 97: 111, 1975). The current study confirms these findings in the immature rat treated with 0.1 µg/kg body wt. of estradiol for 4 days, and given a single injection of progesterone. Progesterone in doses of 0.2 mg and 0.8 mg/kg body wt. injected at 9.30 a.m. resulted in a 7-fold increase in LH and 2-fold increase in FSH by 4.00 p.m. whereas the 0.4 mg and 3.2 mg/kg body wt. dose levels had either no effect or were suppressive. In the castrated rat various doses of progesterone did not have any effect on gonadotropin secretion in the absence of estradiol priming. In order to examine whether the effect of progesterone on the estradiol-primed rat was manifested at least in part at the level of the pituitary, and whether such an effect was dependent
on the dose of progesterone used, groups of animals were castrated and treated with 0.1 µg/kg body wt. of estradiol for 4 days starting on the day of castration. On the 4th day post castration they were injected with vehicle or 0.8 or 3.2 mg/kg body wt. of progesterone. After serum LH levels stabilized for the evening at 6.00 p.m., the rats were either given saline or 10 ng, LHRH at 2-hour intervals and multiple samples collected for assay. The 0.8 mg/kg body wt. dose of progesterone was stimulatory for pituitary content and release of LH while the 3.2 mg/kg dose was inhibitory as compared to estrogen primed controls.

96 The Relation of Gestational Age to Microviscosity of Amniotic Fluid (AF) Lipids Measured by Fluorescence Polarization (FP)

Thomas Blumenfeld, Raymond I. Stark, Vincent J. Freda and L. Stanley James
Division of Perinatal Medicine, College of Physicians and Surgeons, Columbia University, New York, N.Y.

FP techniques are used to study the microviscosity of lipid dispersions. FP measurements are rapid, easy to perform and precise (coeff. of var. 0.48%). The microviscosity of lipid micelles in AF is related to the relative concentrations of various micellar lipids and is a good approximation of L/S ratio. The phospholipid composition of AF changes during gestation and reflects fetal lung maturation. To determine if a similar change occurs in AF microviscosity, FP values were determined on serial AF samples obtained during 19 isoim-munized pregnancies. Patients were grouped by the interval in gestation of sequential samples.

<table>
<thead>
<tr>
<th>Group</th>
<th>Gestational age</th>
<th>No. of patients</th>
<th>No. of samples</th>
<th>FP value – mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 33wks</td>
<td>4</td>
<td>17</td>
<td>0.372 (0.386–0.333)</td>
<td></td>
</tr>
<tr>
<td>&gt; 33wks</td>
<td>4</td>
<td>14</td>
<td>0.334 (0.345–0.301)</td>
<td></td>
</tr>
<tr>
<td>26to38wks</td>
<td>11</td>
<td>66</td>
<td>0.368 (0.385–0.353) before change 0.345 (0.368–0.328) after change</td>
<td></td>
</tr>
</tbody>
</table>

There was a significant change in slope of FP values vs. gestational age in group III, occurring between 29 to 35 weeks (mean = 31.5 weeks). This study establishes a definite relation between FP values of AF and gestational age. Changes in FP occur over the same interval as changes in AF phospholipids. The precision, rapidity and ease of FP measurements of AF lipid microviscosity may facilitate and enhance the ability to predict fetal lung maturity.

97 Interrelationship between Risk Factors of Pregnancy, Perinatal Events and Outcome

Henry R. Rey, Jean D. Joseph, Raymond Stark, R. Vande Wiele and L. Stanley James
Division of Perinatal Medicine, College of Physicians and Surgeons, Columbia University, New York, N.Y.

Analysis of perinatal data in 665 patients has shown a statistically significant inverse relationship between the Hobel antepartum and intrapartum risk scores and neonatal complications (p < 0.01). Risk scores were inversely related to Apgar scores at both 1 and 5 min when controlling for severity of neonatal complications. For fetuses of gestational age (GA) ≥ 32 weeks, a significant positive correlation was found between risk scores and abnormalities in heart rate-uterine pressure patterns during labor (p < 0.01). For high risk mothers (Hobel A.P. score ≥ 10 and Hobel I.P. score ≥ 20), several unexpected relationships were found between type of delivery and outcome. For infants < 32 weeks, the incidence of mortality and morbidity was 50% lower in those delivered by cesarian section (CS).
than in those delivered by mid-forceps (MF), breech (BR), or vacuum extraction (Vac). At 32–36 weeks, mortality was 5 times greater in those delivered by MF, BR and Vac than in those delivered spontaneously or by low forceps, and twice that found in the CS group. At 36 weeks or more however, that relationship was reversed with 75% of the mortality and 50% of the morbidity associated with cesarian section. This study demonstrates the importance of controlling for GA if outcome is to be related to mode of delivery. It appears that the immature fetus has a poor tolerance of labor and vaginal delivery irrespective of risk.

98 Fetal Vasopressin (AVP) Levels during Adrenocorticotrophin (ACTH) Induced Parturition in the Lamb
Raymond I. Stark, Kazim Husain, Jacques M. Milliez, Salha S. Daniel, Hisayo O. Morishima and Raymond L. Vande Wiele
Division of Perinatal Medicine, College of Physicians and Surgeons, Columbia University, New York, N.Y.
Activation of the fetal neurohypophysis during labor has been documented and implicated as a potential trigger for the initiation of labor. To investigate the relation of AVP measured by a sensitive radioimmunoassay to the onset of parturition, 9 fetal lambs were instrumented at 121 days of gestation. At 129 days, 7 fetuses were infused with ACTH (10µg/kg/h), 2 with saline. During infusion fetal pH (7.36 ± 0.002) and pCO2 (42 ± 2 mm Hg) were constant, p02 decreased (22 ± 2 to 18 ± 2 mm Hg, r = 0.96). Delivery occurred after a mean of 74 h infusion. Fetal AVP levels during infusion prior to labor (1.8 ± 1.8 pg/ml) were not different from controls (1.85 ± 1.1 pg/ml). Levels rose progressively only after the onset of labor to a mean peak at delivery of 720 ± 1,470 pg/ml. Fetal AVP during active labor (40 ± 73 pg/ml), pushing (173 ± 404 pg/ml) and 30 min after delivery (360 ± 340 pg/ml) were predictive of AVP levels in cord blood (r = 0.955, 0.985 and 0.992). Fetal levels of AVP prior to labor and during early labor were not predictive of levels at birth. Maternal AVP rose only during the pushing phase (2.1 ± 1.4 to 6 ± 4 pg/ml) and never exceeded fetal levels. We conclude that in parturition induced by ACTH, fetal AVP rises only after the onset of labor, reaches a peak at delivery and is unrelated to maternal levels.
Fetal vasopressin does not appear to be related to the initiation of labor, but could be related to the maintenance of labor or fetal cardiovascular adjustments during labor.

99 Quantitative Classification of Baseline Variability
Bruce K. Young, Howard M. Weinstein, Howard M. Hochberg and Michael E.D. George
Department of Obstetrics-Gynecology, New York University School of Medicine, New York, N.Y., and Roche Medical Electronics, Cranbury, N.J.
Simultaneous tape recordings of fetal scalp ECG, or cardiac Doppler, maternal ECG, and uterine contractions were obtained from 32 patients in labor. Neonatal ECG and instantaneous heart rate were recorded at birth and 24 h. Computer-derived distributions of beat-to-beat changes were used to develop a simple numerical and graphical description of the long- and short-term variability patterns. The visually observed variability may be described by the R-R interval change (beat-to-beat change) which is greater than 90% of the beat-to-beat changes. Thus the 90th percentile of R-R interval changes quantitatively describes the baseline variability. The variability may be classified as fixed, minimal, moderate, or marked, based on this simple calculation. The effects of meperidine HC1 on the observed maternal and fetal variability were described clearly by this method. Maternal and fetal baseline heart rates and
variability often moved in the same direction. Newborn heart rates showed marked baseline variability and were unrelated to fetal heart rate variability.

100 Obstetrical Intensive Care: 3 Years’ Results
Bruce K. Young, Howard M. Weimtein, Jon R. Snyder, Howard M. Hochberg and Michael E.D. George

Department of Obstetrics-Gynecology, New York University School of Medicine, New York, N.Y., and Roche Medical Electronics, Cranbury, N.J.

An obstetrical intensive care unit (OBICU) utilizing fetal and maternal monitoring equipment was used for monitoring during labor in the highest risk patients. Continuous maternal ECG, respiration, blood pressure, and beat to beat heart rate were recorded with fetal heart rate and uterine contractions. In selected cases central venous pressure was monitored. In the first 401 patients, there were 5 perinatal deaths. Corrected perinatal mortality was 10/1,000, below the 15.5/1,000 of our general obstetrical population over the same period. There were 2 maternal deaths, both due to catastrophic hemorrhage, compared with none in the general obstetrical population. The maternal deaths were due to carotid artery laceration and ruptured spleen respectively. The favorable perinatal results in these parturients with the most serious medical, surgical, and obstetrical complications demonstrated that the OBICU is practical, and may have a favorable impact on patient care in the high risk category.

101 Effects of Magnesium Sulfate on Toxemic Patients in Labor
Bruce K. Young and Howard M. Weimtein

Department of Obstetrics-Gynecology, New York University School of Medicine, New York, N.Y.

144 toxemic patients in labor were treated with magnesium sulfate. 97 patients, including 4 eclamptics, received intermittent intravenous ‘pushes’ of 2 g every 1–2 h. 47 including 3 eclamptics, received a continuous intravenous infusion of 1 g/h. All patients had continuous electronic monitoring of maternal respiration, electrocardiogram, blood pressure, uterine contractions, and fetal heart rate. In the patients treated by i.v. push, maternal blood pressure fell briefly in 93%, transient respiratory depression was seen in 79%, and nausea, flushing, and occasional vomiting was often encountered. No hypotension, respiratory depression, or side effects, were seen in patients treated by continuous infusion. Neither series showed a significant inhibition of uterine contractions, or changes in maternal or fetal ECG. Intravenous magnesium sulfate should be given by continuous infusion.

Scientific Abstracts
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102 The Variability of Uterine Blood Flow, Arterio-Venous 02 Content and 02 Consumption in Pregnant Sheep during 24 Hours
Egon Lanz, Donald Caton, Helene Schlereth and Donald H. Barron
Department of Obstetrics-Gynecology and Anesthesia, University of Florida, Gainesville, Fla.

Four sheep (90–140 days pregnant) were prepared with an electromagnetic flow probe around one uterine artery and with catheters in a femoral artery (A) and in both uterine veins (UV). UBF and arterial pressure were recorded continuously, A and UV-02 contents and partial pressures were measured every 4 h.

The variations between lowest and highest values during 24 h were in %:

<table>
<thead>
<tr>
<th>Animal</th>
<th>UBF</th>
<th>A-UV C02</th>
<th>Q02</th>
</tr>
</thead>
<tbody>
<tr>
<td>(140 days)</td>
<td>33</td>
<td>69</td>
<td>43</td>
</tr>
<tr>
<td>(120 days)</td>
<td>23</td>
<td>43</td>
<td>36</td>
</tr>
</tbody>
</table>
02 consumption was highest between midnight and 4.00. Variations of Q02 correlated primarily with A-UV C02. Data suggest there may be a diurnal pattern in the Gyconsump-tion of the pregnant uterus and its contents.

103 Fetal Brain Function, Metabolism and Neuropathology following Acute Hypoxia L.I. Mann, N. Peress, A. Bhakthavathsalan, H. Szeto and M. Liu Department of Obstetrics-Gynecology, University of Vermont College of Medicine, Burlington, Vt., and Department of Pathology, State University of New York Medical School, Stony Brook, N.Y.

Fetal brain function and metabolism were correlated with neuropathology following acute hypoxia in nine fetal sheep preparations. The brains of experimental animals and age-matched controls were perfused and fixed in situ. Fetal brain function was studied in terms of the fetal electroencephalogram (EEG) and fetal brain metabolism in terms of carotid arterial (FA) minus sagittal vein (SV) differences of blood gases and substrate. The length of hypoxia was altered by specifically prolonging the state of isoelectricity (Flat) of the fetal EEG. The isoelectric stage of the EEG appeared at a mean p02 of approximately 5 mmHg (FA; 1 vol%) and was always preceded by fetal bradycardia or irregularity. Brief periods of hypoxia lasting less than 11 min with an isoelectric stage of less than 2 min were associated with a rapid recovery of the EEG following reintroduction of oxygen and no significant neuropathology. Longer periods of hypoxia and isoelectric EEG resulted in a severe metabolic acidosis during recovery, a longer period to recovery or no recovery of the EEG, and more frequent pathologic involvement of the cerebral white matter on light and electron microscopic evaluation. Nonmyelinated fibers and poorly myelinated regions appeared more vulnerable and brain stem lesions were not observed. The neuropathology was similar to that found in human infants dying with developmental disabilities. The observations suggest that hypoxia with lactacidemia and metabolic acidosis in contrast to hypoxia without acidosis leads to irreversible brain damage.

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104 Comparison of Cardiovascular Responses to Hypovolemia in Fetal and Immediate Neonatal Periods


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We have previously postulated that the umbilicoplacental circulation and the vascular shunts act as ‘buffering’ structures which dampen fetal cardiovascular response to stressful stimuli. To test further this hypothesis, near-term fetal lambs were studied acutely under maternal phenobarbital and spinal anesthesia and chronically without anesthesia. In addition, acutely prepared fetuses were studied in the immediate neonatal period following cord clamping and lung ventilation.

Blood volume (BV) was measured or estimated in all animals in addition to heart rate (HR) and arterial pressure (AP). Ascending aortic flow (QAA) was also measured in all acute preparations. Each lamb was studied during control, hemorrhagic hypovolemia, blood reinfusion and recovery periods. Results show: (1) in the acute fetal group, BV reduction of 28% to lower AP 50% in pentobarbital group, whereas in spinal group the BV reduction was 40%; (2) in the chronic unanesthetized fetal group a BV reduction of 44% resulted in a 31% AP reduction; (3) in neonate BV reduction of 18% reduced AP 50%; (4) the pattern of change in pressure and flow was
similar in all groups; (5) bradycardia occurred in all groups but was more profound under pentobarbital. Conclusions: (1) chronic unanesthetized fetal preparations have a greater tolerance to hypovolemia; presence and type of anesthesia effect the fetal cardiovascular response to hypovolemia; fetus tolerates a greater loss of BV than neonate; (4) fetal tolerance to blood loss is related to umbilico-placental circulation and vascular shunts.

105 Effects of One-Kidney Renal Hypertension on Uterine Hemodynamics in Pregnant Sheep
C.R. Brinkman, III, J.R. Woods, jr., A. Dandavino and N.S. Assali Department of Obstetrics-Gynecology, UCLA School of Medicine, Los Angeles, Calif.

We have previously reported the uterine hemodynamic effects of a two-kidney model of renal hypertension in pregnant sheep, which are: (1) a prompt increase in the mean arterial pressure (MAP); (2) a transient decrease in uteroplacental blood flow (QUP) lasting 7–10 days, and (3) a significant increase in uteroplacental vascular resistance (UVR) which returns toward control levels, but remains slightly elevated for the duration of the pregnancy. This report deals with a group of pregnant sheep which were chronically instrumented for measurement of MAP and QUP at 85 gestational days. At 100 days a right renal artery flow transducer and externally adjustable constrictor implanted and a contralateral nephrectomy performed. Approximately 9 days later the right renal blood flow was reduced by an average of 26%. Results show: (1) a prompt and significant increase in MAP of 18% which remained elevated for the next 3 weeks; (2) a steady decrease in QUP during the 3 weeks following renal artery constriction; (3) a 50% increase in UVR by the 3rd week when compared to the week of renal surgery. Conclusions: (1) the effects of one- and two-kidney renal hypertension on MAP are similar; (2) one-kidney renal hypertension has a progressive and prolonged effect on QUP and UVR; (3) behavior of uteroplacental circulation differs in various forms of renal hypertension. Data on plasma renin activity and pregnancy outcome will also be presented.

Scientific Abstracts

106 Lamb Ductus Arteriosus: 02 and PGE,
Ronald I. Clyman, Michael A. Heymann and Abraham M. Rudolph
CVRI and Departments of Pediatrics and Obstetrics-Gynecology, University of California, San Francisco, Calif.

It previously has been suggested that (a) delayed closure of the ductus arteriosus in premature infants is related to an ineffective constriction in response to increases of pO2 and that (b) prostaglandin E, (PGE,) which relaxes the vessel in low pO2 in fetal life has little effect in the raised pO2 of postnatal life. However, in the experiments reported here there was no significant difference between the tension developed in oxygen of rings of lamb ductus arteriosus in vitro from immature (70 ± 4 days gestation, n = 9) and mature (137 ± 3 days gestation, n = 11) fetuses incubated in a dark enclosed box. It is suggested that earlier reports of ineffective oxygen induced tension in vessels from immature animals may be related to the effects of light on this tissue. Overhead room light inhibited the tension developed in oxygen of immature vessels by 63 ± 10% (n = 9) but had no effect on that of mature vessels. In another series of experiments PGE1 relaxed rings of ductus arteriosus at both low (14–20 torr) and high (680–720 torr) pO2 and the ED50s of PGE, relaxation were 5.5 ± 0.7 × 10^-11 M and 8.5 ± 3.4 X 10^-10 M, respectively (n = 6). The magnitude of relaxation was greater for the oxygen contracted ductus arteriosus than for that exposed to low pO2. It is suggested that earlier reports of the lack of response to PGE, in high pO2 following relaxation in low pO2 may be related to the loss of response of the ductus
arteriosus to repeated doses of PGE, rather than to differences in pO2. The roles of pO2 and PGE, need to be reevaluated in persistent patency of the ductus arteriosus of premature infants.

107 Vascular Compliance in the Maternal Rabbit Placenta
Raymond D. Gilbert, Gwendolyn L. Brownfield and Gordon G. Power Loma Linda University School of Medicine, Loma Linda, Calif.

We studied compliance on the maternal side of the placenta in 20 New Zealand white rabbits, using slCr and 125I labels to determine erythrocyte, plasma and whole blood volumes per g placental tissue under varying maternal pressure conditions. At normal maternal arterial (Pa) and venous (Pv) pressures of 71.8 and 5.5 mm Hg, placental blood volume was 0.453 (± 0.051 SEM) ml/g placental tissue. When venous pressure was raised (Pa = 45.5, Pv = 12.2) by clamping the IVC, blood volume increased to 0.706 (± 0.066) ml/g, a significant 56% rise. However, when pressure was lowered by clamping the aorta in two steps, dropping to Pa = 33.8, Pv = 7.0 and Pa = 13.5, Pv = 5.4, volume did not decrease significantly. We calculated intervillous space pressure from arterial and venous pressures assuming a ratio of arterial to venous resistance of 9:1. Over the intervillous space pressure range from normal to high, placental compliance was 0.068 ml/mm Hg/g. Maternal placental hematocrit averaged 30%, appreciably less than the circulating hematocrit of 41%, indicating that erythrocytes transit the placenta faster than plasma. Overall, the results suggest that maternal volume and its placental oxygen reserve would be maintained during hypotension and would increase when venous pressure is elevated.

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108 Magnesium Sulfate Metabolic Effects in Mother and Infant
Dwight P. Cruikshank, Roy M. Pitkin, W. Ann Reynolds, Gerald A. Williams and Gary K. Hargis
Department of Obstetrics-Gynecology, University of Iowa College of Medicine, Iowa City, Iowa, and Departments of Anatomy and Medicine, University of Illinois College of Medicine, Chicago, 111.

Magnesium (Mg), total calcium (Ca), ionized calcium (Ca++), phosphorus (P), parathyroid hormone (PTH), and calcitonin (CT) were measured in (1) serial maternal blood samples, (2) umbilical arterial (UA) and umbilical venous (UV) blood at delivery, and (3) capillary blood from the newborn. Subjects included pre-eclamptic gravidas treated with intravenous MgSO4 infusions, and controls (both normotensive and hypertensive) infused with dextrose-water solutions. Maternal: MgSO4 infusion raised maternal Mg levels by 82–135% and lowered maternal Ca and Ca++ by 9–25%. That more marked hypocalcemia did not occur probably reflected increasing maternal PTH secretion which averaged 62% above baseline. CT did not change significantly in either treated or control subjects. Delivery: Mean Mg levels at delivery in treated (and control) subjects were 3.05 (1.27) mEq/liter in maternal serum, 2.64 (1.43) in UA, and 2.71 (1.45) in UV; thus, MgSO4 treatment did not raise fetal Mg levels to the same degree as maternal, resulting in a reversal of the placental gradient (maternal-fetal ratio 0.88 in controls and 1.12–1.22 in treated subjects), and indicating a partial ‘protective’ action of the placenta against fetal hyper-magnesemia. UA and UV Ca++ levels were 7 and 10%, respectively, lower in treated than in control subjects. Newborn: Elevated Mg and lowered Ca persisted for at least 48 h (e.g., at 24 h Mg was 58% higher and Ca 5% lower in treated than in controls). Conclusion: MgSO4 treatment influences calcium metabolism in mother, fetus, and newborn, but adverse effects are minimized by adjustments involving principally PTH.
109 Incomplete Surfactant Phospholipid Complex Formation: Absence of Phosphatidylglycerol
M. Douglas Cunningham, John W. Greene, jr. and John L. Duhring
Department of Pediatrics and Obstetrics-Gynecology, University of Kentucky, College
of Medicine, Lexington, Ky.
Fetal formation of surface-active pulmonary phospholipids (PPL) was studied in amniotic fluid
of 73 high-risk pregnancies: 49 diabetic, 18 normal-repeat cesarean section, 8 Rh sensitized, and
8 hypertensive. Individual PPL were separated and identified by TLC and reflectance
densitometry. Mean L/S ratios for all groups exceeded 2 between 35 and 36 weeks of gestation.
One or more PPL were absent in 35 of 100 specimens: phosphatidyl-dimethylethanolamine,
4/35; phosphatidylinositol, 2/35; phosphatidylserine, 1/35, and phosphatidylglycerol (PG), 32/35.
PG concentration in remaining specimens was 10.4% of total amniotic fluid PPL from 33 to 38
weeks, increasing to 14.5% through 40 weeks. PG was absent from 48% of specimens assayed
during the L/S ratio transitional period of 34 to 37 weeks. Diabetic pregnancies comprised 67%
of the study and 78% (25/32) of PG deficiencies in the transitional period. Rh-sensitized
pregnancies accounted for 8% of the study, and 19% of PG deficiencies. Six of 10 Rh-sensitized
specimens assayed in the transitional period were without PG. Nine instances of transient
neonatal respiratory distress occurred in the study: no PG was detected in 6/9. All cases were
diabetic and delivered in the transitional period with L/S ratios of 2 or greater. PG may be an
adjunctive index to fetal lung maturation in diabetic and Rh-sensitized pregnancies.

Scientific Abstracts

110 Perinatal Effect of Fetoscopy and Fetoplacental Blood Sampling in the Rhesus Monkey
Ezra C. Davidson, jr., John Anderson, Andrew G. Hendrickx and John A. Morris Department of
Obstetrics-Gynecology, Charles R. Drew Postgraduate Medical School, Los Angeles, Calif., and
California Primate Research Center, University of California at Davis, Davis, Calif.
This is the first phase evaluation of the long-term perinatal effect of fetoscopy/ fetoplacental
blood sampling in the subhuman primate. Two prior study groups of pregnant ovines used to
select endoscopy devices, refine surgical approach and collect blood samples formed the basis
for this current protocol. Despite technical advances in the ovine, there was a disturbing 36% and
39% uncorrected fetal loss, respectively. Present studies subject 15 pregnant rhesus monkeys to a
scheduled dual endoscopy approach – laparoscopy and fetoscopy – with sampling. Laparoscopy
affords preselection of the uterine puncture site under direct vision to minimize injury and
hemorrhage in the monkey with its characteristic bidiscoid placenta which in part occupies the
anterior uterus. The ‘free space’ between the placental discs arching over the uterine fundus
between the utero-tubal junctures provide the puncture site. A 2.7 mm O.D. Storz Hopkins rod-
less fibre-optic endoscope contained in a 3.1 mm O.D. rigid cannula with a 25 g sampling needle
was introduced. Dissociative Ketamine and light endotracheal halothane anesthesia with aseptic
surgical preparation, precede conventional development of pneumoperitoneum and laparoscopy.
The discussion will include photo documentation of the procedure with description of its
advantages. Preliminary conclusions: (a) fetoscopy /sampling is feasible in anterior placentation
with current devices when the puncture site can be preselected; (b) fetal loss is an unlikely event;
(c) no adverse effects on neonate, and (d) the prospects for human application are favorable.

111 Effect of Placental Lactogen (PL) on Maternal and Fetal Carbohydrate Availability
Peggy J. Rapoport, Yoshio Miyazaki, David L. Bolam, Hobart E. Wiltse and Charles L. Paxson,
jr.
Department of Pediatrics and Physiology, University of Nebraska Medical Center, Omaha, Nebr.
The current concept of the role of PL during human gestation is that it inhibits peripheral maternal carbohydrate utilization and thereby ensures adequate carbohydrate for use as a fetal fuel. To test this concept we have chronically prepared 5 pregnant ewes of 90–120 days gestation and following baseline studies infused PL into the maternal circulation. Surgical preparation consisted of implantation of bilateral uterine and femoral artery electromagnetic flow transducers, bilateral uterine, femoral, jugular vein catheters, and femoral and cystic artery catheters. Following a minimum 4-day recovery period and during optimum maternal nutrition, PL was infused at a constant rate and whole blood samples for glucose analysis were drawn at 1–4-hour intervals. Peripheral maternal glucose uptake as measured via hind limb uptake, and uterine glucose uptake were calculated by the Fick equation. A total of 34 infusion studies was completed.

The infusions produced no consistent alterations in maternal glucose levels, uterine blood flow or peripheral blood flow. Samples obtained at the hourly intervals revealed a 40% increase in uterine glucose uptake (p < 0.005), and peripheral glucose uptake decreased by approximately 35% (p < 0.01). We conclude that PL inhibits peripheral maternal glucose uptake and concomitantly increases uterine glucose uptake. The conclusions support the current concept of the role of PL, however the exact mechanisms involved remain to be elucidated.

112 Cervical Dilatation Patterns in Spontaneous and Induced Labor

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The development of an ultrasonic cervimeter has created the possibility to continuously monitor cervical dilatation during the first stage of labor (Am. J. Obstet. Gynec. 726: 288, 1976). By means of this method cervical dilatation patterns were recorded in 37 primigravidas (group I) in clinically normal spontaneous (12) or oxytocin-induced (25) labor, and in 28 multigravidas (group II) in spontaneous (12) or induced (16) labor. Intrauterine pressure was simultaneously measured. Signals were stored on magnetic tape, sampled by an LPS/AD 12 analog/digital converter at 1-sec intervals, and the resulting tape was read into a PDP 11/10 computer, programmed to supply all previously defined parameters of both signals. It was found that (1) no differences could be demonstrated between cervical dilatation patterns in spontaneous and induced labor; (2) significant acceleration of cervical dilatation occurred at a mean dilatation of 5.0 (range 4.2–6.1) cm in group I and at 3.3 (range 2.2–4.6) cm in group II; (3) mean speed of cervical dilatation (cm/h) before acceleration was 0.5 in group I and 0.4 in group II, whereas after acceleration it was 2.7 (group I) and 3.7 (group II); (4) in group I the mean active pressure area × 10~3/cm of dilatation was 77.5 before the acceleration point was reached and 26.0 thereafter; values in group II were 48.6 and 23.0, respectively; (5) the observed increase in magnitude of cervical excursions in response to uterine contractions (effectivity) was less pronounced in group I than in group II. The data indicate that cervical dilatation depends less on uterine activity than on intrinsic qualities of the cervix itself.

113 Amniotic Fluid Fatty Acid Side Chain Analysis for Assessment of Fetal Lung Maturation

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Amniotic fluid (AF) lecithin fatty acid side chain analysis has been performed on AF samples from 150 pregnant patients. The lipid extract of AF was subjected to thin layer chromatography
and the lecithin fraction was analyzed by gas liquid chromatography. The palmitic/stearic ratio (P/S) was utilized as an indirect measurement of the amount of dipalmitoyl lecithin present relative to other lecithins in the AF. Of the 150 patients studied, there were 33 cases in which samples were obtained within 72 h of delivery of the infant which will be considered here. Sixteen of these patients were insulin-dependent diabetics and 17 were non-diabetic. Of the 17 infants of nondiabetic mothers, 6 developed the respiratory distress syndrome (RDS). The mean P/S ratio in the RDS AF was 3.75 ± 1.2 (SD) while the mean value of the non-RDS AF was 11.4 ± 4.7 (SD), (p < 0.001). Of the 11 patients with P/S ratios of 5 or greater, only one developed RDS (P/S 5.2). Of the 6 patients with values less than 5, all except one developed RDS (P/S 4.3).

Of the 16 infants of diabetic mothers, 6 developed RDS. The mean P/S ratio of the diabetic RDS AF was 5.5 ± 1.7 (SD) while the mean P/S ratio of the diabetic non-RDS AF was 12.7 ± 5.2 (SD), (p < 0.003). Of the 9 patients with values of 9 or greater, none of the infants developed RDS. Of the 7 patients with values less than 9, all except one developed RDS (P/S 4.3).

These initial results suggest that AF lecithin fatty acid side chain analysis may be a useful method for assessment of fetal lung maturation.

114 Effect of the Combination of Vascular Restriction and Maternal Hypoxia on Fetal Brain Development in the Rabbit
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The model utilized is a pregnant rabbit. At 26–27 days a laparotomy is performed. The fetuses are identified and 1 of the 3–4 vessels of every other fetus in both horns omitting the fetus closest to the ovary is ligated. The nonligated fetuses have 1 drop of Evans blue injected subcutaneously. The laparotomy incision is closed and the mother allowed to recover. She is placed in a 10% oxygen environment for 3 h on days 27, 28 and 29. At birth fetuses are weighed and half the litter sacrificed. The cerebrum and cerebellum are quick frozen and later analyzed for protein, DNA and RNA by a modified Lowrey method for protein, Burton’s assay for DNA and Orncinol assay for RNA. The other half of the litter is allowed to live for 2 months and then sacrificed for similar cerebellar and cerebral studies. Suitable nonoperated and nonexposed to low oxygen controls have been studied. In a few animals exposed to low oxygen a catheter was placed in the uterine vein to demonstrate a decreased O2 environment for the fetus. Results of protein, DNA and RNA contents will be presented.

115 Calcitonin Secretion in Response to Hypercalcemia in the Fetal Monkey
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The capacity of the fetus to cope with excess calcium loads by releasing calcitonin (CT) was studied in the last trimester of pregnancy in the macaque. Calcium gluconate (12–30 mg/kg) was infused into a maternal vein or directly into a fetal interplacental vein over a 2-hour interval. Total calcium was measured by autoanalyzer and CT by radioimunoassay in both fetal and maternal plasmas over the ensuing 4 h.
Within 15 min after direct infusion of calcium into the fetus or mother, CT began to rise and reached levels of 46–78% above baseline by the end of the infusion. Maternal infusion of calcium resulted in but modest increases in fetal serum calcium levels (11–22%) and in appropriately lesser elevations in fetal CT levels (15–46%). Baseline values of CT were similar in mother (0.28 ± 0.04 ng/ml) and fetus (0.33 ± 0.04 ng/ml) as were the extents and patterns of release of CT in response to hypercalcemia.

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Fetal CT response was also examined by infusion of glucagon (100 µg/kg), a CT secretagogue, directly into the fetal circulation for 1 h. An attenuated response was noted reaching levels 43–47% above baseline values some 2 h after the end of the infusion. Thus, the primate fetus is capable of responding to either hypercalcemia or glucagon by the release of immunoreactive calcitonin.

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116 Concentrations of Metanephrine in Amniotic Fluid
Raul Artal, Calvin J. Hobel, Robert W. Lam and Delbert A. Fisher UCLA School of Medicine, Harbor General Hospital, Department of Obstetrics-Gynecology and Pediatrics, Torrance, Calif. Catecholamine secretion is known to increase with stress and aging. Thus a practical method to determine catecholamines in amniotic fluid might prove useful in assessing the fetoplacental unit and/or the relative maturity of the fetus. Concentrations of metanephrine in amniotic fluids from pregnancies differing in gestation age and associated conditions have been measured using a newly developed specific radioimmunoassay. Metanephrine, a major metabolite of epinephrine, was found in the free and conjugated form. Results available to date in 37 pregnancies (mean values pg/ml, and the free/total metanephrine ratios) were as follows:

The results indicate: (a) a positive correlation of amniotic fluid metanephrine concentrations with gestational age, and (b) an increase in amniotic fluid metanephrine concentration during labor at term.

117 Steroid Changes during the Menstrual Cycle of the Baboon and Human: a Model for Corpus luteum Function OR. KlingandP.K. Westfahl
Department of Obstetrics-Gynecology, University of Oklahoma College of Medicine, Oklahoma City, Okla. Estrone (E1), estradiol (E2), testosterone (T), dihydrotestosterone (DHT), andros-tenedione (A) and progesterone (P) were simultaneously measured by radioimmunoassay following celite chromatography during a complete menstrual cycle in the peripheral serum of 5 baboons (Papio cynocephalus) and 5 humans. A similarity in hormonal patterns during the cycle was observed between the two species. An analysis of variance using the log normal distribution of all steroid measurements verifies significant variation between individual cycle days for all steroids measured in each species except for DHT. No significant difference between human and baboon at p &gt; 0.05 were noted during the midfol-

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icular, periovulatory or midluteal phases of the cycle for E1, E2, T and P. The level of A in the baboon rose during the periovulatory phase but remained significantly lower than the human at midcycle while no significant difference was observed during the foUicular or luteal phase. A
noncyclic secretory pattern for DHT was observed in both the human and baboon, with the mean serum level significantly higher in the baboon 74.3 ± 19.2 ng% than in the human 48.7 ± 14.9 ng% (p < 0.001, mean ± SD). Contrary to a previous report (Goncharov et al.: Acta Endocr. 82: 396, 1976) we observed a midcycle rise in T, a secondary rise in Et and E2 during the luteal phase and did not find a significant rise in A during the luteal phase of either the human or baboon. We propose the baboon is an appropriate model for studying corpus luteum regulation of implantation and gestation.

118 Serum Calcitonin Levels before and after Pentagastrin Stimulation in Rhesus Monkeys during Pregnancy, Lactation, Infancy, Early Childhood, and Adulthood
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We have previously reported that the immunoreactive serum calcitonin (iCT) in man is elevated in the neonate and pregnant mother at basal level compared to that found in normal nonpregnant subjects. We have also shown that the serum iCT concentration is high in early life but diminished with age (Am. J. Obstet. Gynec. 121: 622–625, 1975).

Because of the ethical considerations of intravenous (i.v.) pentagastrin administration in pregnant mothers, infants, and children, we measured the iCT concentration in the serum of Rhesus monkeys at basal and after pentagastrin stimulation. We studied 5 pregnant, 6 nursing mothers, 6 nursing infants, and 6 juveniles, and the results were compared to that found in 6 adult unbred females and 4 adult males.

Intravenous pentagastrin administration produced a significant rise of the serum iCT in all groups of monkeys studied. The serum iCT concentration was significantly high at basal and after pentagastrin stimulation in pregnant mothers, infants, and juveniles compared with adult nonpregnant monkeys (p < 0.05 or less). The lactating mothers had a higher mean level of serum iCT but this was not significantly different from nonpregnant adults (p < 0.1). These results extend our observation in man and suggest that calcitonin may play an important role in the calcium metabolism during pregnancy, infancy, and childhood.

119 Correlation between Ovulation as Determined by Corpus Luteum (CL) Biopsy and Serum Levels of Gonadotrophins and Steroids in Women
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Periovulatory serum levels of LH, FSH, estradiol-17(3 (E2), estrone (Ei), progesterone (P), 17α-hydroxyprogesterone (17P), and androstenedione (A) were measured by radioimmunoassay in sera collected serially every 8 h for 6 days from 6 normally ovulating women. On the estimated day of ovulation the ovaries were examined and photographed at laparotomy. Fresh CL or preovulatory follicles were excised. CL dating established ovulation time ± 12–24 h. All subjects had discrete, coincident LH and FSH peaks. Data from one subject are inconsistent with present concepts of normal ovulation. Three subjects were postovulatory at surgeries 38, 52, and 84 h after their respective LH peaks. In two with very early Society for Gynecologic Investigation 82 (12–24 h) CL for which histologic dating is most precise, LH peaked 14–26 and 29–41 h and E2 peaked 22–34 and 58–70 h prior to ovulation. E2 peaked 8 and 29 h before LH. 17P peaked 8
and 16 h after LH and 6–18 and 13–25 h before ovulation. In the third the CL was 24–48 h old and LH and E2 peaked 37–61 and 99–123 h, respectively before ovulation. 17P peaked 13 h before LH and 50–74 h before ovulation. Two subjects, operated 12 and 5 h before their LH peaks, had not ovulated. In both, E2 peaked 11 h before surgery. In all subjects, E, essentially mirrored E2 and A did not vary relative to ovulation. Five additional subjects are presently under study. Regression analysis is in progress and will additionally correlate time of first significant rise and ovulation.

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120 Inhibition of Rat Pituitary Prolactin Release during Perfusion of Pituitary Gland Explants
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A new system using in vitro perfusion of explanted rat pituitary glands has been developed in order to study factors regulating the secretion of rat pituitary prolactin (rPRL). The technique employs the transplantation of two female rat pituitary glands beneath the kidney capsule of a third female. 3 weeks following pituitary transplantation, the kidney containing the explant is removed and perfused in a closed system with an oxygenated solution of Krebs bicarbonate buffer containing albumin. Aliquots from the solution are obtained at frequent intervals during the 2-hour perfusion and frozen until assayed for rPRL by radioimmunoassay. Utilizing this system, rPRL concentrations in the perfusate progressively increased from 0 to 70.4 ± 8.0 ng/ml by 120 min (n = 11). Various substances were then added to the perfusate to test their ability to affect prolactin secretion. Addition of haloperidol (100 ng/ml), a specific dopamine receptor blocker, did not significantly change either the rate of rPRL release or amount of rPRL released by 120 min. Addition of Bromocryptine (BR-C), 20 ng/ml, after 15 min of perfusion prevented any subsequent increase in rPRL concentration so that at 120 min the mean rPRL concentration was 17.0 ± 2.5 ng/ml (p < 0.001). When added to the perfusate prior to BR-C, haloperidol successfully blocked the ability of BR-C to inhibit further rPRL release. These results are consistent with the hypothesis that inhibition of prolactin secretion by BR-C is at the site of dopamine receptors in the pituitary gland.

121 The Effect of Total Hypophysectomy on Peripheral Luteinizing Hormone-Releasing Hormone Levels (LHRH) in Human Subjects
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Three females and two males underwent transphenoidal total hypophysectomy for treatment of metastatic cancer. Circulating levels of LH, FSH, E2, testosterone and LHRH were determined by radioimmunoassay prior to surgery, every 6 h for 24 h and every 12 h for 96 h after surgery. All had extremely low or nondetectable levels of circulating testosterone and/or estradiol, although one female and two males received hormonal therapy up to 3 days prior to surgery. Preoperative plasma LH (mean = 82.8 mlU/ml) and FSH (mean = 83.7 mlU/ml) declined precipitously following hypophysectomy in the females to a mean LH of 23.2 mlU/ml at 6 h and a mean FSH of 27.9 mlU/ml at 24 h. At 120 h post hypophysectomy, mean LH and FSH were 9.5 and 12.5 mlU/ml, respectively. In comparison, male preoperative
levels were low (mean LH = 5.6 mlU/ml; mean FSH = 1.8 mlU/ml) and fluctuated at barely detectable levels throughout the postoperative period. Mean preoperative plasma LHRH (methanol extracted) was 5.78 pg/ml. At 36 h, plasma LHRH was significantly (p = < 0.05) elevated (mean = 8.67 pg/ml) and at 96 h was 11.12 pg/ml when the entire group was examined. The rise in plasma LHRH activity appeared temporally related to marked declines in the level of plasma LH. The data indicate persistence of LH and FSH activity at low levels 5 days after ‘total’ hypophysectomy and provides evidence for the existence of a regulatory influence of pituitary LH on LHRH secretion.

122 Ethinyl Estradiol (EE) Administration and Plasma Steroid Concentrations in Ovariectomized Women

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The administration of estrogens to women might result in an altered adrenal steroid hormone pattern by a direct affect on the adrenal, by increasing the plasma concentration of transcortin or by affecting tissue metabolism of the steroids. Changes in liver metabolism (a major site of steroid metabolism) might be especially important since the administration of estrogens may result in the development of hepatomas. Ovariectomized women were studied before (I), during – 3 days (II) and 3 weeks (III) – and 3 weeks after (IV) the oral administration of 0.2 mg EE/day. Plasma concentrations of F, corticosterone (B), 11-deoxy-corticosterone (DOC), testosterone (T), dehydroepiandrosterone plus its sulfate (DHEA) and P were measured by the double antibody RIA method (androstenedione and estrone, in progress). Plasma F increased from 3.3 ± 0.7 (I) to 8.2 ± 1.5 µg/100 ml at II, 17 ± 1.2 at III and remained elevated 5.2 ± 0.6 µg/100 ml at IV. Plasma B also increased with EE administration: 135 ± 47 ng/100 (I), 208 ± 72 (II), 243 ± 19 (III) and back to 138 ± 47 (IV). Although the plasma DHA values changed from 224 ± 28 µg/100 ml (I) to 272 ± 39 (II) to 191 ± 23 (III) and back to 213 ± 25 (IV), the differences were not statistically significant. Plasma DOC, P and T did not change. The production rate (MCR X concentration) of F was significantly higher during estrogen administration and remained significantly higher 3 weeks after discontinuing EE. The results indicate that whereas the major effect of EE treatment is to increase plasma binding of F and B, it may also increase the adrenal secretion of cortisol and alter the metabolism of cortisol.

123 ACTH Is Trophic to the Fetal Zone of the Fetal Adrenal (Macaca mulatto)I. John Davies, Koji Yoshinaga, Kurt Benirschke and Kenneth J. Ryan Harvard Medical School, Boston Hospital for Women, Laboratory of Human Reproduction and Reproductive Biology, Department of Obstetrics-Gynecology, Boston, Mass., and University of California at San Diego, Medical School, Department of Pathology, San Diego, Calif.

The authors previously reported that the administration of dexamethasone (Dex-Rxd) to pregnant monkeys resulted in atrophy of the fetal zone of the fetal adrenal. While this was interpreted as evidence for trophic support of the fetal zone by ACTH, a mechanism other than suppression of ACTH secretion could not be excluded. In the present experiments, pregnant monkeys were Dex-Rxd according to the previous regimen (8 mg/day i.m. Society for Gynecologic Investigation

84 from day 150 until parturition), and, in addition, ACTH was injected transabdominally into a fetal limb (20 IU 3 times each week). The fetuses were delivered near term by cesarean section. The mean weight of the fetuses did not differ from that of Dex-Rxd or untreated controls. The combined weight of the adrenals in untreated controls (n = 5) was 798 ± 221 (SD) mg, and in
Dex-Rxd animals (n = 5) it was reduced by 60%, 310 ± 195 (SD) mg (p < 0.02). The fetuses which were Rxd with ACTH in addition to maternal Dex (n = 3) had adrenal weights of 774, 1,133, and 1,148, mean 1,018 ± 212 (SD). This is greater than that of the Dex-Rxd animals (p < 0.007), and also greater than that of untreated controls (p < 0.01) Histology confirmed that ACTH prevented regression of the fetal zone in the Dex-Rxd monkeys. We conclude that ACTH is trophic to the fetal zone of the fetal adrenal in the rhesus monkey.

124 Comparison of Unconjugated and Total Plasma with 24-Hour Urinary Estriols in the Management of the Pregnant Diabetic

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62 consecutive diabetic women (class A:7, B:41, C:6, D:5, F:3), hospitalized from 1 to 8 weeks prior to delivery who volunteered for daily plasma estriol (E3) assays were included in this prospective and blinded evaluation of unconjugated (UPE3) and total plasma E3 (TPE3) assays in the management of diabetic pregnancies. Some 1,100 simultaneous UPE3, TPE3, 24-hour urinary E3 (UE3) and creatinine (C) assays were performed on an almost daily schedule. Clinical management was based upon a weekly oxytocin challenge test and daily 24-hour UE3 and C determinations. 20 patients had spontaneous onset of labor and 34 were delivered electively at 38 weeks, while 3 were delivered for maternal and 5 for fetal indications. Gestational age at delivery averaged 38 and ranged from 35 to 42 weeks. A total of 840 day-to-day variations of UPE3, TPE3, UE3 and the UE3/C ratio were computed as percent rise or fall from the highest mean of 3 consecutive preceding values. Observed were 370, 419 and 428 decreases in UPE3, TPE3 and UE3/C, respectively, averaging 12.8 ± 9.6 (SD), 13.4 ± 10.1 and 14.4 ± 10.6%. One perinatal death occurred, a stillbirth, which was preceded by a 42% decrease in UPE3, but unheralded by either a drop in TPE3, UE3, or UE3/C. There were fewer significant ( > 40%) falls unassociated with perinatal morbidity and mortality with UPE3 (n = 3) than with TPE3 (n = 8) and UE3/C (n = 8). These data indicate that UPE3 is the most predictive test among presently available E3 assays for managing the pregnant diabetic.

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125 Secretion of HCG-α in Seminal Plasma of Normal Males

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Recent evidence supports the view that HCG-like material is produced in the nonneoplastic human testis (Braunstein et al: New Engl. J. Med. 293: 1339, 1975). As considerably higher levels of LH as compared to FSH have been found to occur in human seminal plasma (Sheth et al: Fertil. Steril. 27: 933, 1976), we investigated whether or not this discrepancy might be due to a cross-reaction between LH and HCG. The concentrations of LH, FSH, and prolactin were determined by RIA in the seminal plasma and serum of 53 normal males. No significant difference between prolactin levels in serum and seminal plasma were found, but FSH was invariably lower (0.87 ± 0.40 vs. 2.14 ± 1.4 ng/ml) and LH higher (4.0 ± 0.93 vs. 1.95 ± 0.83 ng/ml) in semen as compared to serum. Consequently, we measured HCG-0 by a homogenous RIA supplied by NIA-MDD. The standard curve for HCG-0 was found to be
parallel to that obtained by diluting a pool of seminal plasma. Accordingly, the concentration of HCG-0 in seminal plasma of 14 fertile male volunteers was significantly higher in serum (3.2 ± 1.1 vs. 1.6 ± 0.5 ng/ml). It is concluded that the actual LH level in seminal plasma is lower than in serum, and that the HCG-like material identified in testis homogenate is also secreted in semen.

126 Organ Culture of a Gonadoblastoma from a Patient with Secondary Amenorrhea
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A 16-year-old patient was evaluated for secondary amenorrhea and found to have full Mullerian structures and to be 46XY karyogram. Exploratory laparotomy revealed bilateral gonadoblastoma containing ovarian stroma, Leydig cells, sustentacular granulosa and germ cells similar to those found in disgerminoma.

Samples weighing 200 mg divided in small pieces were cultured in plastic organ culture dishes in Medium 199 plus 20% fetal calf serum under air and 5% CO2. The medium was changed on day 2, 6 and 9 and frozen until radioimmunoassay determinations of progesterone, estrogens and androgens were performed.
The tissue from both sides produced steroids. Progesterone was secreted in similar amounts bilaterally until day 6 when the left side exceeded the right side (114.4 ± 2.8 to 32.4 ± 1.7 ng/200 mg tissue). This difference was markedly accentuated by the addition of luteinizing hormone.

127 The Pharmacokinetics of Diethylstilbestrol in the Pregnant Rat
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Can the prenatal environment, especially placental transport function, contribute to the increased susceptibility of the progeny to tumor induction following the maternal administration of diethylstilbestrol (DES)? Placental transfer studies in the 20-day pregnant Wistar rat were performed using femoral vein infusions or fetal injections of 14C- or 3H-DES. After 3 h of infusion, the maternal plasma levels of radioactivity (C-H) were constant, and the fetal to maternal plasma ratio for the C-H was 2.69 ± 0.30. Both the chorioallantoic placenta (CAP) and the visceral yolk sac (VYS) concentrated the C-H to tissue/maternal plasma ratios of 4.26 ± 0.85 and 5.10 ± 1.21, respectively. In addition, fetal tissues concentrated the C-H to even higher levels, especially the ovary, testis, uterus, adrenal. When the fetuses were injected with 14C- or 3H-DES, the C-H rapidly appeared in the maternal circulation; however, the tissue/fetal plasma ratios < 1 for both the CAP and VYS.

Using thin layer chromatography, DES, dienestrol and glucuronides were separated. The C-H was associated with the DES in the maternal plasma (75%), fetal plasma (85%), CAP (85%), VYS (92%). The remaining C-H was associated with the glucuronides, except for the maternal plasma where 10% remained unidentified.
Thus, in addition to the elevated C-H within the fetal reproductive tissues, the con-centrative placental transport of DES and not dienestrol may contribute to the increased prenatal susceptibility to DES carcinogenicity. (Supported by GRSG RR-05403.)

128 Hypothalamic-Pituitary Function in Patients with Primary Amenorrhea

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It is not known whether primary amenorrhea with normal or low LH, FSH and E2 is an hypothalamic or pituitary disorder. 8 women with this syndrome were studied by a sequential pituitary stimulation test (SST) of i.v. insulin followed by Gn-RH-TRH and 2 h later by a second dose of Gn-RH. 2 patients had normal responses while the other 6 patients had abnormal PRL responses to insulin, but normal responses to TRH, suggesting hypothalamic disorders. 6 patients had LH and FSH responses to Gn-RH-TRH which were significantly lower than the controls while only 2 patients had abnormally low FSH. Following the second dose of Gn-RH, 6 patients had significantly lower LH and FSH responses. 6 of the 8 patients had TSH responses to TRH which were significantly lower than 95% confidence limits of the control group. In order to determine whether the abnormal gonadotropin response was of pituitary origin three of these patients were then given 10 µg Gn-RH for 4 days and on the fifth day the SST was repeated. At this time the LH response was significantly greater and in the normal range while the FSH response was similar to the pretreatment results. In conclusion, patients with primary amenorrhea with normal or low LH, FSH and E2 have a pituitary dysfunction secondary to derangement of the hypothalamus or higher CNS center(s). Furthermore, gonadotropin responses to Gn-RH in some patients with primary amenorrhea resemble those of prepubertal girls. The etiology of primary amenorrhea in this group of patients may be due to failure of maturation of the hypothalamus.

129 Hormonal Effects on Calcium Uptake by Uterine Microsomes

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Progesterone inhibits myometrial contraction. This effect could be due, in part, to sequestration of free calcium within the cell since this ion is required for smooth muscle contraction. We examined the uptake of 45Ca by microsomes prepared from myometrium of immature rabbits treated with estrogen (E) or progesterone (P). The uterine microsomes were incubated with 45Ca and ATP and the incubation was stopped by rapid filtration. 45Ca uptake was maximal in 8 min; was saturable and reversible, and was consistently greater in the groups treated with P. Thermodynamic analysis of binding indicates that the concentration of binding sites was 0.94 nm/mg protein and $K_{ij} = 3.10 \times 10^{-6} M$ after P treatment and after E was 0.72 nm of sites/mg protein and $K_{ij} = 8.27 \times 10^{-6} M$. We conclude that myometrial microsomes from P treated rabbits bind 45Ca at more sites and with greater avidity than after E and propose that these alterations account, in part, for observed differences in contractility.

130 Relationship between Metabolic Clearance Rate (MCR) and Sex Steroid Binding Protein (SBP) in Adult Rhesus Monkeys
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A proposed physiological role of SBP is in regulating the metabolic clearance of androgens from the circulation. We have measured the MCR of dehydroepiandrosterone (DHA) and testosterone (T), the plasma binding capacities of dihydrotestosterone (SBP) and corticosterone (CBG), and the metabolism in vitro of T by skin. Chronically castrated adult rhesus males (M), females (F) and prenatally androgenized females (AF) were treated for 8 weeks with silastic implants of estradiol (E2) that increased plasma concentrations 3–4 fold (83, 97 and 77 pg/ml, respectively). The initial sex difference in SBP was eliminated by the treatment as the mean values (µg bound/ml) for M increased (3.95 ± 0.42 to 4.46 ± 0.53) and those for F and AF decreased (5.85 ± 0.40 to 4.54 ± 0.27, and 4.88 ± 0.46 to 4.65 ± 0.27). SBP values increased in every M and decreased in all but one F; the response by AF varied. CBG decreased in all groups.

The MCRj of M was significantly reduced by E2 (7.1 ± 0.8 to 4.9 ± 0.6) and was also decreased in 5 of 6 F and in most AF; MCRjha was unchanged in F but was reduced in most M and AF. These data indicate an inverse relationship between the MCRj and SBP binding capacity only in adult male rhesus monkeys, and physiological concentrations of E2 suppress SBP values in females of this species.

(Supported by PHS grants No. HD08736, and HD00272.)

131 Comparison of Peripheral Metabolism Estimated in vitro and Metabolic Clearance Rate (MCR) in vivo of Dehydroepiandrosterone (DHA) and Testosterone (T) in Normal and Perinatally Androgenized Rats
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Enzymatic transformations and inactivation by binding are the major mechanisms for the metabolic clearance of free hormonal steroids from the circulation. To relate transformations and clearance, we have compared the specific activities of several steroid reductases, dehydrogenases, or hydroxylases found in liver or skin from 105-day-old Sprague-Dawley rats with the MCR of DHA and T.

The MCRj of normal males (M), 97 ± 17 liter/day/kg (mean ± SD) was similar to that of females (F), 125 ± 38, but hepatic hydroxylation of DHA by M, 3.38 ± 0.89 was significantly greater than that of F, 1.36 ± 0.19 µmol mg-1 min-1. The MCRj of M, 66 ± 17 was the same as that of F, 75 ± 16, but hepatic production of DHT was significantly greater in F: 26.1 ± 4.8 vs. 5.5 ± 1.0 for M. In contrast, abdominal skin from M metabolized T to Δ4-A and 5α-A at greater rates than F. T metabolism was greatest in genital skin of F.

These data indicate that enzyme activities of skin or liver do not accurately reflect the MCR but different organs are likely to have quantitatively different enzyme specific activities, the presumed sum of which produces equal clearances between sexes of this species. This preliminary conclusion was confirmed by study of perinatally androgenized (A) rats; AF had 2-fold greater clearance rates of both DHA and T than AM, but the skin and liver metabolic activities measured did not necessarily reflect either the magnitude or direction of the change in MCR.

(Supported by PHS grant No. HD08736.)
Microsomal-Estradiol Receptor of Rabbit Uteri

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Properties and levels of estradiol (E2) binding in microsomal preparations were studied in estrous and pseudopregnant (day 7) rabbit uteri. When suspensions of microsomes in buffer containing 0.25 M sucrose were incubated in the presence of 10^{-10} to 10^{-9} M 3H-E2 evidence for high affinity as well as low affinity binding of the steroid was observed. The high affinity binding of 3H-E2 to the microsomes was not displaced by progesterone or testosterone. Following extraction of microsomes with hypotonic buffer only low affinity-binding remained in the particulate fraction while 90% of the high affinity binding was accounted for in the extract. The binding protein of the extracts had properties similar to those of the cytosol E2 receptor; namely, sedimentation as 4S (high salt) or 8S (low salt) on sucrose gradients, a $K_c$ of 0.9 X 10^{-10} M, and specificity for estrogen binding. In estrous rabbit uteri (n = 6) the level of receptor in microsomes and cytosol was 0.24 ± 0.05 pmol and 11.5 ± 1.9 pmol/g tissue, respectively, while in the pseudopregnant animal (n = 4) receptor was not detected in the microsomal extracts and the level in cytosol was 4.1 ± 0.3 pmol/g tissue. No significant estradiol binding was detected in the mitochondrial or lysosomal fractions. The endogenous concentration of E2 in cytosol and microsomal fractions was 63 ± 10 and 38 ± 10 pg/g during estrus and 20 ± 8 and < 10 pg/g during pseudopregnancy. Our data confirm the presence of an additional intracellular site of estradiol binding and retention where progesterone may regulate the mode of action of estrogen.

Progesterone Metabolism by the Placenta and Uterine Decidua at Various Stages of Human Gestation

Leon Milewich, Norman F. Gant, Barry E. Schwarz, Grace T. Chen and Paul C. MacDonald

Department of Obstetrics and Gynecology, University of Texas Southwestern Medical School, Dallas, Tex.

Progesterone is metabolized by human fetal membranes at declining rates after 33 weeks’ gestation. To ascertain if this declining rate of progesterone metabolism is unique to fetal membranes or rather a generalized phenomenon in target tissues with advancing human gestation, progesterone metabolism was studied in human placenta and uterine decidua from various stages of pregnancy. Isolated uterine decidua and placental tissue were incubated with (3H) progesterone and added NADPH. The results of these studies are summarized in the table below.

From this data it is apparent that as pregnancy advances, there is no decrease in the rate of progesterone metabolism in the placenta or uterine decidua. Thus the declining rate of progesterone metabolism in human fetal membranes may represent a specific phenomenon that is related to cellular or subcellular progesterone deprivation in these tissues.

Prostaglandin E Levels in Nonpregnant and Pregnant Sheep

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Numerous reports have indicated that uterine venous prostaglandin E (PGE) levels are elevated during pregnancy in several species. In addition, earlier reports from our laboratories have shown that estrogen increases uterine PGE production. Since systemic estrogen levels are known to increase during pregnancy, the possibility that PGE levels were also elevated in pregnant sheep was investigated. Nonpregnant and 80-day pregnant sheep were chronically instrumented for arterial pressure measurements, uterine blood flow determinations and arterial (carotid artery, CA) and venous (jugular vein, JV; uterine vein, UV) blood samples. Blood samples were taken weekly and levels of PGE determined by radioimmunoassay. Results: CA blood samples of nonpregnant sheep contained 226 pg/ml of PGE while JV levels of PGE were slightly higher (233 pg/ml). These values were not significantly different in the pregnant sheep. In contrast, uterine venous effluent of pregnant sheep in the latter half of gestation contained PGE levels which were approximately 30 pg/ml higher than systemic arterial plasma. This elevation in uterine venous PGE levels was not observed in the nonpregnant sheep. Conclusion: (1) systemic levels (CA and JV) of immunoreactive PGE were not altered during pregnancy; (2) uterine venous levels of immunoreactive PGE appear to be elevated in the unanesthetized chronically instrumented pregnant sheep; (3) when arterial-uterine venous differences are multiplied by uterine blood flow, uterine production rates are elevated during pregnancy and tend to increase during gestation.

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135 Relationship of Placental Blood Flow to the Placental Clearance of Maternal Plasma Dehydroisoandrosterone Sulfate (DS) through Estradiol (PC-DSE2)
Paul C. MacDonald, Norman F. Gant and John C. Porter
Department of Obstetrics-Gynecology, University of Texas Southwestern Medical School at Dallas, Dallas, Tex.

We have proposed that PC-DSE2 is proportional to maternal placental blood flow (F). In an elegant mathematical analysis, Clewell and Meschia showed that PC-DSE2 was related to F as follows: Cobs = F(1 – e-c/F), where Cobs = PC-DSE2 and C = placental clearance of DS. They assumed that C was constant. Using 19.7 ml/min for C, they allowed PC-DSE2 to vary widely and computed F. In some cases, F was unrealistically low; and they concluded that PC-DSE2 was not related to F. They erred in assuming that PC-DSE2 and C did not vary directly with one another. Indeed, negative values for F obtain for low values of PC-DSE2 when C = 19.7 ml/min, an impossible result. It is apparent that PC-DSE2 and C have closely related values since C varies little when PC-DSE2 = 19.3 ml/min despite wide variation in F. C is the sum of all routes of irreversible clearance of DS by the placenta, i.e., C = PC-DSE2 + C1+C2+C3+..Cn, where C1+C2+C3+..Cn must increase. It is more likely that C bears a constant relationship to PC-DSE2 such that Cobs = kC, where k &lt; 1. If so and if k were known, C can be computed; and the formula of Clewell and Meschia can be utilized to compute F from PC-DSE2. An analysis of MCR-DS shows that 0.92 &lt; k &lt; 0.99; k is likely 0.97.

136 Free and Protein Bound Hormones in Amniotic Fluid
Chung H. Wu, Michael Mennuti and G. Mikhail
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Human mid-pregnancy amniotic fluid (n = 97, 14–18 weeks’ gestation) was analyzed for its hormonal contents. The biologic activity of steroids based on their protein binding properties was determined.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Concentration ± SE Free, %</th>
<th>Specific binding, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androstenedione (A), male</td>
<td>658 ± 33*</td>
<td>32.3 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>360 ± 28</td>
<td>27.1 ± 2.7</td>
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<tr>
<td>Testosterone (T), male</td>
<td>277 ± 16*</td>
<td>13.6 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>41 ± 3.7</td>
<td>11.7 ± 0.7</td>
</tr>
<tr>
<td>FSH, mIU/ml</td>
<td>male 1.36 ± 0.14*</td>
<td>female 10.1 ± 1.6</td>
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<td></td>
<td>* p &lt; 0.001.</td>
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The concentration of estrone (Et) was 280 pg/ml with 27% nonprotein bound and only 2% bound tightly to protein. The corresponding values for estradiol (E2) were 94 pg/ml, 15% free and 13% specifically bound; for progesterone (P) 55 ng/ml with 20% free, 4% bound with high affinity. In the amniotic fluid T and E2 have the lowest % free fraction and highest specifically bound fraction; however, the % free is more than 10 times that found in maternal plasma. There was no sex difference in the total concentration of E,, E2 and P, or in the binding properties of all the steroids studied. Sex differences are reflected in hormones that play a role in sex differentiation and are primary products of the fetus. Accuracy in sex prediction based on A concentration is 80%, T concentration is 97%, FSH is 94% and for combined T and FSH is 100%. The determination of amniotic fluid T and FSH provide a useful supplement to cell karyotype studies in prenatal genetic diagnosis.

137 The Development of Rhythmic Patterns of Gonadotropin and Estrogen Excretion before, during and after Puberty J.D. Hoff, S. Kundell, B. Hopper and S.S.C. Yen Department of Reproductive Medicine, UCSD School of Medicine, La Jolla, Calif.

To define the pattern of gonadotropin (GTP) and estrogen (E) secretion during the period of sexual maturation, daily morning urinary GTP and E levels, corrected for creatinine, were measured in a cross sectional study of 15 healthy schoolchildren over a period of 57 days. In boys, urinary excretion of GTP was low and flat with FSH exceeding LH during stage I puberty. As pubertal development progressed, from stages 2 to 5, mean LH and, to a lesser extent, FSH levels increased. In girls, urinary excretion of GTP in stage I of puberty is similar to that of stage I boys. In stages 2 and 3, prior to menarche, there is a rise in mean GTP levels and both LH and FSH assume a clear pattern of day-to-day fluctuations of greater than 100%. Spectral analysis confirmed a 2-day rhythm as dominant and, in contrast to a similar study by Hansen et al. (Science, N.Y. 190: 161, 1975), longer rhythms of cyclic pattern were not found. The LH and FSG excretion in post-menarchial girls, assumed the monthly rhythm of adult pattern and became more pronounced as pubertal stages advanced from 3 to 5. Although in girls, mean urinary E excretion increased progressively through the pubertal stages, in all premenarchial girls from stages I to 3, the pattern of E excretion was flat, even in those subjects showing marked day-to-day fluctuation in GTP. After menarche, the daily E excretion showed a cyclic pattern similar to that of adult women. These data suggest that (1) hypothalamic-GTP maturation during pubertal development is associated with a gradual onset of rhythmic release of GTP from a short (2 days) to a long and cyclic pattern, and (2) ovarian E plays little or no role in the maturation of hypothalamic-GTP system prior to menarche.
138 Further Delineation of the Role of Dopamine (DA) in the Regulation of LH and Prolactin (PRL) Secretion in Humans S.J. Judd, J.S. Rakoff, L.A. Riggand S.S.C. Yen Department of Reproductive Medicine, UCSD School of Medicine, La Jolla, Calif. We have reported that DA and DA receptor agonists cause a decrease in circulating LH and PRL in eugonadal subjects. In the present study, the effect of DA infusion (4 µg/kg/ min) in subjects with elevated LH and normal PRL levels were investigated. In addition, the site of the inhibitory action of DA was studied. During DA infusion, the mean maximum decline of LH is significantly greater in 5 patients with polycystic ovary disease (PCO) than in 5 agonadal women (45.6% vs. 36.6%; p &lt; 0.005) and the maximum decline in both groups was significantly greater than the normal subjects (p &lt; 0.01). The decrease in PRL levels was also significantly greater in PCO than in agonadal women (p &lt; 0.05). Upon cessation of DA infusion, the significant rebound of LH release observed in normal subjects did not occur in either group. In contrast, the PRL rebound in both PCO and agonadal women was present but the latter was significantly smaller than the former (p &lt; 0.05). The LH response to 10 µg of LRF was significantly less (p &lt; 0.05) during DA infusion as compared to preinfusion control which is independent of gonadal function (9 normal women, 4 normal men and 5 agonadal women). These findings suggest that (1) the inhibitory effect of DA on LH-release is, in part, acting at the pituitary level; (2) the increased sensitivity to DA in conditions with accelerated LH secretion may reflect either an increased number of pituitary DA-receptors or the presence of a facilitating factor for DA action, and (3) the dissociation of rebound between LH and PRL upon cessation of DA inhibition in both PCO and agonadal women implicates a difference in the DA-receptor activity of the lactotrophs and gonadotroph.

139 Hypothalamic-Gonadotropin (H-GTP) Maturation in the Absence of Gonadal Feedback: Chronologic Studies in Gonadal Dysgenesis R. Rebar, A. Lucky, J. Rakoff, R. Johnsonbaugh, J. Vaitukaitis and S. Yen La Jolla, Calif., Bethesda, Md., Boston, Mass. The syndrome of gonadal dysgenesis with its absence of functioning gonads provides a unique model for the delineation of the maturational events of the H-GTP system during human puberty. Chronological changes in basal LH and FSH secretion and responses to an i.v. pulse of 10 µg LRF were analyzed in 12 patients with Turner’s syndrome ranging in age from 9.5 to 56 years not previously treated with estrogen. Basal levels of LH and FSH were elevated above those found in normal women in all patients, supporting an inhibitory role for normal prepubertal gonads on the releasing mechanism of the H-GTP system. In response to LRF, the preteenage subjects had greater release of FSH than LH. Through the teenage years, the magnitude of peak release increased concurrently with rising basal LH and FSH levels, and the greater FSH response was progressively shifted in favor of LH response. This differential response between FSH and LH and the reversal with chronological age are clearly independent of gonadal feedback and qualitatively similar to pubertal changes noted in normal girls. Sequential studies in an elderly patient from age 56 to 60 revealed lower basal GTP levels and diminished release in response to LRF, implying possible GTP exhaustion. These data indicate that the increasing functional activity of the H-GTP system during pubertal development represents either an inherent maturational event of the CNS independent of target organ control and/or its development is temporally coupled with the progressive increase in the hypothalamic-ACTH axis and the associated androgen secretion at adrenarche.
140 Intravaginal and Intranasal Absorption of Micronized 170-Estradiol (E2)
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Department of Reproductive Medicine, UCSD School of Medicine, La Jolla, Calif.

We have reported that a rapid conversion of E2 to E1 occurs following oral ingestion of E2.
Thus, alternate routes of administration of E2 to circumvent this conversion were explored. E2
suspended in saline was placed in the vaginal vault of 8 castrate women or intranasally in 8
eugonadal and 3 castrate women. Blood samples were obtained at frequent intervals before and
after E2 administration for 24 h. Changes in serum levels of E2, E1, LH and FSH were analyzed.
At 1- or 0.5-mg doses, the absorption of E2 is extremely rapid

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(within 5 min) and reaches comparable maximum serum levels in 2 h for both doses (900–1,000
pg/ml or 120 X basal level). Thereafter, a more sustained level of E2 is maintained for at least 8
h for 1 mg dose, but a progressive decline to basal level is seen at 24 h for the 0.5-mg dose. The
increments of serum E1, are much slower and of much smaller magnitude (mean 240 ± 40 pg/ml
or 8 X basal level). The ratio and the time course of increments of E2/E1 can account for the
endogenous conversion of E2 to E1. At both doses, comparable maximal suppression of FSH
(17%), and LH (48%) levels occur at 7–8 h and return to basal levels at 24 h. Absorption of E2
via intranasal route (1 mg) is also rapid but short lasting. Peak E2 levels (11- to 15-fold) are
reached in 15 min and followed by a sharp decline to basal level at 7 h. The increments of serum
E1 follow an identical time course of that of E2 initially, but exhibit a relatively large and
sustained rise (3.5- to 5-fold) lasting for at least 24 h. The most plausible explanation for this
finding is the local enzymatic or microorganis-mal conversion of E2 to E1 in the nasal mucosa.
Thus, vaginal administration constitutes an effective mode for the delivery of E2 in the
circulation.

141 Baroreceptor Activity in Pregnancy-Induced Hypertension (PIH)
Kenneth Leveno, Stanley Shoemaker, Gary Cunningham, Richard Worley, Jack Pritchard and
Norman Gant
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Dallas, Tex.

The purpose of this study was to characterize baroreceptor activity in patients with PIH. Acute
decreases in systolic pressure, concomitant with increased heart rate brought on by lateral to
supine position changes of the mother were used to identify baroreceptor activity in four patients.
Baroreceptor function was analyzed by measuring continuously radial artery systolic pressure
simultaneous with R-R intervals and expressed as the slope of \( \Delta \) msec of heart rate and \( \Delta \) mm Hg
calculated by the least squares’ method.

Baroreceptor activity in PIH was depressed to values between 3.6 and 4.7 msec/ mm Hg. These
values in PIH are less than the 10.3–19.9 msec/mm Hg range seen in normal pregnancy, but are
similar to the 2.9–5.7 msec/mm Hg range seen in pregnancies complicated by chronic
hypertension (CHBP) reported by Seligman.

Baroreceptor function is decreased in PIH such that there is less change in heart rate per mm Hg
change in systolic pressure. The decreased baroreceptor sensitivity observed in patients with PIH
is similar to the depressed baroreceptor activity reported in gravidas with CHBP. Furthermore,
animal studies by Guyton have shown decreasing baroreceptor activity associated with
increasing arterial pressure, a situation that appears analogous to the findings of this study. These
observations and the similarly depressed baroreceptor activity seen in patients with PIH suggest that depressed baroreceptor activity in PIH is the result of HBP and not its cause.

142 Long-Term Effects of Dexamethasone (Dex) on 24-Hour Patterns of LH, FSH and Androgens in Polycystic Ovarian Syndrome (PCO)
H. Judd, S. Swanson, M. Hauck, G. Lachelin, D. Parker and S. Yen
Department of Reproductive Medicine, UCSD School of Medicine, La Jolla, Calif.
To examine the long-term effects of Dex on 24-hour hormonal patterns 4 patients with PCO and 4 normal women on the 1st day of menses were studied. Blood samples were drawn every 20 min for 24 h beginning at 8 a.m. Following this 1 mg Dex was given nightly at 11 p.m. and daily 8 a.m. samples were obtained for 30 days (PCO) or until next menses.

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(normals). On the last day of Dex hourly samples were drawn for 24 h beginning at 8 a.m. Serum LH, FSH, Testosterone (T), androstenedione (Δ), dehydroepiandrosterone (DHEA), Δ5-androstenediol (A) and cortisol were measured on each sample.

During the baseline day the mean LH but not FSH, T and Δ, but not DHEA, A or cortisol were significantly elevated in the PCO patients. In both groups episodic fluctuations of all 5 steroids were observed and the pulsatile pattern of cortisol, DHEA and Δ were parallel and most prominent. No correlation was apparent between the pulsatile release of any of the steroids and the periodic fluctuations of either LH or FSH. Significant diurnal fluctuations of all steroids were seen with the most prominent being cortisol and DHEA. During Dex, ovulation occurred in the normal but not PCO patients. There were large and prompt decreases of DHEA, A and cortisol with an obliteration of both the pulsatile and diurnal release of these steroids. Dex had no significant effect on T, Δ, LH or FSH.

These data indicate that long-term administration of nightly Dex suppressed the mean level, and obliterated the pulsatile and diurnal release of DHEA, A and cortisol. It had no significant effect on elevated T and Δ levels.

143 Origin of Ring B Unsaturated Estrogens in the Pregnant MareB.R. Bhavnani and C.A. Woolever
Departments of Obstetrics-Gynecology and Clinical Biochemistry, University of Toronto, St. Michael’s Hospital, Toronto, Ont.
In vivo studies in the pregnant mare have shown that the ring B unsaturated estrogens equilin and equilenin are formed from acetate, mevalonic acid and isopentenylpyrophos-phate, but not from squalene or cholesterol. In order to define more clearly the point at which the classical pathway of steroid biosynthesis bifurcates to give rise to the ring B unsaturated estrogens, the precursor role of farnesylpyrophosphate (FPP) was investigated. A mixture of 1.25 mCi 4,8,12–14C-FPP and 19 µCi 7–3H-dehydroisoandrosterone (3H-D) was injected into a 10-month horse fetus in utero. Maternal urine was collected for 4 days. Steroid conjugates were extracted by absorption onto a 2 kg Amberlite XAD-2 column, eluted, hydrolysed and separated into neutral and phenolic fractions. Estrone and equilin were isolated from the phenolic fraction and their radiochemical purity established. Estrone contained both 3H and 14C while equilin contained only 14C indicating that it is formed from 14C-FPP but not from 3H-D. Therefore, the bifurcation in the classical biosynthetic pathway of estrogens occurs just before the formation of squalene. This is the first in vivo demonstration that FPP can be transformed to steroids.
(Supported by Medical Research Council, M.R.C. grant No. MT-3724.)

144 Adrenal Steroid Synthesis and Hyperprolactinemia due to Pituitary Microadenoma
Prolactin receptor sites have been identified in the adrenal cortex, and prolactin has been implicated in the development of adrenal hyperplasia, in cholesterol storage in steroid-producing cells and as a second trophic stimulus to fetal adrenal C-19 hormone production. These considerations prompted us to examine the relationship between hyperprolactinemia and adrenal function in adult women.

The mean concentration of serum dehydroisoandrosterone sulfate (DS) in 8 normal ovulatory women studied daily throughout the menstrual cycle (samples obtained between 08.00 and 10.00 h) was 2,062 ± 137 (mean ± SEM) ng/ml. In 2 women of similar body weight and height with hyperprolactinemia, hypogonadotropic hypogonadism, and poly-tomographic evidence of an intrasellar microadenoma, the concentrations of DS between 08.00 and 10.00 h (7 determinations for each patient) were 3,379 ± 109 ng/ml and 3,943 ± 433 ng/ml. The respective 24-hour mean concentrations of prolactin (hPr) when sampled at 20-min intervals were 858 ± 8.6 ng/ml and 96 ± 2.7 ng/ml in these 2 patients. There was no sleep-associated rise in hPr. The 24-hour secretory pattern and mean concentrations of cortisol (F) when sampled at 20-min intervals were normal. The 24-hour secretory patterns of DS and F when sampled at frequent intervals in the hyperprolactinemic individuals are remarkably similar and resemble the normal endogenous rhythm. These findings are consistent with the view that high concentrations of hPr may act in concert with ACTH to promote increased secretion of Δ5-3β-hydroxy-C-19 steroids by the adrenal.

The Effect of Intraamniotic Thyroxine on Thyroid Function in the Human Fetus and Newborn

Calvin J. Hobel, Joseph Sack, Larry M. Cousins and Delbert A. Fisher
UCLA School of Medicine, Harbor General Hospital, Departments of Obstetrics-Gynecology and Pediatrics, Torrance, Calif.

Thyroxine (T4) can be administered to the human fetus by intraamniotic injection. Moreover, in the sheep we have shown that T4 injected into amniotic fluid is quantitatively absorbed by the fetus within 24 h. This route of administration was used to assess the effect of exogenous T4 on fetal serum TSH and on the TSH and thyroid hormone responses to birth.

200–700 µg T4 was injected intraamniotically (IA) to 10 term pregnancies 24 h before elective cesarean section. Serum T4, triiodothyronine (T3) and thyrotropin (TSH) were measured in cord blood and serially during the first 4 h of life. Increasing IA-T4 progressively increased mean cord serum T4 (15.3 µg/dl in control to 26.6µg/dl at 300–700 µg IA-T4 doses) and suppressed mean cord blood TSH concentrations 12 µU/ml in control to 5.5 µU/ml at 300–700 µg IA-T4 doses). Mean serum T3 levels remained low (37 ng/dl at 300–700 µg IA-T4 vs. 47 ng/dl in controls). The 30-min mean peak of the postnatal TSH surge decreased progressively with increasing IA-T4 (from 67 µU/ml in control to 11 µU/ml at 300–700 µg IA-T4 doses) but the 4-hour mean peak of the postnatal T3 surge remained unchanged (173 ng/dl at 300–700 µg IA-T4 vs. 173 ng/dl in controls).

We conclude: (a) that fetal serum TSH is suppressible by T4 at term; (b) T4 is effective in suppression in the absence of conversion to T3; (c) the TSH surge can be (at least partially)
suppressed by T4; (d) the newborn T3 surge can be dissociated from the TSH surge suggesting that the T3 surge is due (at least in part) to increased T4 to T3 conversion.

Interrelationships of Maternal 17α-OH-Progesterone (17P), 16α-OH-Progesterone (16P), Progesterone (P), Estradiol (E2), Estriol (E3), and Dehydroepiandrosteronesulfate (D-S) Levels in Normal Third Trimester Pregnancies


Serial serums from 19 normal pregnant women between 26 and 40 weeks of gestation were assayed for 17P, 16P, P, E2, E3 and D-S. After plotting concentrations semilogarithmically against gestational age, individual curves were analyzed for slope segmentation by sequential regression lines utilizing 95% confidence interval future Y value predictions as initial markers of slope change and were compared by log X on log Y regressions utilizing the log log slope (LLS) line of unity 1.0 to indicate identity. 17P and 16P have near identical LLS (0.993; r 0.986; p &lt; 0.01), positive, 3 segment curves beginning at 26–27 to 32–33 weeks as shallow slopes (17P 0.015; 16P 0.016), transforming at 32–33 to 37 weeks to steeper slopes (17P 0.069; 16P 0.062), and terminating at 37–40 weeks as shallow slopes (17P 0.014; 16P 0.00006).

P and E2 have mutually similar LLS (0.900; r 0.974; p &lt; 0.01), shallow, positive (P 0.025; E2 0.022) single segment curves. E3 and 16P are similar (LLS 0.852; r 0.985; p &lt; 0.01). D-S has a shallow, negative (-0.015), single segment curve which is similar to 1/E2 (LLS -0.697; r -0.697; p &lt; 0.05) and 1/P (LLS -0.855; r -0.794; p &lt; 0.01) curves and much less similar to E3 (LLS – 0.694; r -0.786; p &lt; 0.01) and 16P (LLS 0.620; r -0.764; p &lt; 0.01).

Conclusions: (1) nearly identical 17P, 16P, and E3 curves suggest common feto-placental regulatory mechanisms; (2) same applies for E2 and P; (3) nearly identical 1/E2 and D-S curves probably reflect placental conversion of D-S to E2.

Effects of Oral Contraceptive Steroids on Pituitary Function

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51 subjects who had used various formulations of oral contraceptives (OC) for periods of time ranging from 1–9 years were stimulated with 50 µg of Gn-RH during the last week of OC ingestion. 44 (86%) had LH and FSH responses which were lower than the 95% confidence limits of a control group indicating pituitary suppression. The remaining 7 (14%) subjects had normal responses indicating that inhibition of ovulation occurred due to hypothalamic suppression. No correlation was found between these 2 responses and age, type of OC used, or length of use. In order to determine whether these responses vary in individual women over time, 30 of the original subjects were again stimulated, 3–6 months later. The responses to the second Gn-RH stimulation were similar to the first in all women tested, indicating that the pituitary suppressive effect of OC on LH and FSH release is related more to the individual woman than the type of formulation or length of use. Stimulation with 250 µg of TRH was also performed in these subjects. 27 of the 30 had a PRL response greater than controls. This study indicates that OCs have a direct effect on the pituitary as well as the hypothalamus in the majority of women. This suppressive effect of LH and FSH and stimulating effect on PRL may persist in some women after stopping OCs accounting for the syndrome of post-OC amenorrhea-galactorrhea.
Galactorrhea and Infertility Associated with Elevated Serum TSH and PRL: Restoration of Fertility with Bromocryptine
Theresa M. Siler-Khodr, Adnan M. Mroueh, Gabriel S. Khodr, Zuheir Hemadeh and Samir Najjar
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In 12 patients with infertility and galactorrhea basal TSH and PRL were increased. In another 2 patients elevated TSH and PRL was associated with galactorrhea and precocious puberty. Thyroid deficiency was found in 8 patients. However, in 3 cases circulating thyroid hormones were normal and in the other 3 they were not determined.

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Seven of the 12 infertile patients were amenorrheic and the other 5 had regular menses. In the amenorrheic women LH was greater than FSH and in 3 cases LH was above 20 mlU/ml. FSH was suppressed or in the low normal range in 5 patients. Serum testosterone was normal in all the infertile women. However, androstenedione was decreased in the amenorrheic patients. In addition, the plasma estrogens in the amenorrheic women were sizable, estrone (171 ± 30, mean ± SE) greater than estradiol (88.1 ± 8.3, mean ± SE).

Treatment with bromocryptine in 6 amenorrheic patients resulted in suppression of PRL, cessation of lactation, return of normal ovarian function and conception in 3 cases. Correction of hypothyroidism with exogenous thyroid hormone in 3 cases produced similar results as well as suppressing TSH. It is proposed that the abnormal gonadal function often associated with primary hypothyroidism is a result of hyperprolactinemia, and not an alteration in estrogen metabolism induced by the hypothyroid state, since normal ovarian function can be restored by bromocryptine while hypothyroidism persists.

Postpartum Serum Prolactin and Cortisol and Their Relationship with Maternal and Affective Behaviors in the Macaca nemestrina.
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The purpose of this investigation is to measure postpartum prolactin and cortisol as well as to seek a correlation with maternal and affective behaviors for the first 4 weeks. At term delivery 12 Macaca nemestrina monkeys were immediately separated from their infants and housed in individual cages. Venous blood (3 cm^3, without anesthesia, within 5 min of capture) was drawn at 8 a.m. on alternate days, 3 times a week. Serum was analyzed by radioimmunoassay for prolactin and by competitive protein binding for cortisol. A testing chamber with several choice compartments was used to measure maternal preference for her infant. The subjects were observed by time-lapse video recording 3 days per week for 10 h a day nonblood drawing days. Statistically significant findings were as follows. Prolactin showed an elevated level during days 1 and 2, rapidly dropping till day 4, then peaking at days 10–12 followed by a gradual decline through day 28. Cortisol showed a drop after the first day and remained decreased until day 9 when they rose to a peak occurring on day 12 and remained elevated through day 28. Maternal behavioral data revealed decreased preference for her infant during days 1–8, a sudden rise of infant preference which reached a peak on days 9 and 10, and which remained elevated through day 22. Affective behaviors revealed exploring and locomotion to be essentially constant and huddling to be elevated days 1–6. The most striking finding was the consistent relationship
between the increase in maternal infant preference and the rise in serum prolactin and cortisol levels on day 10 ± 1 day.

150 The Pulsatile Pattern of Gonadotropin Release in Normal Men, Normal Women, and Amenorrheic Women
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Department of Obstetrics-Gynecology, St. Michael’s Hospital, University of Toronto, Toronto, Ont.
Serum FSH and LH levels were measured in blood samples drawn every 10 min during 3 or 6 h from 6 healthy men, 6 women during an ovulatory cycle, and 8 acyclic women. The pulsatile patterns of relative (rather than absolute) variation were studied by examining means, standard deviations, variances, and peak frequencies after a logarithmic transformation of the data. Similarly, relative day-to-day variation in gonadotropin levels was studied throughout the ovulatory menstrual cycle of 5 women. In men, cycling women, and amenorrheic subjects, LH and FSH levels, their magnitudes of variation, and their time pattern of release vary independently. Differences in variation pattern were random and unrelated to mean levels, to the phase of the normal cycle, or to the clinical pathological diagnosis – i.e. to the sex steroid hormone environment. We conclude that (1) the amplitude of absolute variation in gonadotropin pulses is merely in proportion to the mean level, while the relative variation and the pulsation frequency are fairly constant under a variety of normal and abnormal conditions; (2) the analysis of pulsatile pattern of gonadotropin release suggests no diagnostic value.

151 Progesterone Deprivation in the Chorioamnion from Laboring Women
Barry E. Schwarz, Charles L. Heaton, Leon Milewich, Robert A they and Paul C. MacDonald
Department of Obstetrics-Gynecology, University of Texas Southwestern Medical School at Dallas, Dallas, Tex.
We have presented evidence supporting a central role for the fetal membranes (chorion laeve and amnion) in the initiation of human parturition, and have suggested that this role may be subserved by the action or metabolism of progesterone in these tissues. While it is clear that there is a dramatic decline in maternal plasma progesterone concentration prior to the onset of labor in many mammals, such a decrease does not obtain in most normal gravidas. For these reasons, we measured the progesterone concentrations in whole homogenates and subcellular fractions of human chorioamnions obtained prior to the onset of labor or after vaginal delivery. Samples were prepared for radioimmunoassay employing a technique which eliminated the major metabolites of progesterone which are present in human fetal membranes, viz. 5α-dihydroprogesterone and 20α-dihydroprogesterone. The mean progesterone concentrations in chorioamnion before and after labor were 26.4 ± 3.5 (SEM) ng/ml protein and 13.1 ± 1.6 (SEM) ng/mg protein, respectively. These concentrations are significantly different (p < 0.01) as were the mean progesterone concentrations of each subcellular fraction investigated except that fraction containing predominantly mitochondria. Considered in context with the dramatic increase in the amount of human fetal progesterone binding protein associated with the chorioamnion after the 37th week of gestation, this progesterone deprivation, at a local tissue site and in most but not all subcellular fractions of this tissue, argues in favor of a hypothesis in which a decline in available progesterone within the human fetal membranes precedes the onset
of labor in women in a manner analogous to the decline in maternal plasma progesterone concentration in other species.

152 Isolation of Mycoplasma from the Endocervix in Patient Population of the Endocrine Infertility Clinic of the B.M.H., N.Y.
Zeev W. Koren, Michael Lev Gur and Eli Spigland
Department of Obstetrics-Gynecology, Albert Einstein College of Medicine, Bronx, N.Y.
Investigation was performed to examine the relationship between the presence of mycoplasma in endocervix; habitual abortion; infertility of unknown origin. Endocervical culture for mycoplasma was taken from 262 patients. The patients were divided into four groups: (a) 32 women with history of 2 or more consecutive spontaneous abortions; (b) 112 women with primary or secondary infertility; (c) 72 women during their first or second trimester of pregnancy, and (d) 46 women from the family planning to serve as controls. Only 30 of total 262 patients revealed mycoplasma in their endocervix. No significant differences were found among the four groups. Our results indicate that the presence of mycoplasma in endocervix is of no clinical importance.

153 Progesterone-Altered Protein Synthesis in Human Endometrium
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Human endometrium contains more protein per unit wet weight or DNA during secretory than during the proliferative phase. Proliferative endometrium in organ culture can be stimulated to synthesize increased amounts of protein by the addition of progesterone (P). The present protocol was designed to establish whether P is also a stimulus to the production of specific endometrial proteins. Human endometria obtained at various times in the menstrual cycle were evaluated for cytoplasmic protein profiles, new protein synthesis and P altered protein synthesis using polyacrylamide gel electrophoresis. Freshly extirpated endometrium was incubated for 2 h in MEM containing either 14 C- or 1/8 labeled leucine. The 100,000 X g supernatants from tissue homogenates were electrophoresed either singly or after combining samples (opposite labels) from two different patients. Gels were then either stained and scanned or sliced and counted. Proliferative endometrium was maintained in organ culture for up to 4 days with and without the addition of P (0.1 µg/ml of medium). Cultured endometria were isotopically labeled after various periods of culture. Supernatants from a single culture experiment, having opposite labels, were combined, electrophoresed and counted. Analysis of gel scans from various cycle days showed significant profile differences. Isotope ratios in gels combining pre- and post-ovulatory samples showed ratio changes in the same area as did the scans. Isotope ratios in gels from culture experiments showed a single peak ratio change. This peak was at the same Rf as one of the scan and ratio changes found in the experiments involving comparison of tissues from different cycle days. The mol wt of proteins at this Rf is estimated to be 22,500. These changes are consistent with P-induced specific protein synthesis.

154 The Effects of Halothane and Enflurane on Calcium Accumulation by Sarcoplasmic Reticulum from Bovine Smooth Muscle
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School of Medicine, Los Angeles, Calif.
The uterine relaxant effects of anesthetics such as halothane have been well documented though the cellular site of action is not presently known. This laboratory has previously shown that sarcoplasmic reticulum (SR) which controls the maintenance of free calcium in the cell is modified in its ability to take up calcium by contractile and relaxing hormones. The direct effect of anesthetics on SR derived from pregnant bovine uterus were studied. Halothane up to 4% or enflurane 10% in equilibration with the incubation medium produced no effects on ATP-dependent calcium binding. 10% halothane caused a decrease in ATP-dependent calcium binding. There was no change in SR calcium in the absence of ATP. Since an agent which causes relaxation should increase the calcium binding in the presence of ATP, the anesthetics do not seem to work through this mechanism. The effects of very high levels of halothane which produce a decreased accumulation of calcium by SR may represent a toxic effect of halothane but this is not the mechanism by which it produces relaxation under clinical conditions.

155 Heart Rate Variability in Brain-Damaged Adults
Richard I. Lowensohn, Martin H. Weiss and Edward H. Hon
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Short- and long-term heart rate (HR) variability as seen on the cardiotachometer records in the fetus and neonate appear to reflect the integrity of the central nervous system. For this reason, a study was done of HR variability and patterns in a group of normal and a group of neurologically damaged adults. These results were then compared to normal fetal and newborn values. To limit the known effect of subject age on variability, the normal group was composed of 8 individuals at rest, aged 28–34. The normals were homogenous, with mean HR of 82 b.p.m. and range of 70–90. Short-term variability (STV) was greater than 3 b.p.m./beat, and long-term variability (LTV) was 6–10 b.p.m./min in two cases, 11–25 b.p.m./min in six. There was uniform variability throughout the monitoring period of 30 min in all cases. Normal STV is 2–5 b.p.m./beat in the fetus and 2–12 b.p.m./ beat in the neonate; normal LTV is 6–25 b.p.m./min in the fetus and in the neonate.
The neurologically damaged group consisted of patients in coma from trauma or intra-cerebral hemorrhage; with no medication given. Their patterns during coma were characterized by wide cyclic swings in variability. Almost all cases had periods of STV and LTV of 0–2 b.p.m. which were associated with quiet periods clinically, and periods of marked LTV of 30–60 b.p.m./min associated with STV of less than 10 b.p.m. – in most instances less than 5 b.p.m./beat. These active periods were associated with decerebrate posturing and heart rate accelerations in all cases. This STV/LTV dissociation is not seen in the normal fetus or neonate, nor in our group of normal adults.

156 Interaction of Adrenergic Agents, Oxytocin (OT) and Prostaglandins (PG) on the Rat Uterus in vivo
Mutuo Ishikawa and Anna-Riitta Fuchs
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The effect of adrenergic receptor activation and inhibition on oxytocin and prostaglan-din stimulation on the rat myometrium has mainly been studied in vitro, and the results do not
necessarily apply in vivo. The interaction of sympathomimetics and oxytocic substances was therefore studied in conscious, unrestrained rats by means of intrauterine balloons for pressure recording (IUP) and extracellular electrodes for recording of electrical activity. Ovariectomized rats were treated with vehicle oil (O), 1 µg estradiol-17β (E) or 5 mg progesterone (P) for 3 days. In E animals, OT and PG caused an immediate increase in electrical activity, consisting of bursts of action potentials synchronously along the uterine horn. Norepinephrine (NE) also initiated synchronous bursts of action potentials, while epinephrine (EP) caused relaxation and cessation of all electrical activity. Phenoxybenzamine, 5 µg, i.v., and α-receptor blocker, inhibited the response to NE, PGF₂α, (5 µg i.v.) and to 1 mU OT; the effect of 5 mU OT was not inhibited but the conduction of the electrical activity was impaired. In the P-rats, both NE and EP caused relaxation and abolished electrical activity, but ß-receptor blockers prevented this effect. The stimulatory effect of OT and PGF₂α was enhanced by 3-blockers. In O rats, the results were ambiguous. The results suggest that the balance of α- and ß-receptors in the rat uterus is controlled by steroids and that adrenergic mechanisms modulate the uterine response to oxytocic agents.

The results suggest that the balance of α- and ß-receptors in the rat uterus is controlled by steroids and that adrenergic mechanisms modulate the uterine response to oxytocic agents.

157 Dissociation of Mechanical and Electrical Activities of Rat Myometrium in vivo by Progesterone
Anna-Riitta Fuchs and Mutsuo Ishikawa
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Previous studies (Fuchs: 1974, 1975) have shown that the classical concept of stimulation of uterine activity by estrogen-17β (E₂) and inhibition by progesterone (P) does not hold for the rat, where the opposite effects are found. To elucidate this paradox, intra-uterine pressure (IUP) was recorded in conscious, unrestrained rats simultaneously with electrical activity, recorded by thin insulated wires (OD 90 µ) inserted at several sites along the uterus. 3 days after ovariectomy, daily injections of vehicle oil (O), 1 µg E₂, or 5 mg P were given i.m. Electrical activity of the longitudinal muscle layer consisted of bursts of action potentials (AP); the duration, amplitude and frequency of bursts were hormone-dependent. Ovariectomy was followed by an increase of burst frequency and duration and a decrease of amplitude and conduction velocity along the uterine horn. The frequency of IUP changes increased with the increase of burst frequency. E₂ treatment resulted in infrequent bursts of short duration, high amplitude and rapid conduction, associated with IUP changes. Treatment with P resulted within 24 h in marked depression of AP and complete disappearance of burst activity, but marked contractile activity persisted. The IUP changes recorded at different sites were asynchronous. After withdrawal of P and treatment with E₂ the electrical activity reappeared.

158 T and B Lymphocytes in Normal and Abnormal Pregnancies
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The percentage of Thymus derived (T) (sheep RBC rosette forming) lymphocytes responsible for cellular immune responses and Bone marrow derived (B) (immunofluorescence of membrane bound immunoglobulins) antibody producing cells in maternal blood has been established for normal gestation as follows:

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Group  Lymphocytes/ T cells B cells
mm$^3$ ± SEM  % ± SEM  % ± SEM
Nonpregnant (n = 10) 1,278.7 ± 131.9 64.5 ± 1.9 16.8 ± 1.0
Pregnant: first trimester (n= 10) 1,000.5 ± 111.1 58.2 ± 2.2 18.9 ± 1.3
second trimester (n = 16 1,167.4 ± 106.7 58.7 ± 1.9 18.6 ± 1.3
third trimester (n = 14) 1,167.4 ± 111.5 59.2 ± 2.3 18.5 ± 1.1
Postpartum(n = 5) 1,346.2 ± 241.7 67.5 ± 5.0 20.2 ± 1.9

These data are in conflict with a recent proposal that reversal of the T/B cell ratio associated with the serum HCG peak of early pregnancy assists in fetoplacental allograft acceptance but support our contention that it would be unlikely that a single clone of blocking antibody producing B cells could appreciably alter the proportion of circulating T or B lymphocytes. Moreover, variability in lymphocyte dynamics in 4 women followed serially throughout pregnancy as well as similar T and B cell values in 17 patients whose pregnancy complications are potentially related to maternal-fetal immunologic aberrations (abortion, hydatidiform mole, preeclampsia, Rh immunization, twins) suggest that this type of immunologic monitoring of the host immune response will not be as clinically useful in obstetrics as it has been in renal transplantation.

159 A New Mechanism for Late Deceleration of the Fetal Heart Rate
Ming-Neng Yeh, Hisayo O. Morishimo, Raymond I. Stark, Leonard Indyk and L. Stanley James
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Late deceleration of the fetal heart rate (FHR) is a sign of severe fetal asphyxia, but is also seen occasionally when the fetus is neither acidotic nor hypoxic. In a search for other possible causes we postulated that with partial occlusion of the umbilical cord during uterine contractions, the low pressure venous flow would be reduced before changes in arterial flow. This would result in the accumulation of fetal blood in the placenta. Release of the partial occlusion after the contraction would be followed by an increase in venous return and bradycardia from parasympathetic stimulation.

Catheters and electrodes were inserted into 12 fetal baboons, mean gestational age 153 days and an occluding device was placed round the intraabdominal portion of the UV. After 2 h recovery (fetal pHa 7.36 ± 0.004 and Sat02 62 ± 2.3%) water was gradually injected into the cuff in a volume previously shown to partially occlude the UV. With partial occlusion, FHR rose from 189 to 203 beats/min. These changes in heart rate were significantly different from control (p < 0.001). The bradycardia was accompanied by a significant elevation of BP.

These observations provide an alternative explanation for the pattern of late deceleration of the FHR and stress the importance of monitoring the fetal acid-base state for correct interpretation of fetal heart rate patterns.

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160 Response of the Fetal Lamb Kidney to Vasopressin and Norepinephrine
Jacques M. Milliez, Salha S. Daniel, Raymond I. Stark, Ming-Neng Yeh and L., Stanley James
Division of Perinatal Medicine, College of Physicians and Surgeons, Columbia University, New York, N.Y.

Following asphyxia from occlusion of the umbilical cord there is a loss of electrolytes in the urine of the fetal lamb. Since both vasopressin (VP) and catecholamine levels are elevated in fetal blood during asphyxia, experiments have been conducted on 12 fetal lambs, chronically
instrumented to determine whether there is a relationship between these hormones and the changes in the renal function. Administration of VP (5.0–10 mU/kg over 1 min) increased urinary output from 0.17 to a maximum of 0.58 ml/kg/min, and urine osmolality from 149 to 310 mOsm/kg at the end of 1 h. Urine sodium and chloride concentrations increased and free water clearance decreased from 0.08 to 0.02 ml/kg/min. These changes persisted over 2 h after the administration of VP. Fetal BP increased only transiently by a maximum of 15 mm Hg following VP. Administration of norepinephrine at a rate of 0.05 µg/kg/min over 30 min resulted in an increase in urine output from 0.31 to 0.53 ml/kg/min. Urine osmolality decreased from 170 to 130 mOsm/kg. Free water clearance increased from 0.13 to 0.28 ml/kg/min, while urine sodium and chloride concentrations remained the same. Control values were achieved 1 h after the end of the infusion. At this rate of administration norepinephrine had minimal and only transient effect on fetal BP and HR. Thus, in the doses given vasopressin elicited a sodium diuresis and norepinephrine a water diuresis. The combined effect of these two hormones could thus lead to a loss of water and electrolytes.

161 The Effects of Local Anesthetics on Blood Flow and O2 Consumption of the Uterus of Nonpregnant Sheep
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Department of Anesthesia and Obstetrics-Gynecology, University of Florida, Gainesville, Fla.
This study was undertaken to define effects of commonly used local anesthetics (LA) on the blood flow (UBF) and O2 consumption (QO2) of the uterus.
Ten nonpregnant sheep were prepared with an electromagnetic flow probe around one uterine artery and catheters in the femoral artery (A) and both uterine veins (UV). UBF and arterial blood pressure (AP) were recorded continuously, A- and UV-O2 contents (Van Slyke) and partial pressures before and at the end of a 30-min infusion of the 4 LA, administered at rates resulting in clinically observed blood concentrations.
In the absence of marked changes of AP the % changes between pre- and postinfusion values were:

<table>
<thead>
<tr>
<th>LA</th>
<th>UBF</th>
<th>A-UVD</th>
<th>QO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>(0.06 mg/kg/min)</td>
<td>-38.5</td>
<td>+35.2</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>(0.2 mg/kg/min)</td>
<td>-14.7</td>
<td>+23.0</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>(0.06 mg/kg/min)</td>
<td>-7.0</td>
<td>+23.8</td>
</tr>
<tr>
<td>2-Chloro-procaine</td>
<td>(0.5 mg/kg/min)</td>
<td>-24.0</td>
<td>-13.1</td>
</tr>
</tbody>
</table>

The data suggest that these LA decrease O2 consumption of uterine tissue with concomitant vasoconstriction in the resistance vessels.

162 Dihydrotestosterone-Binding by Human Endometrium
Eberhard K. Muechler and Donna Kohler
Department of Obstetrics-Gynecology, University of Rochester, School of Medicine and Dentistry, Rochester, N.Y.
The properties of dihydrotestosterone-binding proteins in the human uterus were investigated. Human endometrial tissue was obtained from hysterectomy specimens. The tissue was homogenized in 0.05 M Tris-0.002M EDTA buffer (pH 7.4 at 4 °C) with or without 10% glycerol. The 160,000 x g supernatant was used for dextran-coated charcoal separation of bound hormone after overnight incubation with (1,2–3H) dihydrotestosterone (DHT) at 4 °C and
sucrose density ultracentrifugation. The Krj and binding capacity for DHT were calculated by Scatchard analysis (results represent mean ± SE). The I½ for all endometrial samples (n = 7) was 5.3 ± 0.2 × 10⁻¹⁰ M and the binding capacity was 186.8 ± 28.5 fmol/mg protein. The results for proliferative and secretory endometrium were not significantly different. The Krj and binding capacity in the proliferative phase (n = 3) were 5.2 ± 0.5 X 10⁻¹⁰ M and 206.6 ± 55.7 fmol/mg protein. The respective values for the secretory phase (n = 4) were 5.3 ± 0.1 X 10⁻¹⁰ M and 172 ± 33.3 fmol/mg protein. Heating of cytosol at 56 °C for 1 h destroyed DHT-binding. Nonlabeled steroids competed with DHT-binding in the following order: DHT &gt; testosterone &gt; estradiol &gt; norethindrone &gt; dimethisterone. Sucrose-density and glycerol gradients in Tris-EDTA buffer of low ionic strength result in DHT-binding with a 4S. The addition of Trasylol (1,000 U/ml) and 10% glycerol to the buffer and a high protein concentration (&gt; 10 mg protein/ml cytosol) result in 8S and 4S sedimentation coefficients. These experiments suggest that androgens may influence the development of the endometrium by binding with high affinity to a specific androgen receptor.

163 Influence of Fetal and Newborn Ovaries and Testis on the Onset of Meiosis in vitro Abram B. Fajer, Isadore G. Ances, S. Efthimios Polakis and Alden H. Reese Departments of Physiology, Biochemistry and Obstetrics-Gynecology, School of Medicine, University of Maryland, Baltimore, Md.

The factors regulating the onset of meiosis in female germ cells in fetal or newborn animals and male germ cells at puberty are poorly understood. It is well established that meanwhile meiosis can proceed in organs maintained in vitro, its onset under the same conditions has not been established.

We have studied in vitro the reciprocal influence of tissues in which meiosis is occurring on premeiotic tissues, male and female. Hamster ovaries and testis of fetuses and newborn animals of known age were maintained in a medium in which 15% fetal calf serum was the only element of undefined composition. Ovaries showing various stages of the meiotic prophase – days 15–16 postcoitum (p.c.) and days 1–10 postpartum (p.p.) – were incubated with premeiotic ovaries (days 12–14 p.c.) and testis.

After various periods of coculture (4–10 days) the following results were observed: (1) meiotic ovaries may induce meiosis in premeiotic ovaries and fetal testis, and (2) fetal testis may inhibit the initial stages of the ovarian meiotic prophase, up to zygotene in very young ovaries, but have no influence on more advanced stages and the consequent follicular organization in the more developed ovaries.

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164 Liver and Ductus Venosus Flow in Fetal Lambs
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The circulation of the fetal liver was studied 7 times in 5 chronically prepared fetal lambs (123–136 days’ gestation). Radioactive microspheres were injected simultaneously into inferior vena cava, portal vein (PV), and umbilical vein (UV). Hepatic arterial (HA), PV and UV blood flows (ml/min/100 g liver) to the left and right lobes were determined. Mean total liver flow was 472 ± 85 (± SD) consisting of HA 76 ± 69, PV 76 ± 27 and UV 320 ± 60. Total liver flow and the proportion supplied by UV were relatively constant between fetuses, yet the flow to each lobe fluctuated widely. The relative and absolute HA, PV and UV flows within each lobe also varied.
considerably. The left lobe was perfused primarily by UV without significant PV flow (see table). The right lobe was supplied by all 3 circulations, but predominantly by UV. Of UV flow to the liver, 39% was directed to the right lobe. Ductus venosus (DV) flow ranged between 59 and 154 ml/min/kg fetal weight and was unrelated to fetal or liver weight.

The results suggest that the fetal liver is able to maintain its flow within a relatively constant range by altering lobar and DV flows. Since umbilical vessels do not extend to the right lobe, its large UV blood flow is probably related to mixing in the portal sinus with flow through portal vessels; distribution may be determined by the relative vascular resistances in each lobe and DV.

165 The Effects of Maternal Hyperventilation Associated with Exercise on Fetal Oxygenation
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The chronically instrumented ewes and their fetuses were studied before and during graded maternal exercise which produced varying degrees of maternal respiratory alkalosis. In six ewes where maternal pCO2 fell to less than 25 mm Hg umbilical arterial pO2 fell from 17 ± 0.7 mm Hg to 10 ± 1.5 mm Hg and umbilical arterial oxygen content fell from 6.4 ± 0.3 vol% to 4.1 ± 0.8 vol%. Despite these observations there was no fall in fetal oxygen consumption, mean values being 9.7 ± 0.5 cm3/kg/min and 10.1 ± 0.5 cm3/kg/min. When maternal exercise produced a pCO2 of less than 25 mm Hg there was a concomitant decrease in both uterine (235 ± 15 ml/kg/min to 184 ± 16 ml/kg/min) and umbilical blood flow (287 ± 18 ml/kg/min to 263 ± 17 ml/kg/min) resulting in increased exposure time of maternal and fetal bloods at the placental site. With increased exposure time the oxygen difference
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across both placental circulations increased, thereby maintaining oxygen uptake. In these six animals the uterine arteriovenous oxygen difference increased from 4.1 ± 0.3 vol% to 5.9 ± 0.6 vol% and the umbilical venoarterial oxygen difference from 3.4 ± 0.3 vol% to 3.9 ± 0.2 vol%.
(Supported by National Foundation March of Dimes No. 1–402.)
166 Light Microscopic, Transmission and Scanning Electron Microscopic Studies of Vaginal Colonization
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To understand the relationship between the vaginal microflora and the underlying epithelium the bacterial content of the genital tract was compared to the cytological and ultrastructural characteristics of the vaginal epithelium. During the estrous cycle bacterial counts varied cyclically and were highest during estrus. Cytologic examination showed large numbers of bacteria associated with exfoliated cornified epithelial cells. These results were corroborated by scanning electron microscopy of vaginal epithelium of ovariectomized rats with or without estrogen replacement. Scanning electron microscopy showed that prior to estrogen treatment the vaginal epithelium was composed of an intact layer of epithelial cells with microvillous-like projections but lacked any associated bacterial forms. Following estrogen treatment bacterial colonization increased as vaginal cornification increased. Bacterial forms associated with the vaginal epithelium as microcolonies predominantly segregated along intercellular borders. Bacterial colonization of exfoliated cornified vaginal cells appeared to be greater than colonization of the underlying epithelium. Transmission electron microscopy of the estrogen...
stimulated vaginal epithelium also suggested that the exfoliated vaginal epithelial cells were more heavily colonized than the underlying epithelium. Transmission electron microscopy also indicate; that enhanced colonization of the cornified epithelium may have been related to degradation of keratoprotein.

167 Isolation, Characterization and Spectrum of Activity of an Antibacterial System in Amniotic Fluid (AF)

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The low molecular weight polypeptide component of the inhibitory system was isolated by ultrafiltration, gel filtration, and ion exchange chromatography. Purity was determined by polyacrylamide gel electrophoresis and amino acid composition by an amino acid analyzer. The necessity for zinc as part of the peptide inhibitor complex was demonstrated by dithiazone chelation. The necessity for the peptide as part of the inhibitor complex was shown by loss of activity following carboxypeptidase digestion.

The antibacterial activity of the inhibitory complex against a variety of bacterial species was determined. Using the bacterial plate count technique and an inoculum size of between 103 – 104 organisms the effect of the inhibitor on bacterial growth was compared to that in a noninhibitory control. Organisms tested include gram positive and gram negative aerobic and anaerobic bacteria. With the P04-Zn ratio between 100 and 200 the inhibitory effect on the organisms tested varied from bacteriostatic, e.g., Escherichia coli /3-hemolytic Streptococcus group B to bactericidal, e.g., Klebsiella pneumoniae, Proteus vulgaris, Staphylococcus aureus. Exceptions were Pseudomonas aeruginosa and Streptococcus faecalis which were not inhibited by the peptide-zinc complex using this method. This variability emphasizes the need for a better understanding of the inhibitory nature of the peptide-zinc complex in AF.

168 The Preejection Period of Cardiac Cycles in Fetal Lambs

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Preejection period (PEP) of the cardiac cycle in fetal lambs was estimated by measuring an interval between the onset of Q-wave on fetal ECG and the onset of upstroke of arterial blood pressure tracing. 22 pregnant ewes (gestational age 110–148 days) were used for this study. Fetal ECG electrodes, femoral artery and venous catheters were implanted surgically for continuous biophysical monitoring of the fetus as well as periodic sampling for biochemistry. Electromagnetic flow probe was placed around a fetal carotid artery and an external maxillary branch of jugular vein was catheterized for subsequent injection of radioactive microspheres (51Cr and 141Ce). The animals were permitted to recover and experiments performed to study the cardiovascular effect of vagotomy, atropine, hypoxemia and hypercarbia on fetuses. All information was recorded on magnetic tapes which subsequently were played back for PEP analysis.

Due to the difference in location of a tip of catheter, PEP values were varied between different fetuses. PEP, however, exhibited significant increase as the fetal gestational age advanced (p <
An inverse relationship was found between PEP and arterial blood pH (p < 0.01). The was a tendency for a decrease in PEP when coronary blood flow (ml/g/beat) increased.

169 Systolic Time Intervals of Cardiac Cycle in Fetal Rhesus Monkeys – Ventricular Ejection Time
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Ventricular ejection time (VET) of the fetal cardiac cycle was studied in chronic rhesus monkey preparations. VET was measured as the interval from the opening to closing signals of semilunar valves on ultrasound Doppler cardiogram. Determinations of VET were carried out on fetuses under physiologic conditions as well as during various experimental and spontaneous stresses. Fetal ECG and BP were recorded continuously, and fetal blood pH and respiratory gas tensions were sampled intermittently.

In normal fetuses, VET exhibited a linear increase as the R-R interval increased. The increment of VET was larger at R-R intervals between 240 to 320 msec than those between 320 to 400 msec. There was no further increase in VET at R-R intervals of more than 400 msec. Accordingly, all values of VET were corrected for R-R interval for all subsequent analysis. VET showed an inverse linear correlation with diastolic blood pressure (p < 0.05) and a positive correlation with pulse pressure (p < 0.05). VET was shortened in fetuses with combined acidosis and hypoxemia, but either one alone did not change the VET. Epinephrine tended to shorten the VET while atropine produced no consistent change. These findings suggest that VET reflects myocardial contractility and is potentially a useful indicator for evaluation of fetal well-being.

170 The Preejection Phase of the Fetal Cardiac Cycle in Diabetic Patients: Antepartum Evaluation
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Several studies have evaluated fetal cardiac performance using noninvasive techniques to determine the preejection period (PEP). Antepartum fetal PEP examinations in diabetic patients were carried out to assess the applicability of this test in a population at risk for sudden fetal distress.

A method obtaining fetal PEP using maternal abdominal wall fetal ECG (AFECG) and Doppler cardiogram (DCG) has been previously described. A total of 82 fetal PEP determinations from 41 hospitalized patients with diabetes mellitus, classes A through D, were studied. The gestational ages (GA) ranged from 33 to 40 weeks. Ten determinations were discarded because of poor DCG record (4) or poor AFECG record (6). All fetuses had normal outcomes with no fetal or neonatal distress. Comparison of fetal PEP with GA showed a positive correlation with r = 0.60, n = 71, p < 0.01. When fetal PEP, obtained within 7 days of delivery, was compared to neonatal body weight, which ranged from 2,200 to 5,440 g, there was a direct correlation with r = 0.63, n = 21 and p < 0.01.

Previous studies have determined normal ranges for antepartum and intrapartum fetal PEP values. Present data suggest that in addition to the variable of gestational age, fetal body weight
must be taken into consideration as a possible etiology in prolongation of PEP, especially when fetal macrosomia is suspected.

171 A Fever Index Evaluation of Chloramphenicol and Clindamycin
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This random study measured the effectiveness of either chloramphenicol or clindamycin in seriously ill patients by use of the fever index. Other antibiotics were always employed, usually penicillin and an aminoglycoside. During a 24-month interval, 102 patients were studied, 53 received chloramphenicol and 49 clindamycin. The calculation of the fever index in degree hours was performed with the F program of the USC-PACK program, available nationwide on the GE terminal system. All calculations will be expressed in degree hours. Of the 53 women receiving chloramphenicol, the median was 75.1 the mean was 160.2, SD was ± 296.7, SE ± 40.8. For the 49 women receiving clindamycin, the median was 93.8, the mean was 126.9, the SD was ± 128.2, and the SE was ± 18.3. The difference between these two populations is not statistically significant. This fever index evaluation indicates there is no therapeutic advantage of either of these antibiotics over the other in women with serious pelvic infections. The decision on which antibiotic is to be selected, should be made on the basis of the physicians concern about the relative toxicity of these two agents.

172 Microbiologic Etiology of Acute Salpingitis
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In an attempt to establish the microbiologic etiology of acute salpingitis, specimens for culture were obtained by culdocentesis and laparoscopy from peritoneal fluid and tubal exudate in patients with acute salpingitis. The diagnosis of acute salpingitis was visually confirmed laparoscopically. Cultures were obtained from the endocervix for N. gonorrhoeae, Chlamydia trachomatis, Herpes virus and genital tract mycoplasma. Peritoneal fluid and tubal exudate were cultured for aerobic and anaerobic bacteria, N. gonorrhoeae, C. trachomatis, Herpes and mycoplasma.
Despite the isolation of TV. gonorrhoeae from the endocervix in 46% of salpingitis cases, this organism was recovered from peritoneal fluid and tubal exudate in only 18% of these patients. Bacterial isolates from the peritoneal fluid have revealed mixed aerobican aerobic bacteria in 25%, aerobic bacteria only 17% and anaerobic only 58%. Although mycoplasma has been isolated from the endocervix in 40% of salpingitis patients, no isolates of mycoplasma have been recovered from peritoneal fluid.

173 Dopamine Agonists and Serotonin Antagonists in the Management of Hyperprolactinemic States
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Dopamine agonists and serotonin antagonists have been used for the inhibition of puerperal lactation and the treatment of hyperprolactinemic amenorrhea. 34 puerperal women received the dopamine agonist bromocriptine (2.5 mg b.i.d., p.o. for 14 days) while 20 were treated with
serotonin antagonist, metergoline (4 mg b.i.d., p.o. for 5 days). Puerperal lactation was effectively suppressed by both regimens. The subjects treated with bromocriptine showed a rapid lowering of plasma prolactin (12 ng/ml ± 4 SD on the 4th day of treatment) while in those who received metergoline the decrease was less pronounced (35 ng/ml ± 18 SD) but still significant (lactating women 97 ng/ml ± 21 SD) p < 0.025. In 4 patients with amenorrhea-galactorrhea (A-G) the intravenous infusion of dopamine (5 µg/ kg/min for 2 h was followed by a clear decrease of plasma prolactin levels. In 16 patients with A-G (5 with adenoma), chronic bromocriptine administration (2.5 mg b.i.d., p.o.) markedly lowered plasma prolactin levels; galactorrhea was stopped in all patients and menses reappeared in all patients but 2, who had evidence of pituitary tumor. 4 patients became pregnant. The long-term treatment with metergoline (4 mg b.i.d., p.o.) induced menses in 7 of 12 patients and pregnancy occurred in 1 of them after 2 months of treatment. Plasma prolactin was constantly depressed by metergoline in patients without signs of pituitary tumors (5) while in the adenoma group (7) the trend was quite variable. As in puerperal women, also in A-G patients the effect of metergoline on prolactin levels was less pronounced and more gradual than that exerted by bromocriptine.

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174 Human Fetal Breathing Movements at 34–35 Weeks’ Gestation
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Human fetal chest wall movements have been suggested as an indicator of fetal health but ultrasonic A-scan methods used to record fetal chest wall movements are technically difficult and include many artifacts. This study was designed to define human fetal breathing movements in utero using a real time ultrasonic scanner.

Continuous recordings were made on 10 fetuses of 34–35 weeks’ gestational age between 09.00–17.00 h. Longitudinal scanning of each fetus permitted continuous observation of fetal chest and abdominal wall echoes. During each fetal breathing movement the anterior and posterior fetal chest walls each moved inwards 2–5 mm and the anterior abdominal wall moved outwards 3–8 mm. Breathing movements were irregular in amplitude and rate and occurred episodically. Movements described as hiccoughs were observed from time to time in all fetuses. The mean percent time spent breathing from 12.00–17.00 h was 35.0 ± 2.5% (SEM) and was higher than the mean of 26.4 ± 3.3% measured from 09.00–12.00 h (p 0.05). During the hour preceding lunch the mean percentage time spent breathing was 18.2 ± 4.6% and was significantly less than during the hour following lunch when the fetus breathed 43.6 ± 5.8% of the time (p < 0.02). The mean rate of breathing movements was 49 ± 0.7/min and did not change significantly with the time of day.

Real time ultrasonic scanning permits identification of fetal breathing movements. At 34–35 weeks’ gestation human fetal breathing activity is related to the time of day and to ingestion of food by its mother.

175 Inhibition of Leukocyte Migration by Progesterone (P) in vivo and in vitro A.N. Contopoulos, L.E. Clemens, S. Ortiz, D.P. Sîtes and P.K. Siiteri Departments of Obstetrics-Gynecology, Anatomy, Medicine and Laboratory Medicine, University of California at San Francisco School of Medicine, San Francisco, Calif.

Inflammatory and cellular immune responses are mediated by leukocytes that migrate to the site of antigenic stimulation. In the present studies we have observed the migration of cells into the
placentas of pregnant rats ovariectomized for 0, 4, 8, 12 or 24 h on the 11th day of pregnancy. Placental P concentrations, measured by radioimmunoassay, decreased from 266 to 78 ng/g tissue between 4 and 12 h after ovariectomy. A marked infiltration of macrophages and neutrophilic leukocytes into material vessels was apparent 4 h after ovariectomy. 8 h after ovariectomy the cell populations were reversed so that the predominant cells were lymphocytes and very few polymorphs were observed. At 8 and 12 h histological examination demonstrated maternal lymphocytes in the processes of diapedesis and blasto-genesis. The integrity of fetal trophoblast began to degenerate at 12 h and by 24 h it was marked with large hemorrhagic areas and almost complete disruption. The direct effect of P on neutrophil migration was also measured in vitro. Replicate samples (5–7) of human neutrophils were placed in wells in 1% agar gels containing either P, estradiol (E), testosterone (T) or cortisol (C) each at 20 µg/ml. The opaque areas of cell migration were measured after 20 h. In three experiments, P and E were inhibitory, T had no effect and C stimulated cell migration (P, -32%, E, -19%, C, + 29%). These data suggest that placental and/or decidual P may restrict the movement of leukocytes into the normal placenta prior to parturition.

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176 Ovum Transport in the Ampulla of the Rabbit Oviduct: the Role of Muscle Sheridan A. Halbert and Richard J. Blandau Center of Bioengineering and Department of Biological Structure, University of Washington, Seattle, Wash.

The transport of the egg in cumulus may be effected by either cilia or muscle or both. The purpose of this study was to differentiate between the effectiveness of these two mechanisms. To assess separately the role of muscle, surrogates for cumulus masses were used which were not transported by the cilia. Boluses of petroleum jelly stained with Sudan black were used as surrogates, and their transport was studied in ovulatory rabbits by using the in vivo abdominal dish preparation of Blandau. The surrogates were introduced into the ampulla with a small pipette. Those deposited within 1 cm of the ostium were all regurgitated. When placed more than 1 cm past the ostium, the stained boluses were usually retained. Their motion consisted of discrete, high velocity (up to 2 mm/sec), forward and backward movements. About one third of the surrogates made no net progress in the direction of the ampullary-isthmic junction (AIJ). An equal number moved forward to the AIJ at net velocities from 0.02 to 0.2 mm/sec but did not reach it. The remainder were transported to the AIJ at net velocities ranging up to 0.1 mm/sec. All normal cumulus masses were transported to the AIJ at about 0.1 mm/sec net velocity. Our observations show that muscle activity is capable of effecting ampullary cumulus mass transport but that the muscle mechanism is much less efficient and effective than the cilia. The relative behavior of surrogates and cumulus masses observed in the first centimeter of the ampulla indicates that cumulus mass transport is not possible without the cilia mechanism.

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177 A Stochastic Model of Oviductal Egg Transport
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A mathematical description of the relationship between apparent movements of the ovum in the Fallopian tube and the various forces generated by the mechanical effectors of this organ will be
presented. Within the framework of a stochastic approach, we have used Langevin’s equation to formulate a description of tubal transport which is deduced from qualitative features of this phenomenon rather than induced from numerical fitting of experimental data. We show that egg transport in the tube can be represented as a one-dimensional random walk in a field of external force. The motion of the egg can be described by:

\[ m^\ddot{v} = -fv + A(t) + F \quad (1) \]

where \( v \) is the velocity of the egg. The influence of the intraluminal forces on the motion of the egg are represented by: a frictional force \(-fv\); a randomly fluctuating force \( A(t) \), generated by the muscle component of the oviductal wall; and the driving force \( F \) generated by cilia.

Accordingly the description of egg transport in terms of the probability distribution of ovum positions along the tube has the general form of the Fokker-Plank equation. The specific constraints of the model provide the identification and characterization of the mechanisms involved and predict the various potential alternatives for physiologic regulation of the egg transport processes.

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178 In vitro Reduction of the Stretch Modulus of Human Cervical Tissue by the Prostaglandins, PGE2 and PGF2a,

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Samples of human cervical tissue were obtained from women immediately following term delivery from spontaneous labor or oral PGE2-induced labor. An informed consent was obtained in each case. The tissue was cut into strips, measured and placed in a well-oxygenated Ringer’s solution bath at 37 °C. The tissue samples were stretched at a constant rate while continuously recording length and tension. The resulting data were converted to stress-strain diagrams from which a stretch modulus was computed for each sample. A total of 44 strips from 21 patients was used. During the course of the stretch, one of the prostaglandins, PGE2 or PGF2a (10-6 g/ml), was added to the test strip of the pair of matched strips. The resulting changes in the stretch modulus were noted and compared to the untreated matched strip.

The PGE2 reduced the stretch modulus an average of 36.2%, as compared to the control; PGF2a reduced the stretch modulus by an average of 51.2%. The reduction of the yield value was 48.4% for PGE2 and 50.4% for PGF2α. Both PGF2α and PGE2 reduce the stretch modulus of pregnant human cervical tissue in vitro, and it appears that PGF2α does so to a greater degree.

(Supported by a grant from the Upjohn Company.)

179 Spectral Analysis of Individual Pressure Wave Forms in Spontaneous Active Labor

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Previous statistical analyses of selected pressure wave-form parameters discriminated between normal spontaneous, hypocontractile and hypercontractile labor. Spectral analyses of individual wave forms were investigated to define more discriminating wave parameters. 182 contractions obtained from 10 women selected according to a definition of normal spontaneous labor were analyzed. The data was prefiltered at 0.045 Hz. Of the first six harmonics investigated, the first
harmonic contained on average 91% of the amplitude and 96% of the total power in the wave. The fundamental cosine term which is of significance in spreading contractile wave models contained on average 86% of the amplitude and 92% of the total spectral power. The fundamental sine term contained on average 4% of the total power and accounted for a major portion of the wave asymmetry. The phase angle of the first harmonic ranged between + 140° and + 220° corresponding to longer or shorter wave tails. Although the 2nd through 6th harmonics contain little spectral power, on average less than 4%, they contributed significantly to the first derivative of the pressure and hence to the rates of rise and decay of the wave form. The experimentally determined linear relationship between maximum uterine pressure and maximum rate of pressure rise when analyzed in terms of spectral coefficients indicates that deviations from linearity are related to the magnitudes of the higher order frequency terms. Repetitive patterns in normalized spectral coefficients obtained from series of contractions suggest individual fingerprint characteristics.

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180 An Alternative to Prophylactic Antibiotics in the Prevention of Serious Infection following Cesarean Section
Gere DiZerega, Carol L. Gee and William J. Ledger
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This random study evaluated the effectiveness of two antibiotic regimens in the post-cesarean section patient at the first clinical sign of infection. This strategy avoided both the use of antibiotics in all high risk patients undergoing cesarean section and the transplacental passage of antibiotics to the fetus. The initiation of therapy parallels the animal model of Gorbach et al. with early onset infection prior to abscess formation. To evaluate the significance of Bacteroides fragilis, the regimens included either penicillin or clindamycin used with gentamicin. To date, 36 patients have received penicillin-gentamicin and 31 clinda-mycin-gentamicin. The differences in treatment outcome have been striking. For those patients receiving penicillin, the median fever index was 91.3 degree hours, the mean 119.2, SD ± 103.7, and SE 17.3. 13 women (36%) required a third antibiotic for cure. For the clindamycin group, the median fever index was 85.5 degree hours, the mean 81.2, SD ± 38.4, SE ± 6.9. Three patients (9.7%) required a third antibiotic for cure. Seven patients receiving penicillin had a fever index that exceeded the highest in the clindamycin group. If this therapeutic response trend continues an alternative to prophylaxis may be the use of systemic antibiotics limited to patients with clinical evidence of infection.

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