Hospitality Hour  Wednesday, March 24, 1976, 6 p.m.

Courtesy of Ross Laboratories Columbus, Ohio Burgundy Room, Lobby Floor Bellevue Stratford Hotel

Registration
Thursday, March 25, 1976, 7.30 a.m., and Friday, March 26, 1976, 7.30 a.m. Elevator Foyer, Ball Room Floor Bellevue Stratford Hotel

Scientific Sessions  Thursday, March 25, 1976, 8 a.m. to 4.30 p.m., and Friday, March 26, 1976, 8 a.m. to 4 p.m. Grand Ball Room, Clover Room or Red Room

Bellevue Stratford Hotel Ball Room Floor Plan on page 108

Introduction First Plenary Session Concurrent Session A Concurrent Session B Concurrent Session C Concurrent Session D Concurrent Session E

Thursday, March 25, 1976 8 a.m.
8.15 a.m. to 10.15 a.m. 10.45 a.m. to 12 noon 10.45 a.m. to 12 noon 1.45 p.m. to 4.30 p.m. 1.45 p.m. to 4.30 p.m.

Grand Ball Room Grand Ball Room Grand Ball Room Clover Room Grand Ball Room Clover Room

Second Plenary Session Guest Lecture Concurrent Session A Concurrent Session B Concurrent Session C Concurrent Session D

Friday, March 26, 1976 8 a.m. to 10.15 a.m. 8 a.m. to 9 a.m. 10.45 a.m. to 12 a.m. 10.45 a.m. to 12 a.m. 1.45 p.m. to 4 p.m. 1.45 p.m. to 4 p.m.

Grand Ball Room Grand Ball Room Grand Ball Room Clover Room Grand Ball Room Clover Room

Business Meeting (members only)
Thursday, March 25, 1976, 4.30 p.m. Grand Ball Room

Program of Events
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Reception Thursday, March 25, 1976, 6.30 p.m.
Banquet Thursday, March 25, 1976, 7.30 p.m.

Upper Egyptian Room Museum of the University of Pennsylvania
Charter buses will provide transportation from the Bellevue Stratford Hotel to the University of Pennsylvania.

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 Foyer located between the Grand Ball Room and the Clover Room during intermissions on Thursday morning and afternoon and on Friday morning.

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Concurrent Session E, Thursday, March 25, 1976, 1.45 p.m  33
Cycling female rats were sacrificed at various time intervals during the 4-day estrous cycle. LH-RH in the medial basal hypothalamus (MBH) and preoptic area (POA), serum LH-RH, LH and ovarian steroids were analyzed by radioimmunoassays. A distinct circadian rhythm in POA LH-RH content, nadir around noon and peak activity between 18.00 and 22.00 h, was observed during the cycle. This POA LH-RH rhythm was temporally associated with daily elevations of progesterone levels in peripheral blood. LH-RH in MBH was generally higher during diestrus than at estrus. Frequent sampling at short intervals during proestrus revealed significant fluctuations in MBH and serum LH-RH in conjunction with high serum estradiol values. In the afternoon of proestrus, prior to the critical period, there was a significant decline in LH-RH activity in serum and MBH between 14.07 and 14.45 h followed by an abrupt rise between 14.55 and 15.55 h which preceded the preovulatory discharge of LH. LH-RH activity in serum and MBH declined gradually to the early afternoon levels by 20.00–24.00 h while the peak in serum LH was observed at 18.00 h. These studies demonstrated a circadian POA LH-RH rhythm which appeared to be associated with peripheral progesterone levels and suggested that MBH LH-RH may be involved in the preovulatory surge of LH. 

(Supported by grants from the Population Council and NIH RO HD 08634–0A.)
8.30 a.m. 2 Luteinizing Hormone Receptor Binding Inhibitor and its Effect on Luteinizing Hormone Receptors from Male and Female Tissues Paul Yang, Darrell N. Ward and Naguib A. Samaan Departments of Medicine and Biochemistry, University of Texas, System Cancer Center, M.D. Anderson Hospital, Houston, Tex.

A luteinizing hormone receptor site binding inhibitor (LH-RBI) has been characterized and partially purified from aqueous extracts of ovaries from pseudopregnant and pregnant rats, but not in mature nonpregnant or immature rats. LH-RBI appeared to be tissue- and hormone-specific as it was not found in extraovarian tissues such as liver, oviduct, and testis; and it did not inhibit the binding of \(^{125}\)I-labeled ovine prolactin to ovarian prolactin receptors. LH-RBI did not appear to have endogenous gonadotropin or endogenous lysosomal enzyme activities as it was resistant to heat denaturation. There was no detectable quantity of \((^{125}\)I\)oLH bound to the LH-RBI. It was therefore concluded that LH-RBI blocked the LH binding at the receptor level. We also found that LH-RBI did not inhibit LH binding to testicular LH receptors, although the inhibition was highly significant in the ovary. No inhibition of \((^{125}\)I\)oLH binding to testicular LH receptors was observed even when the concentration of LH-RBI was significantly increased or when the testicular LH receptors were first incubated with LH-RBI prior to the addition of \((^{125}\)I\)oLH. Scatchard analysis revealed that the dissociation constant of \((^{125}\)I\)oLH binding was essentially the same in the presence or absence of LH-RBI. The results suggest that (1) the LH receptor of ovaries, but not of testes, has a specific LH-RBI binding site in addition to the LH binding site, and (2) the binding of LH-RBI produces an ‘allosteric’ type of inhibition to the binding of LH at the binding site.

8.45 a.m. 3 Immunologically Induced Fetoplacental Growth Retardation James R. Scott Department of Obstetrics-Gynecology, University of Iowa College of Medicine, Iowa City, Iowa

It is not clear whether the high incidence of SGA infants born to mothers with renal transplants is related to underlying nonimmunologic maternal problems or due to the immunosuppressive drugs these women are taking. However, since maternal-fetal immunogenetic disparity facilitates growth of the fetus and placenta, nonspecific depression of the maternal immune response could result in adverse effects in the progeny. To explore this possibility and elucidate its basis, groups of 6–8 healthy virgin female inbred rats of similar age and weight mated with males differing at the major histocompatibility locus were treated with daily intraperitoneal injections of (1) saline, (2) cyclophosphamide 1.5 mg/kg, or (3) 3.0 mg/kg, (4) azathioprine 1.0 mg/kg, (5) 2.0 mg/kg, or (6) 5.0 mg/kg, or were mated with males of the same strain and treated with (7) saline, or (8) cyclophosphamide 1.5 mg/kg. Although the fetuses and placentas weighed at a fixed time postconception were smaller in the syngeneic than allogeneic pregnancies, fetal and placental weights were markedly decreased in all groups \((p < 0.001)\) treated with immunosuppressive drugs and the effect was dosage-dependent. Composition studies of water, fat, protein, DNA content, and protein/DNA ratio indicate that the smaller placentas and fetuses result primarily from decreased fat content and cell number rather than cell size. Moreover, comparison of conceptus resorption rates, mean maternal weight gain, spleen weight assays, and changes in the lymph nodes draining the uterus in the various groups suggests that maternally administered immunosuppressive drugs reduce placental and fetal size by a combination of nutritional, cytotoxic, and immunologic mechanisms.

9 a.m. 4 A Clinical Evaluation of the ‘Roll-Over Test’ for Pregnancy-Induced Hypertension
Following the presentation of the predictive capability of the roll-over test at the 1974 meeting of the SGI, we instituted a study utilizing our private patients. The methods used were exactly those described by Gant and his associates. 60 primigravid and 60 multigravid patients were studied between the 28th to 32nd week of gestation. These patients were chosen at random by one of our two nurses who conducted all these studies. The decision as to whether or not a patient would be tested depended upon first of all, the exclusion of all patients who were not totally normal up to that point in their pregnancy. Secondly, time available during the office hours dictated whether or not the test would be done. All results were recorded in a notebook and were not available to the physicians. 18 months later, after all study patients had delivered, the hospital charts and patients’ office records were evaluated to determine if pregnancy-induced hypertension had occurred. In primigravid patients a positive test accurately predicted the later development of pregnancy induced hypertension only 50% of the time while a negative test accurately predicted that it would not develop 93% of the time. The multigravid test results were even less significant. Only 25% of the patients who had positive tests later developed hypertension. The negative test in multigravid patients was accurate 94% of the time.

Immunological and Biological Activities of Antisera to Peptides of the C-Terminus of (3HCG Subunits

Vernon C. Stevens
Department of Obstetrics-Gynecology, Ohio State University, Columbus, Ohio

Immunization of rabbits with protein conjugates of peptides of the C-terminal portion of the (3HCG subunit was performed to determine whether antibodies capable of neutralizing HCG but not HLH could be obtained. Antisera from immunizations with peptides containing 13–44 amino acids reacted with HCG in vitro. None reacted at detectable levels with HLH. Antibodies to peptides of 20 amino acids or less failed to neutralize HCG in vivo irrespective of their relationship to the 111–148 sequence of ÖHCG. Sera against a natural 39 residue peptide (109–148) and somewhat shorter synthetic peptides inhibited HCG in vivo in two bioassay systems. The potency of neutralizing capacity of various antisera correlated poorly with antibody levels or avidity, but correlated positively with the length of peptide used as immunogen. Reaction of these sera with radiolabeled short peptides and displacement of 12s I HCG with peptides indicated that antibodies were primarily directed to determinants at the C-terminus of ÖHCG (residues 140–148) and to determinants between residues 109–115. No data were obtained to conclude whether biological neutralization of HCG was due to blockage of receptor sites or due to steric hindrance of HCG by antibodies, however, such action was accomplished with antibodies not directed to residues common with HLH.

Characterization of a Syncytiotrophoblast Plasma Membrane Preparation: Electron Microscopy, Enzymatic Analysis, Sialic Acid Content, and Amino Acid Uptake

Carl H. Smith, D. Michael Nelson, Thomas M. Donohue, Stephen M. Ruzycki and Lucky K. Kelley
Departments of Pediatrics, Pathology, and Anatomy, Washington University School of Medicine, St. Louis, Mo.
To evaluate its usefulness in investigation of processes in maternal-fetal interaction, an isolated syncytiotrophoblast plasma preparation was studied by a combination of morphological and biochemical techniques. Plasma membrane was prepared by a modification of the method of Smith et al, (Nature, 252: 302, 1974). Electron-microscopic examination demonstrated that the vast majority of the pellet was composed of smooth membrane vesicles (0.1-0.2 µm in diameter) stainable with colloidal iron hydroxide. Sheets of syncytiotonal membrane and sparse profiles of intracellular organelles were minor contaminants. Compared with a placental homogenate, the plasma membrane preparation was enriched 12- to 15-fold in alkaline phosphatase and 5'-nucleotidase activity, and 4-fold in sialic acid. Cytochrome oxidase, β-glucuronidase, and NADH-cytochrome c reductase activities were, 20, 25 and 80 % those of the whole tissue homogenate. The plasma membrane vesicles exhibited glycine, serine, and α-aminoisobutyric acid uptake by a temperature-dependent, saturable process. By several criteria, the preparation has the characteristics expected of syncytiotrophoblast plasma membrane with only small contamination by other subcellular membranes. The pattern of amino acid uptake resembles that of intact placental tissue. The membrane preparation should be useful in studying the mechanisms underlying many functions of the placenta.

9.45 a.m. 7 Effect of Progesterone on Estrogen-Induced Uterine Blood Flow R. Resnik
Department of Reproductive Medicine, San Diego School of Medicine, University of California, La Jolla, Calif.

The effect of progesterone on estrogen-induced uterine vasodilation was investigated in repeated experiments in 5 nonpregnant, oophorectomized ewes with chronically implanted electromagnetic flow probes and catheters inserted into branches of the uterine arteries. Administered alone, progesterone has no effect on baseline uterine blood flow levels. Following intramuscular injection of progesterone (3–5 mg/kg body weight), peak uterine blood flow responses to 1 µg estradiol-1β were suppressed by a mean magnitude of 25 % compared to controls (n = 48, p < 0.001). Direct intraarterial infusion of progesterone prior to estrogen stimulation inhibited the peak flow response by 21 % (n = 24, p < 0.01). This latter finding establishes for the first time that the inhibition is a direct effect of progesterone, and not due to a product of progesterone metabolism. Furthermore, it is consistent with other observations that progesterone modulates estrogen-induced flow responses in both the pregnant and nonpregnant uterine vascular bed.

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10 a.m. 8 Sodium – a Trigger of Disseminated Intravascular Coagulation in Pregnancy Irwin R. Berman, Constantine Iliescu, Henny Iliescu and Charles H. Debrovner Departments of Surgery and Obstetrics-Gynecology, New York University Medical Center, New York, N.Y.

Intrauterine instillation of hypertonic saline (HS) is often accompanied by a mild form of disseminated intravascular coagulation (DIC). This study tests the hypothesis that sodium rather than its route of administration, is responsible for DIC complicating saline-induced abortion. Sprague-Dawley rats were divided into 3 groups: male (6 rats); nonpregnant females (6); and pregnant females (8). All animals received HS 2 cm³, 23.4 % into the free peritoneal cavity. Blood was studied at baseline, 2 and 5 h after HS for measurement of electrolytes, hematocrit, fibrinogen, platelets and screen filtration pressure (SFP), a measure of platelet aggregation. In 10 additional rats, tritiated serotonin, a platelet label, was administered intravenously before HS. Reticuloendothelial (RE) uptake was determined 7 h later by scintillation counting of excised spleen. HS was followed by diminution in fibrinogen (47.6%, p < 0.001) and platelet count.
Moderate hypernatremia was noted in all groups, but no pregnant animals aborted. Splenic uptake of radioactive label after HS was 88.1 % greater than in pregnant controls (p < 0.005). These results demonstrate that sodium and pregnancy act synergistically to initiate DIC. This phenomenon is accompanied by acute RE loading and appears to be independent of the route of saline administration. These results have strong implications for mechanisms of DIC in toxemia as well as in saline-induced abortions.

10.15 to 10.45 a.m. Intermission

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Concurrent Session A

Thursday, March 25, 1976

Grand Ball Room – Bellevue Stratford Hotel

10.45 to 12 noon

Moderator: Edward J. Quilligan

10.45 a.m. 9 Plasma Renin Activity (PRA) in Normotensive and Hypertensive Pregnant Sheep
C.R. Brinkman, III, J.R. Woods, Jr., J. Latta and N.S. Assali

UCLA School of Medicine, Department of Obstetrics and Gynecology, Los Angeles, Calif.

Although behavior of PRA in normotensive and hypertensive nonpregnant animals has been studied, it has not been properly assessed during pregnancy. The present report deals with data on PRA in normotensive pregnant and moderate and severe hypertensive pregnant sheep. Chronic studies were carried out in pregnant sheep from 80 gestational days until 2 weeks postpartum. Uteroplacental blood flow (UPQ), arterial pressure (AP), heart rate and renal flow (hypertensive animals) were recorded daily. PRA levels were determined on carotid arterial, jugular and uterine venous blood. Moderate hypertension was produced by constricting the right renal artery for severe hypertension, the contralateral kidney was removed. In addition, 2 animals were sham-operated and served as full control. Results show: (1) in normotensive pregnant animals, PRA levels were maximal at about 120 days and then decreased by about 33 % to term; (2) uterine vein PRA levels were not appreciably higher than jugular vein values; (3) unilateral renal artery constriction causes a transient 5-fold increase in PRA which then decreases to about twice control levels; (4) renal artery constriction results in a 25 % decrease in UPQ and a 25 % increase in AP; (5) in animals with unilateral nephrectomy, there is a greater UPQ and AP response but similar PRA changes. Conclusions: (1) the uterus is not a significant source of renin during ovine pregnancy; (2) renal artery constriction causes an increase in AP and a decrease in UPQ, along with initial but not sustained increase in PRA; these changes were more marked in animals with unilateral nephrectomy. Relationship between changes in PRA, blood pressure and uterine flow will be discussed.

(Supported by USPHS grant HL-13634.)

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11 a.m. 10 New Technique for Uterine Metabolism Studies Robert M. Abrams and Morris Notelovitz

University of Florida College of Medicine, Department of Obstetrics-Gynecology, Gainesville, Fla.

Metabolic rate of the nonpregnant sheep uterus has been determined indirectly by measurement of uterine a-v oxygen content differences and uterine blood flow rate. The usual range of values,
0.004–0.006 cm3 O2/g/min, does not appear to increase after estrogen treatment, although a large body of in vitro evidence suggests that it should. We measured the metabolic rate directly by recording the rate of rise in uterine temperature (ΔT/dt) following three procedures designed to arrest uterine blood flow and thus prevent the loss of metabolic heat. ΔT/dt (°C/min) × estimated specific heat of uterus (0.83 cal/g/°C) = uterine metabolic rate, UMR (cal/g/min).

One estrogenized, anesthetized ewe was laparotomized and cervix and ovarian arteries were ligated. UMR calculated after occlusion of both uterine arteries was 0.0315 cal/g/min. One ewe was fitted with an inflatable cuff encircling cervix, a uterine vein and both uterine arteries. All other uterine vascular connections were ligated and the ewe allowed to recover for 1 week. Two 24 h following 0.1 mg E, , the UMR, calculated from the rate of change in uterine temperature during several 1-min occlusions was 0.025–0.042 cal/g/min. Assuming a calorific equivalent of 4.8 cal/cm3 O2, these rates of heat production were equivalent to 0.0052–0.0088 cm3 O2/g/min.

(Supported by USPHS grant HD 08229.)

11.15 a.m. 11 Carbon Monoxide: Effects on Fetal Oxygenation Lawrence D. L·ongo Division of Perinatal Biology, School of Medicine, Loma Linda University, Loma Linda, Calif. While there is considerable interest in the biological effects of low levels of carbon monoxide (CO) on tissue O2 supply, little is known of CO effects on the fetus. In an effort to explore this question, pregnant ewes with catheters chronically implanted in maternal and fetal vessels were exposed to inspired CO concentrations of 30, 50 and 100 parts/million. Blood carboxyhemoglobin concentration (HbCO) and pO2 values were measured repeatedly during a 36–48 h period of CO uptake and equilibration: and during an 8–12 h period of CO elimination in 4–5 animals exposed to each inspired CO concentration. The pO2 in fetal descending aorta and inferior vena cava (below the ductus venosus) decreased from normal values of 20 and 16 Torr, respectively to 15 and 13 Torr, respectively, at 10 % (HbCO). Fetal IVC pO2 was inversely related to (HbCO), the regression equation being pO2 = 16.5–0.35 (HbCO). During CO uptake fetal (HbCO) rose more slowly than maternal (HbCO). The time for fetal (HbCO) to reach half its final value was 7.5 h, in contrast to 2.5 h for the mother. During steady state conditions fetal carboxyhemoglobin exceeded maternal values by 20–50 %. In conclusion, fetal CO uptake and elimination are relatively slow in comparison with the mother; and during steady state conditions fetal (HbCO) significantly exceeds maternal values. Finally, elevated fetal (HbCO) is associated with decreased blood pO2 values. This may be an important mechanism in the genesis of small for gestational age infants of mothers who smoke. (Supported by USPHS grant HD-03807.)

11.30 a.m. 12 Continuous in vivo Monitoring of Arterial pO2 and pCO2 in Fetal Lambs S. V. Matalon, B.C. Eichorst, P. Manning, B.J. Bernie, C.E. Hunt and A.E. Seeds Departments of Pediatrics, Physiology and Obstetrics-Gynecology, University of Minnesota, Minneapolis, Minn. An in vivo blood gas catheter-mass spectrometer system has been used to continuously and simultaneously measure the fetal arterial pO2 and pCO2. In 7 pregnant sheep (128–135 days gestation) we changed the maternal-inspired mixture and observed the following changes in fetal pO2 and pCO2: (1) 100 % O2 to room air: the fetal pO2 decreased from 21.5 ± 0.8 (mean ± SKM)
to 14 ± 4.1 mm Hg at a rate of 1.47 ± 0.3 mm Hg/min. Following the return to 100 % O2 , the pO2 returned to 21 ± 1.1 mm Hg at a rate of 2.1 ± 0.35 mm Hg/min. (2) 100 % O2 to 12 % O2 and 10 % CO2: after 6 min of ventilation, the pO2 fell to 6.3 ± 0.3 mm Hg at a rate of 3.55 mm Hg/min and the pCO2 rose from 37 ± 8 to 70+5 mm Hg. Following the return to 100 % O2 , the fetal pO2 and pCO2 returned to their previous baseline values within 4 and 10 min, respectively, at a rate of 6.5 mm Hg/min. (3) 90% CO2 and 10% O2: within 8 min pO2 and pCO2 increased 4 and 20 mm Hg, respectively. In all instances, the observed fetal changes were initiated within 1 min after changing the maternal mixture, except in the case of recovery from 12 % O2 and 10 % CO2 , when such changes occurred within 34 ± 12 sec. These results indicate that changes in maternal pO2 and pCO2 are rapidly transmitted to the fetus, and that fetal hypoxia secondary to maternal hypoxia may be rapidly alleviated by the administration of 100 % oxygen to the mother.

11.45 a.m. 13 Comparison of the Uterotrophic and Vascular Effects of Estradiol-17β and Estriol
William H. Clewell, Bonita A. Carson, Giacomo Meschia, Edgar L. Makowski and Frederick C. Battaglia
Division of Perinatal Medicine, University of Colorado Medical Center, Denver, Colo.
Estradiol-17β (E2) has been considered the most potent of the natural estrogens in terms of uterine growth and vasodilatation. As a result of studies of uterine growth in rodents, estriol (E3) has been considered an ‘impeded’ estrogen. In this study, direct comparisons of the actions of E2 and E3 on the sheep uterus were made, using nonpregnant, oophorectomized ewes with bilateral uterine artery catheters and electromagnetic flow transducers. Interanimal variation was eliminated by using the contralateral uterine horn of the same animal for comparison. Two sets of experiments were carried out. In the first set, the artery of one uterine horn was injected daily with 1 µm of E2 or E3 and the contralateral horn injected with saline, for 14 consecutive days. In the 5 animals studied, E2 and E3 promoted equal degrees of vasodilatation and growth in the study horn. Growth consisted of significant (p < 0.01) increases in weight (+35%), total protein (+40%), and protein/DNA ratio (+21 %) in comparison with the control horn.

In the second set of experiments, direct comparison of the action of the two estrogens in the same animal was made by daily injections of E2 into one horn and E3 into the other. There were no significant differences between the two estrogens studied in the same animals (4 ewes). The above results show that the classification of E3 as an ‘impeded’ estrogen, based on studies in rodents, may not be generally applicable.

12 noon to 1.45 p.m. Luncheon
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Concurrent Session B
Thursday, March 25, 1976
Clover Room – Bellevue Stratford Hotel
10.45 to 12 noon Moderator: Robert B. Jaffe
10.45 a.m. 14 Aromatization of Androgens in Discrete Hypothalamic and Limbic Regions of the Male Rat
Previous studies have demonstrated that a number of brain regions are capable of converting testosterone (T) or androstenedione (A) to estrone (E1) and estradiol (E2). We have further elucidated the localization of the enzyme responsible for this conversion, aromatase, to the following discrete brain regions: medial preoptic nucleus-anterior hypo-thalamus (MPN-AH), lateral preoptic nucleus (LPN), medial basal hypothalamus (MBH), lateral hypothalamic area (LHA) and amygdala (Amy). Brains from 20 male, castrated, adrenalectomized rats were dissected using the Palkovits punch technique and pooled for each incubation. Brain fragments were incubated in Krebs-Ringer phosphate buffer pH 7.4 containing 11 mM glucose and cofactors (NADPH generating system) in the presence of either 1.0 µM $^{3}$H-androstenedione or $^{3}$H-testosterone. Steroids were extracted with chloroform and 14C markers added. Metabolites were resolved by liquid-liquid partition chromatography, thin-layer chromatography, acetylation and recrystallization to constant 3H/14Cdpm ratios.

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E1 and E2 formation (pM/h/100 mg protein). * = Less than 0.2.

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The MPN-AH, MBH and Amy, areas involved in androgen related sexual behavior or feedback, showed high levels of aromatase activity. The LPN and LHA, areas not directly involved in the central action of androgens, had lower levels.

11 a.m. 15 Functional Assessments of LRF and Estrogen Interaction on the Gonadotrophs /.
Hoff, B. Lasley and S.S.C. Yen Department of Reproductive Medicine, UCSD, La Jolla, Calif.

Our previous studies have indicated that the functional capacity (sensitivity and reserve) of the gonadotrophs is largely determined by the relative inputs of LRF and E2. The present investigation is designed to gain quantitative information concerning this interaction. The influence of acute exogenous E2 on LRF-induced release was assessed in subjects with already accelerated gonadotropin (GTP) secretion and chronic low estrogen levels (hypogonadals) via prolonged constant LRF infusion (18 h) with or without an E2 infusion (50 µg/h × 4 h)
administered during the course of the LRF infusion. Our data show that during the prolonged LRF infusion GTN levels rose rapidly in the first hour, leveled off and attained a maximum at 8 h followed by a slow progressive decline despite the continuation of infusion. Under this condition, elevation of E2 concentration from 20 to 500 pg/ml via E2 infusion negated significantly the GTP release induced by exogenous LRF within an hour. A transient rebound starting about 1 h after withdrawal of the E2 infusion pushes GTN levels above those attained during the control infusion, and this was followed by a gradual decline during the subsequent course of the infusion. These data show that rapid increases in circulating E2 cause prompt inhibition of the LRF-mediated GTP release without impairment of LRF-mediated GTP synthesis. This is consistent with the finding of a preferential augmentation of pituitary reserve than sensitivity during the late follicular phase of the cycle.

11.15 a.m. 16 Induction of an LH Surge with Estradiol Benzoate: a Clinical Test of Pituitary-Hypothalamic Axis Competence Gerson Weiss, Lite. Nachtigall and Manik Ganguly Department of Obstetrics-Gynecology, New York University School of Medicine, New York, N.Y.

In order to demonstrate that a single estrogen injection at appropriate dosage can be used as a test of the pituitary-hypothalamic axis’ ability to produce a preovulatory-like gonadotropin release (positive feedback response), 6.6 mg of estradiol benzoate (EB) in oil was injected intramuscularly into 31 women. Serum estrogens, LH and FSH were measured daily for 5 days. Six women were normal controls, 2 had poly cystic ovary syndrome (POS), 12 were oligo- or anovulators and 11 were amenorrheic. All the normal controls, 8 of the oligoovulatory but menstruating women and 4 of amenorrheic patients had LH surges to EB challenge. Most LH surges peaked at 48–72 h after EB injection. FSH surges were observed only eight times, three in normal controls, four in oligoovulatory women and one in a women with POS. Of 18 noncontrol women who had been treated with clomiphene in prior cycles, only 4 responded with a biphasic temperature curve. However, 11 responded to EB

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with an LH surge. 16 women in this study were desirous of becoming pregnant and were infertile. Four of these women became pregnant during their EB treatment cycle. Three of these women had FSH as well as LH surges to EB challenge.

Conclusions of this study are that EB challenge can be used to select patients in whom menstrual abnormality is due to a failure of their positive feedback system. EB is effective in inducing ovulation in some anovulatory women refractory to clomiphene treatment.

11.30 a.m. 17 Pathophysiology of Amenorrhea-Galactorrhea in Patients With and Without Pituitary Tumors


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

In an attempt to characterize the pathophysiology of amenorrhea-galactorrhea, ten patients with this syndrome were studied. Insulin was first administered then GnRH-TRH followed in 120 min by a second dose of GnRH. The results in these 10 patients (5 post-birth control pills without radiological evidence of pituitary tumor and 5 with pituitary tumors) were compared to 9 normal controls. Patterns of hypothalamic and pituitary responses in the 2 pathologic groups were different from controls. In contrast to the controls, all 10 patients had elevated baseline hPRL
levels which did not increase further following insulin or TRH stimulation. The 5 post-pill patients, in contrast to the 5 patients with tumors were all characterized by a delay in release of HGH, a higher FSH release to the first GnRH stimulation and a lower LH release to the second GnRH. The 5 patients with pituitary tumors all had a normal LH and FSH response to the first GnRH stimulation but not to the second, indicating a lack of residual pituitary capacity. The results of this study indicate (1) in patients with post-pill amenorrhea-galactorrhea a pituitary dysfunction is most likely the cause of this disorder and (2) in patients with pituitary tumors the use of sequentially administered GnRH is necessary to demonstrate a derangement of the LH and FSH secretion.

11.45 a.m. 18 Regulation of the Two Pools of Pituitary LH / Hoff, B. L·asley and S.S.C. Yen Department of Reproductive Medicine, UCSD, La Jolla, Calif.

The present study further investigates the role of LRF and E2 in the regulation of the two pools of LH in the pituitary – the acutely releasable and the reserve pools. The effect of increasing levels of E2 on the relative sizes of the two pools was assessed in 9 normally cycling women via LRF infusion (0.2µg/min × 4 h) during the early follicular (EFP) and late follicular (LFP) phases. The infusion was followed immediately by 3 repeated pulses of 10 µg LRF at 2-hour intervals. The influence of elevated endogenous LRF during the midcycle surge was studied in a similar fashion. A 2-component response during the EFP denoted activity of the two pools. From EFP to LFP, with rising E2, the LH response during the infusion increases 5-fold. This increase involves the 2nd pool primarily and consequently the distinction between 1st and 2nd pools becomes blurred during LFP. The

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infused LRF has a profound priming effect during both EFP and LFP as evidenced by a greater response to 1st pulse of LRF after the infusion than is found in subjects without prior infusion. The response to the 2nd bolus is augmented only in LFP indicating that E2 supports the self-priming effect of LRF. During the midcycle surge, the LRF infusion induces a single large and rapid release of LH with complete loss of distinction between the two LH pools and with no response to subsequent pulses of LRF. These results suggest that (1) E2 serves to increase reserve LH and (2) LRF activates reserve LH converting it to the releasable form.

12 noon to 1.45 p.m. Luncheon
Society for Gynecologic Investigation

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Concurrent Session C
Thursday, March 25, 1976
Grand Ball Room – Bellevue Stratford Hotel

1.45 to 4.30 p.m.
Moderators: Guy M. Harbert and Lawrence D. Longo

1.45 p.m. 19 Sudden Changes in Amniotic Fluid Bilirubin

Marvin S. Amstey, John W. Choate, Charles W. Hohler and Harold E. Fox Department of Obstetrics-Gynecology, University of Rochester, School of Medicine and Dentistry, Rochester, N.Y.

Large increases in amniotic fluid bilirubin were observed to occur in several Rh-sensitized pregnancies in less than 2 weeks. The outcome of those pregnancies would have been altered significantly by earlier intervention. In order to evaluate the frequency and extent of this problem, a retrospective analysis of all Rh-sensitized pregnancies followed in our Perinatal
Center was done. A total of 197 pregnancies in 194 patients were studied by 639 amniocenteses. An increase of 0.05 optical density units at 450 nm in less than 10 days was selected arbitrarily as significant. 24, or 12 %, of these pregnancies fit this definition of a sudden significant rise. Of this group, there were 19 pregnancies in which the rise in bilirubin occurred within 7 days. The rise in bilirubin occurred between 28 and 32 weeks in 14 pregnancies and after 32 weeks in 2 pregnancies. The fetal salvage rate was only 29 % with 11 stillbirths and 6 neonatal deaths. 14 of the 17 perinatal deaths occurred in pregnancies in which the bilirubin rise occurred within 7 days. The mean cord hematocrit and bilirubin for the 7 surviving infants were 24 % and 7.3 mg, respectively. Three brief case histories are presented to illustrate the importance of a sudden, significant rise in amniotic fluid bilirubin as an important prognostic finding and as a signal for intervention either by intrauterine transfusion or earlier delivery. This would indicate that in all but first-sensitized pregnancies, weekly amniotic fluid bilirubin evaluation is necessary during the gestational periods in which intervention will affect pregnancy outcome.

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2 p.m. 20 Fetal Breathing Movements as Cause of Beat-to-Beat Variability of FHR K. Adamson, R.E. Myers and A. Comas-Urrutia Departments of Obstetrics and Gynecology, Brown University, Providence, R.I.; University of Puerto Rico, Rio Piedras, P.R., and Laboratory of Perinatal Physiology, NINCDS, NIH The effects of respiratory movements upon heart rate and blood pressure was studied in 12 lightly anesthetized fetal rhesus monkeys. In the well-oxygenated fetus, breathing movements occurred at a frequency of 20–60/min. They were readily discernible through the thin-walled uterus particularly in fetuses at or beyond term. The inspiratory effort was associated with a fall in fetal blood pressure lasting about 0.2 sec. This was accomplished by an increase in fetal heart rate of 5 – 10 % affecting one or two beats. The subsequent rise in blood pressure was associated with an essentially synchronous fall in FHR of similarly brief duration. Respiratory movements were facilitated by limb movements and by subjecting the fetus to painful stimuli, and were abolished by the administration of pentobarbital directly to the fetus. Prolonged observations revealed that periods of respiratory movements were interspersed with periods of quiescence in spite of the constancy of the biochemical state of the fetus.

In the absence of breathing efforts and fetal movements FHR remained virtually constant. Breathing movements and the concomitant changes in fetal blood pressure and heart rate were absent in the hypoxic fetus. However, when asphyxia was of sufficient degree to initiate fetal gasping, marked changes occurred in fetal blood pressure and heart rate.

2.15 p.m. 21 Comparison of Ritodrine and Ethanol in Premature Labor Irwin R. Merkatz, Leon I. Mann, Niels H. Lauerse and Fritz Fuchs Departments of Obstetrics-Gynecology, Case-Western Reserve University, Cleveland, Ohio; State University of New York at Stony Brook, Nassau County Medical Center, East Meadow, N.Y., and Cornell University Medical College, New York, N.Y.

Ritodrine is a Ø-mimetic agent which has been found to be useful in the treatment of threatened premature labor. A randomized controlled study comparing ritodrine and ethanol was designed; it was considered unreasonable to use a placebo for the controls when a proven therapy was available. The material comprises 150 patients treated according to the same protocol in 3 institutions. After observation, ethanol was given according to the schedule of Fuchs et al. (Am. J. Obstet. Gynec., 99: 627’, 1967). Ritodrine was given intravenously mixed with 5 % dextrose/water. The infusion was initiated at 50 µg/min and increased by 50 µg/min until
adequate uterine relaxation had been achieved or unacceptable side effects occurred (maximum rate 350 µg/min). After 12 h of infusion, treatment was continued with ritodrine given orally in gradually declining doses. After discharge the patients continued an oral ritodrine for 4 weeks or until the 38th week. All patients were carefully monitored. Both treatments resulted in a marked reduction or total inhibition of uterine activity in all instances. Analysis of the first 70 cases shows that delivery was postponed for more than 72 h in 27 of 35 ritodrine patients and in 26/35 ethanol patients. The mean gain in days was 40.0 for ritodrine and 29.1 for ethanol patients. The overall results were slightly, but not significantly, better for the ritodrine group. Analysis of the total material demonstrates that ritodrine is an effective agent in threatened premature labor, but its use requires careful monitoring of the patients.

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2.30 p.m. 22 In utero Prediction of Intrauterine Growth Retardation by Determination of Total Intrauterine Volume
John C. Hobbins and Parviz Gohari
Yale University School of Medicine, Department of Obstetrics-Gynecology, New Haven, Conn.

Although the fetal brain may be spared in intrauterine growth retardation (IUGR), the fetal body, amniotic fluid volume, and often placenta are small. Since the total intrauterine volume (TIUV), which is calculated from ultrasonically derived dimensions of the uterus, reflects changes in one or all of the intrauterine components, a nomogram was constructed for TIUV from 110 normal gestations. Since then, 102 patients at risk for IUGR were referred for evaluation. 24 of 26 patients delivering growth retarded babies had TIUVs which were more than 1.5 SD below the mean for gestation. TIUVs in the 76 patients delivering normal babies were within 1.5 SD of the mean for gestation. Serial examinations were performed in 15 patients with abnormal TIUV, and in 4 cases a salutary response in TIUV and BPD was noted when the patient was placed on bed rest in lateral recumbent position. In order to evaluate the cause and extent of IUGR, a full ultrasonic profile (including circumference of fetal head, thorax, abdomen, placental volume, and fetal urine production) was performed on all patients with abnormal TIUVs. Preliminary results indicate that information about fetal configuration and placental size is very useful in determining the cause and severity of IUGR. Thus far, TIUV, compared with BPD, is an extremely accurate predictor of IUGR in clinically-at-risk pregnancies.

2.45 p.m. 23 Renal Function in the Term Human Fetus
Juriy W. Wladimiroff, Leen C. v. Otterlo and Henk C. S. Wallenburg
Department of Obstetrics-Gynecology, Erasmus University, AZR-Dijkzigt, Rotterdam

Fetal urine production rate depends on the glomerular filtration rate (GFR) of plasma and the percentage tubular reabsorption of water. The hourly fetal urine production rate (HFUPR) was measured by means of ultrasound. The plasma GFR was estimated on the basis of the creatinine clearance. The latter was calculated from (a) the HFUPR within 24 h before delivery. The HFUPR does not change over this period of time and is not influenced by the process of delivery; (b) the creatinine concentration in umbilical cord plasma. No separate sampling of arterial and venous blood took place since in a pilot study of 18 normal term pregnancies no statistical difference between creatinine concentration in umbilical arterial and venous plasma was found; (c) the creatinine concentration in urine passed by the newborn within 5 min after delivery. This was considered fetal urine. The percentage tubular reabsorption was calculated from the HFUPR and GFR. In normal pregnancy (39–42 weeks; in 25 cases) creatinine
concentration in umbilical cord plasma varied from 62 to 99 µmol/l and in fetal urine from 500 to 1,100 µmol/l (within normal range). HFUPR varied from 18 to 29 ml, the vast majority of these values (22) were within the 5% tolerance limits of our standard curve (25–41 weeks; 170 cases). The GFR of plasma varied from 2.0 to 7.1 ml/min (mean 4.1), which is equivalent to 15.8–58.2 ml/min/1.73 m² (mean 33.3). The percentage tubular reabsorption of water varied from 84.1 to 93.0 (mean 89.8). In 4 growth retarded fetuses (birth weight < 10%; 37–38 weeks), GFR varied from 0.5 to 3.2 ml/min and the percentage tubular reabsorption from 85.3 to 93.4.

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23 3 to 3.15 p.m. Intermission
3.15 p.m.

24 Uterine Production Rate of Prostaglandin during Estrogen-Induced Vasodilatation
D.R. Meldrum, K.E. Clark, D.E. Van Orden, J.R. Woods, jr. and C.R. Brinkman, IIIDepartments of Obstetrics and Gynecology, UCLA and University of Iowa, Iowa City, Iowa

Although the uterine vasodilating effects of estrogens in pregnant and nonpregnant animals have been well established, the mechanisms of action are as yet unknown. Present studies were designed to investigate the role of prostaglandin E (PGE) as the possible mediator of estrogen action. Pregnant and nonpregnant ewes were chronically instrumented for measurement of total uterine flow and arterial pressure and for collection of systemic arterial, jugular and uterine venous blood. Control blood samples and flow values were obtained for 30 min before and at 30, 90, 120 min and 24 h after i.v. administration of 17β-estradiol. Plasma concentrations of PGE were analyzed by radioimmunoassay and uterine production rate was computed by the Fick equation. Results show: (a) uterine venous blood concentrations of PGE increase during estrogen-induced uterine vasodilation while arterial concentrations remain practically unchanged; (b) uterine production rate of PGE showed a 3- to 10-fold increase during peak estrogen effect and returned to near control values after estrogen action had subsided.

Conclusion: (1) estrogen appears to stimulate uterine production of PGE; (2) prostaglandin E may be the mediator of estrogen-induced uterine vasodilatation.

3.30 p.m.

25 24-Hour Rhythms in Uterine and Umbilical Blood Flows of Pregnant Sheep
Adrian M. Walker, Gary K. Oakes, Richard A. Ehrenkranz, Margaret McLaughlin and Ronald A. Chez
Pregnancy Research Branch, NICHD, NIH, Bethesda, Md.

We questioned whether a 24 h rhythm exists in uterine blood flow (UtBF) and umbilical blood flow (UmBF) in near-term pregnant sheep with no uterine activity. In five Dorset ewes of 122–128 days gestation, electromagnetic flow transducers were applied to the main uterine artery of the pregnant horn and to the intraabdominal common umbilical vein. Polyvinyl catheters were placed in maternal and fetal arteries and in the amniotic cavity. Studies were performed 5 days postoperation with a total 7–10 days laboratory acclimation. Ambient temperatures of 68–72 °F and 12 h light-dark (L-D) cycles equated to the seasonal conditions. Data collected at 15-min intervals over 24 h from 08.00 h were analyzed by fitting a Fourier curve with first and second harmonic cycles of 24 and 12 h periods.

The following observations were made: (1) UtBF had a 24 h rhythm (n = 5, p < 0.05) which was not synchronous with L-D cycle; (2) UmBF had a 24 h rhythm (n = 4, p < 0.05) which was not synchronous with L-D cycle; (3) the UmBF 24 h rhythm was antisynchronous with the UtBF 24
3.45 p.m. 26 Effects of MgSO4 on Uteroplacental Circulation in Normotensive and Hypertensive Pregnant Sheep

A. Dandavino, JR. Woods, Jr., K. Murayama, C.R. Brinkman, III and N.S. Assali UCLA School of Medicine, Department of Obstetrics-Gynecology, Los Angeles, Calif.

Despite extensive use of MgSO4 in obstetrics, very little is known about its effects on uteroplacental circulation. Present studies deal with hemodynamic effects of two dosage schedules of MgSO4, in normotensive and renal hypertensive pregnant animals. Pregnant sheep (70–100 days) were chronically instrumented for measurement of arterial pressure (AP), heart rate (HR), total uteroplacental blood flow (UPQ) and renal flow (RQ) (hypertensive animals) and divided in two groups. Hypertensive animals were studied before and after production of experimental hypertension by unilateral renal artery constriction and contralateral nephrectomy.

MgSO4 was given intravenously in bolus injections of 2 and 4 g, followed by continuous infusion of 1–4 g/h, for 2 h; Mg blood levels were monitored. Results show: (a) in normotensive animals, a 10% transient decrease in AP occurred about 2 min after a priming dose but returned to control levels within 5–10 min; HR remained unchanged while UPQ increased 7–15%, particularly after the larger doses; (b) in hypertensive animals, AP fall was similar to normotensive animals, but UPQ and RQ did not change significantly. Conclusions: (a) bolus intravenous administration of MgSO4 results in a transient decrease in AP; (b) normotensive animal has increased UPQ directly related to the MgSO4 concentration infused; (c) UPQ and RQ are not affected by MgSO4 infusion in hypertensive animals.

(Supported by USPHS grant HL-13634; AE Dandavino was supported by the Medical Research Council of Canada.)

4 p.m. 27 Effect of Propranolol Infusion on Sheep Umbilical and Uterine Circulations


Pregnancy Research Branch, NICHD, NIH, Bethesda, Md.

The hemodynamic effects of intravenous propranolol, a β-receptor-blocking agent, were studied in chronically-instrumented Dorset sheep. At 117–121 days gestation, electromagnetic now transducers were applied to the intraabdominal common umbilical vein and the main uterine artery of the pregnant horn. Catheters were placed in maternal and fetal arteries. At 7–13 days postoperation, propranolol was infused intravenously for 60 min to mother (4 µg/kg/min) or fetus (10 µg/kg/min). Data were recorded during a 30-min control, a 60-min infusion, and a 300-min postinfusion period. Umbilical blood flow (UmBF) progressively decreased in both the maternal (n = 5) and fetal (n = 5) infusions to 19 ± 2 and 18 ± 2% below control, respectively (mean ± SEM; p < 0.001) at the end of the infusion. The UmBF did not return to control levels until 180–300 min, mean 210 min. There was no change in fetal arterial pressure (FAP), nor uterine blood flow, maternal arterial pressure, or fetal pH, pO2, pCO2, during either infusion. With maternal infusion, the maternal heart rate (MHR) decreased 18 ± 2% at 60 min; the fetal heart rate (FHR) decreased 10 ± 2%. During fetal infusion, the FHR decreased 15 ± 2% at 60 min; the MHR did not change.
Umbilical vascular resistance (UmVR = FAP/UmBF) increased significantly during both maternal and fetal infusions. Respective peak increments of 25 ± 2 and 25 ± 3% occurred at 60 min of infusion. Control values of UmVR and UmBF were reached simultaneously late in the recovery period. Thus, basal umbilical blood flow may be affected by tonic /β-adrenergic activity in the umbilical vascular bed.

4.15 p.m. 28 Effect of the Prostaglandin Synthetase Inhibitor Meclofenamate on Estrogen-Induced Increases in Uterine Blood Flow in Sheep
K.E. Clark, D.E. Van Orden, D.R. Meldrum, M.J. Brody and C.R. Brinkman, HI Departments of Obstetrics-Gynecology and Pharmacology, University of IA, College of Medicine, Iowa City, Iowa, and Department of Obstetrics-Gynecology, School of Medicine, University of CA at Los Angeles, Los Angeles, Calif.

Earlier studies from these laboratories (Prostaglandins 5: 267, 1974) using two prostaglandin synthesis inhibitors, meclofenamate and indomethacin, suggested that estrogen-induced uterine vasodilatation in rats is mediated in part by vasodilator prostaglandins. These prostaglandin synthesis inhibitors significantly attenuated the estrogen-induced uterine vasodilation observed in rats 2 h after estradiol-170. In the present investigations, non-pregnant chronically-instrumented sheep were used to study the effect of prostaglandin synthesis inhibitors on estrogen-induced increases in uterine blood flow. This model allowed the continuous measurement of uterine blood flow and the local administration of prostaglandin synthesis inhibitors. Electromagnetic flow probes were chronically implanted on the uterine artery and a lateral branch of the uterine artery was cannulated with a polyethylene catheter for intraarterial infusions of drugs. Infusion of estradiol-17/î (3 µg) into the uterine artery of unanesthetized sheep produced a significant increase in uterine blood flow. This increase was abolished by pretreatment with a continuous infusion of the prostaglandin synthesis inhibitor meclofenamate. In a second sheep, infusion of meclofenamate during the peak estrogen-induced increase in uterine blood flow resulted in a return of the uterine blood flow to preestrogen levels. These data suggest that synthesis of vasodilator prostaglandins is essential to the estrogen-induced increase in uterine blood flow.

4.30 p.m.
Business Meeting (members only)
Grand Ball Room – Bellevue Stratford Hotel

6.30 p.m. Reception
Museum of the University of Pennsylvania

7.30 p.m. Banquet
Museum of the University of Pennsylvania

Charter buses are available for transportation from the Bellevue Stratford Hotel to the Museum of the University of Pennsylvania. Reception and Banquet are supported, in part, by the Ortho Pharmaceutical Corporation and the G.D. Searle Company.

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Concurrent Session D
Thursday, March 25, 1976
Clover Room – Bellevue Stratford Hotel

1.45 to 4.30 p.m.
Moderators: LeRoy W. Heinrichs and Edward E. Wallach
1.45 p.m. 29 Regulation of Desoxycorticosterone (DOC) in Normal Pregnancy
Wolfram E. Nolten, Marshall D. Lindheimer, Suzanne Oparil, Patricia A. Rueckert and
Edward N. Ehrlich
University of Wisconsin, Madison, Wisc., and University of Chicago, Chicago, Ill.
DOC and aldosterone (Aid) secretion are increased in normal pregnancy. When sodium retention
is induced by ACTH, urinary Aid decreases but tetrahydro-DOC (THDOC) excretion rises. To
evaluate regulation of DOC secretion in pregnancy, effects of variations in salt intake,
dexamethasone (Dex) suppression and ACTH stimulation upon plasma DOC and urinary
THDOC were studied in normal third trimester women. Neither increasing sodium intake from
35 to 240 mEq/day, nor Dex substantially altered plasma DOC or urinary THDOC, although
plasma cortisol (F) was suppressed by Dex. ACTH increased THDOC from baseline 319.2 ± SE
55 to 697.4 ± 110 µg/day (normal nongravid 5–50 µg/day), but plasma DOC remained
unchanged: baseline 47.6 ± 5.8 ng%, post-ACTH 43.0 ± 5.8 ng% (normal nongravid < 10 ng%).
Plasma F and DOC are bound to transcortin (CBG) with almost the same avidity. Percent
binding of both corticoids was measured by charcoal adsorption. The increment in plasma F
induced by ACTH resulted in a sharp rise in the free fraction of F (35–48 %) and DOC (43–69
%). The free DOC index (total DOC concentration × percent-free DOC/100) increased with
ACTH from 20 to 30, although total plasma DOC was unchanged.
Plasma DOC remains elevated in pregnancy despite volume expansion and Dex. Non-
suppressibility of DOC during pregnancy raises the question whether it contributes to salt
retention in certain complications of gestation. Although total plasma DOC is not increased by
ACTH, the free fraction of DOC rises because of displacement from CBG by F. This increase in
biologically active DOC could contribute to salt retention and account for increased THDOC
during ACTH.

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2 p.m. 30 Angiotensin II (AH) Response to Positional Change in Pregnancy-Induced
Hypertension (PIH) R.H. Hayashiand R.A. Becker
Departments of Obstetrics-Gynecology and Medicine, The University of Texas Health Science
Center, San Antonio, Tex.
The response of endogenous AH to lateral to supine positional change was investigated in a
prospective study of 37 primigravidas during the last half of pregnancy. Of these patients, 25
developed PIH, but none had clinically detectable disease during the study period. At monthly
intervals, AH levels were obtained following stabilization of blood pressure in the lateral
recumbent position (after 10 min) and the supine position (after 5 min). Between 29 and 34
weeks gestation, a significant difference (p < 0.02) was found in mean supine All levels between
control (n = 10) and PIH (n = 16) patient measurements. Between 20 and 40 weeks, a similar
difference (p < 0.02) was found in overall mean supine All levels between control (n = 18) and
PIH (n = 48). In addition, the mean percent relative change of All from lateral to supine was
significantly different (p < 0.01) at 20–28 weeks († 3/17) compared to 35–40 weeks († 13/18) in
PIH but not controls.

Gesta- Mean (± SE) All pg/ml lat./sup.  Mean percent relative Δ All
tion lat. → sup.

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† Significant difference at 20–28 weeks compared to 35–40 weeks in PIH but not controls.
Conclusion: Patients who develop PIH have higher supine All levels and demonstrate increased All responsiveness to positional change. These relationships may be of etiologic significance in pregnancy-induced hypertension.

2.15 p.m. 31 Alterations in Maternal Calcitonin (CT) and Parathyroid Hormone (PTH) during Gestation
W. Ann Reynolds, Roy M. Pitkin, Gerald A. Williams, Gary K. H'argis, Anne R. Baumann and Wanda Kawahara
Departments of Anatomy and Medicine, University of Illinois College of Medicine and West Side VA Hospital, Chicago, 111., and Department of Obstetrics-Gynecology, University of Iowa College of Medicine, Iowa City, Iowa
Pregnancy is associated with profound changes in calcium metabolism, probably related to both maternal endocrinologic adjustments and extensive fetal requirements for this
cation. Maternal total serum calcium levels diminish as pregnancy progresses; less well known is the interplay between calcitonin and parathyroid hormone during this time.
Duplicate samples (plasma for CT and serum for PTH) were obtained cross-sectionally from women at various stages of normal gestations. PTH and CT were measured by radio-
πmunoassay and calcium levels assessed. As would be anticipated, total calcium levels diminished during gestation to a level (8.8 mg/dl) significantly below control values (9.2 mg/dl). Serum PTH levels increased with increasing gestation, reaching a maximum of 7.2 µl-Eq/ml during the third trimester, significantly above the control nonpregnant value (6.2 µl-Eq/ml). Plasma CT was significantly diminished below the control mean (0.22 ng/ml) throughout gestation. There was a significant increase in plasma CT in the middle trimester (to 0.18 ng/ml) above first (0.13 ng/ml) and third (0.15 ng/ml) trimester values. This interesting observation, which represents the first report of CT levels throughout pregnancy, has been supported by studies in the pregnant rhesus monkey, where Δ CT in response to calcium infusion is larger in mid than early or late gestation.

2.30 p.m. 32 Sex Differences of Amniotic Fluid Androgens and Estrogens at Mid-Gestation
Philip E. Young, Howard L. Judd, Jill D. Robinson, Oliver W. Jones and Samuel S.C. Yen
Department of Reproductive Medicine, University of California San Diego School of Medicine, La Jolla, Calif.
The following study was performed to (1) determine if endocrine function of the fetal gonad is present at the time of or shortly after gonadal organogenesis and (2) evaluate if amniotic fluid (AF) androgen and estrogen levels reflect this activity. AF samples were obtained from 48 male and 72 female fetal pregnancies between 14 and 20 weeks gestation. The sex of each fetus was determined either at birth or if undelivered by the karyotype of AF cells. Each sample was measured for testosterone (T), androstenedione (Δ), dehydro-epiandrosterone (DHEA), estrone (E,) and 17(3-estradiol (E2) and the results in pg/ml are shown below:
For each hormone no difference was found in the AF level during any 1 week gestation in comparison to any other for either sex.

These data show that (1) AF levels of T and Δ but not DHEA are significantly higher in male, while E2 but not E, levels are higher in female fetal pregnancies. These differences presumably reflect fetal gonadal activity and suggest that the fetal ovary as well as the testes is endocrinologically active during mid-gestation. This is particularly intriguing since ovarian organogenesis is thought to begin about 11–12 weeks gestation and is not complete until 20–25 weeks. (2) Measurement of AF androgen and estrogen levels appears to be a useful technique for assessing the endocrine function of the fetal gonad.

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2.45 p.m. 33 Oxytocin Levels in Mother and Fetus during Parturition
M. Yusoff Dawood, Celeste Pociask, K. Srinivasa Raghavan and Fritz Fuchs Department of Obstetrics-Gynecology, Cornell University Medical College, New York, N.Y.
Plasma oxytocin was measured by radioimmunoassay using oxytocin antibody raised in rabbits and rabbit anti-7-globulin from goats to separate bound and free hormone. The oxytocin was extracted from the plasma with Fuller’s earth prior to assay. The sensitivity of the assay was 10 pg. During pregnancy, circulating maternal oxytocin ranged from un-detectable (even using 8 ml of plasma to extract oxytocin) to as much as 24 pg/ml. In patients with normal labor, maternal plasma concentrations ranged from 0 44.3 pg/ml during the first stage of labor, increasing fivefold to 18.8 140.0 pg/ml at delivery and falling sharply to 3.9–93.8 pg/ml during the placental stage. Women undergoing elective cesarean section had lower levels (0 20.4 pg/ml)
than women who had emergency sections (30.8–151.7 pg/ml). Umbilical venous plasma levels were 0.26.9 pg/ml after elective section, 3.6–125.0 pg/ml after emergency section during labor and 6.3–107.5 pg/ml after spontaneous vaginal delivery. The umbilical arterial plasma concentrations were 11.5–77.5, 45.3–344.8, and 18.3–350.0 pg/ml respectively in the three groups. Amniotic fluid oxytocin concentrations at elective sections ranged from undetectable levels to 8.8 pg/ml. The umbilical arteriovenous difference clearly demonstrated fetal origin of the oxytocin and in addition, suggested the possibility of placental transfer to the mother.

3 to 3.15 p.m. Intermission

3.15 p.m. 34 Effects of Dopamine (DA) Infusion on Pituitary and Pancreatic Hormone Secretion in Humans
H. Leblanc, G.C. Lachelin, S. Abu-Fadiland S.S.C. Yen Department of Reproductive Medicine, UCSD, La Jolla, Calif.

The importance of catecholamines in the regulation of pituitary hormone secretion and the pancreatic release of insulin and glucagon have recently been amplified, but the effect of peripherally administered DA on the secretion of pituitary and pancreatic hormones has not been explored. DA infused at a rate of 4 µg/kg/min × 3 h unaccompanied by significant changes in cardiovascular dynamics induced (1) a prompt suppression of PRL levels in normal men (20 %, n = 4), normal women (33 %, n = 4) as well as in patients with hyperpro-lactinemia (45 %, n = 4). The net reduction of PRL concentration was 9-fold greater in hyperprolactinemic women (45 ng/ml) than in normal women (5 ng/ml). A rise in GH levels during the infusion was also observed. At the discontinuation of the infusion, there was a marked rebound in PRL levels in normals and a rapid return to basal levels in hyperprolactinemic patients. DA infusion elicited no changes in serum LH, FSH and TSH levels; (2) a prompt (15 min) and significant increase in the release of insulin and glucagon and significant elevation of plasma glucose concentrations (n = 9). Food administered at the middle of the 4h DA infusion (n = 4) induced a further rise in plasma glucose and insulin but a profound suppression of glucagon secretion. Thus, an increase in circulating metabolic fuels can overcome this DA effect on the pancreas. It is concluded that a dopaminergic role exists in the regulation of pituitary PRL and GH release as well as in the pancreatic α- and β-cell function.

3.30 p.m. 35 Influence of Prolactin Secretion on Human Ovarian Luteal Function
John E. Tyson, Howard A. Zacur and Emilio A. Leontic
Department of Obstetrics-Gynecology, Johns Hopkins University School of Medicine, Baltimore, Md.

The endocrine milieu of most cases of galactorrhea-amenorrhea (GA) is similar to that of the early puerperium, namely hyperprolactinemia and impaired cyclic gonadotropin secretion. The precise mechanisms governing such changes are unclear. In a study of GA, a specific subgroup of women was identified whose mean daily HPRL concentration exceeded 60 ng/ml but in whom cyclic menstruation was observed. Thyroid and adrenal function in these women was normal. Daily blood sampling through as many as three menstrual cycles revealed follicular phase estradiol concentrations comparable to those of normally menstruating women. Furthermore, cyclic gonadotropin peaks in the range of normal were observed and daily fluctuations in tonic gonadotropin secretion remained intact. Unfortunately, mean peak plasma progesterone concentrations rarely exceeded 8 ng/ml and the luteal phase was invariably shortened (6–9 days) accompanied by a monophasic basal temperature chart. The administration of the dopamine
agonist, 2-Br-α-ergocryptine, was followed by inhibition of mean basal HPRL concentrations to below 40 ng/ml; in response to which cyclic gonadotropin secretion remained unchanged with enhanced progesterone secretion and a prolongation of the luteal phase interval. These data imply a luteolytic role for HPRL when concentrations exceed the physiologic range. Moreover, LH secretion is not affected by hyperprolactinemia suggesting neither an inverse relationship for HLH-HPRL secretion nor an inhibitory role for HPRL on cyclic gonadotropin secretion. The results further suggest a possible mechanism for infertility in the immediate puerperium.

3.45 p.m. 36 Prevention of Ovulation in Rabbits by Antihistamine G. Eric Knox and Lee R. Beck University of Alabama, Birmingham, Ala.

This study was undertaken to examine the possibility that antihistamine (chlortrimeton) could inhibit ovulation in the rabbit. Estrous female rabbits were injected with either chlortrimeton (10 mg/kg i.m.) (n = 10) every 4 h beginning at time 0 and continuing for 96 h. HCG (100 IU i.v.) was injected into all animals at 48 h. Serum samples were collected at 0, 24, 48, 72, 96 and 144 h and assayed for total immunoreactive serum estrogens and progestins by radioimmunoassay. Ovaries were removed on day 10 for morphological and histological examination. The mean number of ovarian corpora lutea observed in rabbits treated with antihistamine (0.9 ± 0.72) are significantly less than in controls (10.2 ± 2.27) (p < 0.001). Ovaries from rabbits treated with antihistamine contained multiple large hemorrhagic follicles with retained ova and no histological evidence of lutein-ized granulosa cells. Serum levels of estrogen in treated and control animals were similar at each determination (54 ± 9.4 ng/ml). No significant amount of serum progestin was found in rabbits treated with antihistamine and HCG. In control rabbits, levels of progestins increased to a maximum of 7.2 ± 2.4 ng/ml at 144 h following HCG and were significantly different from controls at 96 and 144 h (p < 0.01). Ovaries from rabbits treated with antihistamine contained multiple large hemorrhagic follicles with retained ova and no histological evidence of lutein-ized granulosa cells. Serum levels of estrogen in treated and control animals were similar at each determination (54 ± 9.4 ng/ml). No significant amount of serum progestin was found in rabbits treated with antihistamine and HCG. In control rabbits, levels of progestins increased to a maximum of 7.2 ± 2.4 ng/ml at 144 h following HCG and were significantly different from controls at 96 and 144 h (p < 0.01). Similar results were obtained using mating rather than HCG as the ovulatory stimulus (n = 6). These morphological, endocrinological, and histological findings all suggest that antihistamine has the ability to inhibit ovulation in the rabbit.

4 p.m. 37 Ovulation in the Perfused Rabbit Ovary: the Influence of PGs and PG Inhibitors Yasuo Hamada, Richard Bronson, Karen Wright and Edward E. Wallach Department of Obstetrics and Gynecology, Pennsylvania Hospital and University of Pennsylvania School of Medicine, Philadelphia, Pa.

Ovulation has been achieved in vitro in the isolated perfused rabbit ovary. The ovarian artery is cannulated 8 h after HCG administration and the ovary perfused and removed for in vitro study. The effects on ovulation of the addition of PGE2, PGF2α, indomethacin and HCG to the perfusate were studied. Ovulation occurred in 8 of 12 perfused ovaries in the control group (no drug), 7 of 12 in the group perfused with supplementary HCG (1 IU/ml), 11 of 12 with PGF2α (1 µg/ml), 3 of 12 with PGE2 (1 µg/ml) and 2 of 12 with indomethacin (0.5 µg/ml). Ovulation always occurred in the contralateral ovary which remained in situ as an in vivo control. Addition of indomethacin to the perfusate reduced the incidence of ovulation in vitro when compared to the control group (p < 0.01). Ovulation was also reduced (p < 0.005) when the ovaries treated with indomethacin were compared to those with PGF2α, and when PGE2 was compared to PGI2α (p < 0.001). These observations indicate that the presence of PGF2α within the ovary may be essential to the process of ovulation. The inhibitory effects of indomethacin and PGE2 on ovulation in the perfused in vitro rabbit ovary parallel previous observations in the intact HCG-
treated rabbit. The use of the perfused preparation provides additional evidence that the inhibitory effects of indomethacin and PGE, on ovulation are mediated at the ovarian level.

4.15 p.m. 38 PGF and E2 in Progesterone-Induced in vitro Ovulation Theodore Fainstat and Richard J. Baranczuk

Department of Obstetrics-Gynecology, University of Kansas Medical Center, Kansas City, Kans. The objective of this study was to determine whether progesterone could advance the time that follicles might be induced to ovulate in vitro, and to add insight into sequential interplay and action among gonadotropins, E2, PGF and P4, upon the follicle that ultimately ovulates. After 3 consecutive estrous cycles, mature hamster ovaries were explanted at selected times on proestrus from 12.00 to 24.00 h into chemically defined media ± P4. Explants were incubated at 37 °C until 10.00 h of estrus. E2 and PGF were assayed by RIA techniques. In vitro ovulation (IVO) occurred constantly with a normal in vivo complement of ova in those ovaries explanted after 22.00 h and incubated with P4. Ovaries explanted before 21.00 h or incubated without P4 failed to ovulate or ovulated sporadically with less than a normal number of ova. Furthermore, in vitro ovulation was induced in younger follicles by adding P4 to incubation medium. Significant divergence of PGF patterns was documented in incubation medium ± P4 about ovulation time (24.00 h ± 01.00). With P4 in the medium, PGF levels were significantly lower at ovulation time and higher (2.4 ng/ml medium/ovary) for several hours earlier. In media without P4, the peak level of PGF (6 ng/ml medium/ovary) was at 24.00 h. E2 levels of both groups paralleled each other with peak levels (3 ng/ml/ovary) in both from explantations at 15.00 h; E2 levels then declined, reaching the lowest levels from explantations at 24.00 h. P4 can induce ovulation in vitro, advance ovulation several hours, and promote a higher PG level in incubation medium several hours prior to ovulation and a lower level at ovulation time.

4.30 p.m.

Business Meeting (members only)
Grand Ball Room – Bellevue Stratford Hotel
6.30 p.m. Reception
Museum of the University of Pennsylvania
7.30 p.m. Banquet
Museum of the University of Pennsylvania
Charter buses are available for transportation from the Bellevue Stratford Hotel to the Museum of the University of Pennsylvania. Reception and Banquet are supported, in part, by the Ortho Pharmaceutical Corporation and the G.D. Searle Company.

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Concurrent Session E
Thursday, March 25, 1976
Red Room – Bellevue Stratford Hotel
1.45 to 4.30 p.m.
Moderators: Mortimer L·evitz and CarlJ. Pauerstein
1.45 p.m. 39 Synthesis of 4-Bromoacetamidoestrone 3-Methyl Ether and Study of the Steroid Binding Site of Human Placental Estradiol 17/3-Dehydrogenase
Yudhister M. Bhatnagar, Chang-Chen Chin and James C. Warren
Homogeneous estradiol 17α-dehydrogenase (EC 1.1.1.62), specific activity 7.1 U/mg, was prepared from human placenta as previously described (Steroids 22: 373, 1973). 4-Bromoacetamidoestrone 3-methyl ether was synthesized to affinity label the enzyme for study of the topography of the active site. 4-Aminoestrone 3-methyl ether and bromoaetoic acid were reacted with dicyclohexyl carbodiimide in methylene chloride at room temperature. The crude product was recrystalized from ethanol, and structure assured by IR and UV spectroscopy and elemental analysis (m.p. 162–164 °C; yield, 30%). As the steroid is a substrate for the enzyme, it must bind at the active site. When 1.45 X 10^{-6} M enzyme was incubated at 25 °C with 2.17 × 10^{-5} M steroid in alcoholic 0.05 M potassium phosphate buffer at pH 7.0, the enzyme was inactivated in a time-dependent, irreversible manner. The inactivation followed pseudo first-order kinetics with $t_1/2 = 5'/2$ h. 3H-4-bromoacetamido-estrone 3-methyl ether, synthesized using (2-3H)bromoacetic acid similarly inactivated the enzyme. Aliquots were taken at 25, 59 and 80 % inactivation; total radioactivity bound to the protein indicated stoichiometry of 1 mol of carboxymethyl group incorporated per mole of enzyme inactivated. Amino acid analysis of a hydrolysate of the enzyme which had been inactivated with 3H-4-bromoacetamidoestrone 3-methyl ether reveals 30 % carboxymethyl cysteine and 70 % e-carboxymethyl lysine. These observations indicate that enzyme cysteine and lysine residues proximate the 4-position of the steroid as it binds at the enzyme active site.

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2 p.m. 40 Synthesis of 16α-Bromoacetoxy-6α-methyl-17α-hydroxyprogesterone (16α-BAMHP), and Other Provera Analogs for Study of Their Affect on Pregnancy
Frederick Sweet, Steven W. Clark and James C. Warren
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.

Previously, we described the termination of early pregnancy in rats with 16α-bromoacetoxypregesterone (Biol. Reprod. 11: 519, 1974). 16α-BAP, which is a powerful alkylating agent, inactivates the progesterone-binding enzyme 20j3-hydroxysteroid dehydrogenase (EC 1.1.53) in a time-dependent and irreversible manner (J. biol. Chem. 247: 3424, 1972). This property characterizes affinity-labeling progesterone derivatives. To further explore the affect of such steroids on pregnancy, 6α-methyl-Δ16-dehydroprogesterone was converted, in two synthetic steps, to 16α-bromoacetoxy-6α-methyl-17α-hydroxyprogesterone (16α-BAMHP), a Provera analog. 16α-BAMHP alkylates nucleophilic amino acids and inactivates 20/3-hydroxysteroid dehydrogenase, in an almost identical manner compared with 1βα-BAP. However, under similar experimental conditions 1βα-BAMHP does not terminate pregnancy in rats. The in vivo and in vitro results from the two affinity-labeling steroids are compared and a rationale given to account for the differences.

2.15 p.m. 41 Effects of Estradiol on the Rate of Degradation of Glucose-6-P Dehydrogenase in the Rat Uterus
Kenneth L. Barker and Edward R. Smith
University of Nebraska College of Medicine, Departments of Obstetrics-Gynecology and Biochemistry, Omaha, Nebr.

Administration of estradiol (E2) to the ovariectomized mature rat causes an increase in the rate of uterine protein synthesis. Direct measurement of the effects of E2 on the rate of incorporation
of 14C-amino acids into immunoprecipitable uterine glucose-6-P dehydrogenase (G6PD) indicates that the de novo rate of synthesis of the enzyme is increased 18-fold by E2 (J. biol. Chem. 249: 6541, 1974). The present study was undertaken to determine whether or not E2 might also influence the rate of degradation of uterine G6PD. Total uterine proteins were prelabeled by intrauterine administration of 10 µCi of l-14C-glutamate per rat. After clearance of the precursor from the tissue the rate of loss of 14C from immunoprecipitable uterine G6PD apoprotein was determined. The t½ of uterine G6PD was found to be 24 h in control animals and degradation of the enzyme was totally inhibited by administration of E2. Uterine pools of 14C-precursor were monitored at all times to assure that E2 stimulation of precursor reincorporation was not a contributing factor in the results. The duration of the inhibition of uterine G6PD degradation by E2 is 30–36 h which coincides with the period of time that this enzyme increases after a single E2 injection. Thus, the mechanism of induction of this uterine enzyme by E2 is both stimulation of the rate of enzyme synthesis and inhibition of the rate of enzyme degradation. The mechanism underlying this effect of E2 on uterine G6PD degradation is uncertain but it may be a consequence of the cytoplasmic depletion of lysosomes as they migrate to the nucleus in response to E2 as observed by Szego (Recent Prog. Horm. Res. 30: 171, 1974).

(Supported by NIH grant HD 02851.)

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2:30 p.m.

42 Uterine Amino Acid Uptake in Pregnant Sheep
Frank H. Morris, jr., Eugene W. Adcock, II and Charles L. Paxson
Departments of Pediatrics and Obstetrics-Gynecology, University of Texas Medical
School at Houston, Houston, Tex.

To determine the role of the uterine uptake of 23 individual amino acids (Qaa) during rapid growth of the uterine contents, 9 pregnant ewes were prepared with chronically implanted bilateral uterine artery electromagnetic flow transducers and with femoral artery and bilateral uterine vein catheters. Following recovery and during optimal nutritional intake, 53 determinations of Qaa were obtained from 40 to 145 days gestational age (GA) employing the Fick principle and automated ion-exchange column chromatography.

The x Qaa for all studies was 55.2 ± 15.7 (SEM) µAl/min. Qaa did not change with GA, but exhibited great variability from day to day in each ewe, unrelated to blood (glucose) or (amino acids). A striking difference was observed between twin and singleton gestations which may be important in the pathophysiology of intrauterine growth retardation. Qaa/day/kg of uterus and contents was significantly less for ewes with twins, including growth-retarded fetuses:

Singleton gestation: 26.4 mAl/day/kg
Twin gestation: 14.8 mAl/day/kg

The nitrogen provided by Qaa was 0.55 g/day/kg uterus and contents at a x GA of 112 days. Glutamine (16%), arginine (12%), citrulline (9%), 1-methyl histidine (7%), taurine (7 %), lysine (6 %), leucine (6 %), asparagine (5 %), histidine (5 %), and alanine (5 %) provided 78 % of the total amino acid nitrogen uptake by the uterus. Aspartate had a negative uterine uptake.

(Aided by a Basil O’Connor Starter Research Grant from The National Foundation, March of Dimes.)
Study of the Steroid Binding Site of Estradiol-17/3 Dehydrogenase by Difference Spectroscopy
Jung-Teh Lo and James C. Warren
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.

Homogeneous human placental estradiol-170 dehydrogenase was purified by affinity chromatography as described by Chin et al. (Steroids 22: 373, 1973). Difference spectroscopy was used to search for chromophore amino acid residues perturbed by the binding of steroid and therefore possibly at or close to the steroid binding site. Estradiol-17/3, a substrate of the enzyme, produced a difference spectrum with a strong peak at 292 nm, a weak peak at 283 nm, and a very weak shoulder at 273 nm when it is added to the enzyme solution (in phosphate buffer, pH 7.0, containing 20 % glycerol). The intensity of the difference spectrum was dependent on both enzyme and substrate concentrations. The difference spectrum is similar to the solvent perturbation difference spectrum of tryptophan produced by glycerol. The dissociation constant ($K_s$) of the enzyme-substrate complex was determined by measuring the difference spectrum as a function of substrate concentration. Estrone, another substrate of the enzyme, produced a similar difference spectrum, but with weaker intensities than in the case of estradiol-17/3. However, estradiol-3-methyl ether and testosterone (also enzyme substrates) when incubated with the enzyme produced no difference spectrum in the 270–295 nm range. These results indicate that binding of estra-diol-17/3 at the steroid binding site perturbs a tryptophanyl residue and suggests that this residue proximates the 3-position of the steroid.

3 to 3.15 p.m. Intermission

3.15 p.m. 44 Creatine: Transport by Human Placentae
Richard K. Miller, Kathleen A. Reich, Harold E. Fox, Barbara M. Davis, Robert L. Brent and Thomas R. Koszalka

The placental movement of creatine (CR) in man is characterized using both in vitro slice technics (Am. J. Physiol. 227: 1236, 1974) and in vivo measurements of CR blood levels. In vitro CR-$^{12}$C is concentrated within the human term placental slice to an intra-cellular to extracellular water distribution ratio of 2.51 ± 0.16. This uptake of CR is depressed by dinitrophenol (DNP) (10$^{-4}$ M), N2 (100 %) and ouabain (OU) (10$^{-5}$ M). Glucose (10$^{-2}$ M) prevents the inhibition of uptake by DNP or N2, but did not alter the OU effect. The removal of Na or K from the incubation medium also decreases CR uptake. Guanidino compounds (3-guanidinopropionic acid, guanidinoacetic acid, W-amidino alanine, $\gamma$-guanidinobutyric acid) reduce the uptake of CR, while amino acids ($\alpha$-alanine, $\alpha$-aminoisobutyric acid, methionine, glutamine) do not. Both a saturable uptake process for CR and a diffusional transfer process are demonstrated by Michaelis-Menten kinetics. In vivo, the cord venous blood levels are 41 % higher than the maternal venous blood levels; in addition, the fetal venous plasma levels and placental tissue levels or CR are greater than the maternal plasma levels. Thus, these combined in vitro and in vivo data in man indicate the presence of a saturable concentrative transport process for CR between mother and fetus, which requires energy.
(anaerobic or aerobic), Na, K, Mg-dependent, Na + K-activated ATPase and is specific for
guanidino compounds.
(Supported by GRSG No. RR-05403, HD06360, HD630.)
3:30 p.m. 45 Involvement of Adrenal-Derived Plasma Estradiol in the Regulation of the Uterine
Response to Estradiol
Tran T. Hung and Kenneth L. Barker
University of Nebraska College of Medicine, Departments of Obstetrics-Gynecology
and Biochemistry, Omaha, Nebr.
Fasting (F) and feeding a protein-free diet (PFD) causes an increase in the estradiol (E2)
inducibility of glucose-6-P dehydrogenase (G6PD) activity in the uterus of the ovariectomized
(3–4 weeks) mature rat compared to normally fed rats. The increase is due to a
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2-fold greater rate of de novo G6PD synthesis in the E2-induced F and PFD groups relative to
the control-fed group. Further analysis of the uterus reveals that the E2 binding capacity in the
uterine cytosol is 18 and 30 % greater than controls and in the uterine nucleus is 24 and 21 %
greater than controls for animals in the F and PFD groups, respectively. Measurement of plasma
E2 levels revealed levels of 47 ± 8, 129 ± 24 and 124 ± 15 pg/ml plasma in control, F and PFD
groups, respectively. The inducibility of uterine G6PD (percent increase after injection of E2)
was correlated to (1) plasma E2 levels (before injection of exogenous E2) at r = 0.95 (p < 0.01);
(2) nuclear ‘E2 receptor’ concentration at r = 0.87 (p < 0.01), and (3) cytosol E2 receptor’
concentrations at r = 0.68 (NS). The increased plasma E2 in F and PFD groups appears to be
derived either directly or indirectly from the adrenal cortex since these dietary treatments cause
an increase in adrenal weights, a decrease in thymus weights and the circulating plasma E2 is
totally suppressed (< 10 pg/ml) by administration of dexamethasone. These results indicate that
the uterine response to E2 in ovariectomized mature rats is profoundly influenced by the
circulating levels of adrenal-derived plasma E2, which modulates ‘E2 receptor levels’ without
inducing a complete uterine response and that nutritional stress can be a significant causative
source of this modulation. (Supported by NIH grant HD 02851.)
3:45 p.m. 46 Etiology of XY Gonadal Dysgenesis
Joe L. Simpson, Robert L. Summitt, Irwin R. Merkatz and James German Department of
Obstetrics-Gynecology, Northwestern University, Chicago, 111; University of Tennessee,
Memphis, Tenn.; Case Western Reserve, Cleveland, Ohio, and The New York Blood Center,
New York, N.Y.
Gonadal dysgenesis associated with a 46, XY chromosomal complement (XY gonadal
dysgenesis) probably results from a mutant gene, but the mode of inheritance is uncertain and the
manner in which the mutant acts is unknown. The present investigation offers the strongest
evidence heretofore available that (1) the postulated mutant is inherited in X-linked recessive
fashion, and (2) 45, XY cells are unlikely to be detected in relatively inaccessible organs of
affected individuals.
Two sibs, their maternal first cousin, and probably their deceased maternal aunt were affected.
The sibs had bilateral streak gonads; the cousin and probably the aunt had bilateral gonadal
tumors. Approximately 100 cells were studied from cultures derived from the following: (1) sib
A lymphocytes, skin, various portions of both streak gonads; (2) sib B -lymphocytes, skin, right
round ligament, left Fallopian tube, both streak gonads; (3) cousin – lymphocytes, skin, both
gonadoblastomas. No45, X cell lines were detected. The Y-chromosome was normal by
quinacrine fluorescence. Y-chromatin but not X-chromatin masses were detected in buccal epithelial cells. Genetic analyses of this family and about 100 cases investigated by us and by others indicates that (1) XY gonadal dysgenesis is inherited in X-linked recessive fashion; (2) 25–30 % of affected individuals have an associated gonadoblastoma or dysgerminoma, and (3) even if the XY-gonadal dysgenesis mutant does act by causing monosomy, the monosomy is present in different cells and presumably arises at a different time than the monosomy present in 45, X gonadal dysgenesis.

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4 p.m. 47 Influence of the Epithelium-Zygote Interaction on RNA and Protein Synthesis in the Mouse Oviduct

Uwe E. Freese and Lawrence Devoe
Department of Obstetrics-Gynecology, Chicago Medical School, and Department of Obstetrics-Gynecology, University of Chicago, Chicago Lying-in Hospital, Chicago, 111.

Presumptive evidence for a zygote-epithelial interaction in the mouse oviduct, derived from our previous studies, was suggested by significant decreases in 3H-thymidine uptake in epithelial cells located in the region of the zygote. This observation, we hypothesized, represented conversion of these epithelial cells to another activity, i.e., protein synthesis.

To corroborate this theory, we studied mice divided into groups of control (nonpregnant), pseudopregnant, and superovulated, artificially inseminated pregnant populations. Each of these groups was divided into subgroups, one of which was injected with 3H-uridine, an RNA precursor nucleic acid, and the other with 3H-phenylalanine, an amino acid. In the case of both isotopes, highest overall epithelial labelling occurred in pregnant animals, with maximum specific labelling in the region actually occupied by the zygote. Both overall and local isotope uptakes in tubal epithelium were significantly greater in the pregnant than either pseudopregnant or nonpregnant groups.

We conclude that this data indicates the positive effect of a zygote-tubal epithelial interaction in the stimulation of basic RNA and protein synthesis in the oviduct.

4.15 p.m. 48 Relationship of Electrical Activity of the Rabbit Oviduct to Ovum Transport

Barrie J. Hodgson and Antti Talo
Department of Obstetrics Gynecology, University of Texas Health Science Center, San Antonio, Tex.

Electrical activity of the rabbit oviduct in vitro has been monitored using arrays of suction electrodes placed on the isthmus, ampullary isthmic junction and ampulla. Movements of surrogate ova within the oviduct correlate directly with direction of propagation of electrical activity in the same region. Movement of the ovum past the electrode sites may be accomplished either by a slight bias in the distance or number of contractions in one direction compared to those in the opposite direction, or by short periods of activity where phase lag is appropriate for unidirectional propagation of several contractions. Electrical activity in oviducts from postovulatory rabbits is generated by pacemakers with a frequency of about 150/h and activity propagates 2–3 mm, but distance of propagation and frequency are both location and hormonally dependent. Sphincteric effects at the ampullary-isthmic junction can be explained in terms of ‘trapping’ ova between two regions of high frequency and hence opposing bias. Electrical activity of the oviduct and control of ovum transport can be explained if it is considered to consist of a series of bidirectionally coupled relaxation oscillators.

4.30 p.m.
Distinguished Guest Lecture (made possible by a continuing grant from Ross Laboratories, Columbus, Ohio). ‘Studies on the Pathogenesis of Male Pseudohermaphroditism Due to Androgen Resistance.’ Jean D. Wilson, MD, Professor of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Texas.

9 to 10.15 a.m.
Moderators: Daniel R. Mishell, jr. and Samuel S.C. Yen
9 a.m. 49 Crystallization of Human Placental Estradiol 17β-Dehydrogenase: a New Method for Crystallizing Labile Enzymes
James C. Warren, Chang-Chen Chin and Joseph B. Dence
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.

Human placental estradiol 17β-Dehydrogenase has been prepared in homogeneous crystalline form. Crystallization was effected by a new technique which we call electro-phoretic diffusion; it amalgamates the principles of zone electrophoresis and membrane dialysis. This is the first crystallization of (a) an enzyme from human placenta, and (b) a steroid interconverting enzyme from human source. A solution of enzyme (SA = 7.1 U/mg) in tris-barbituric acid buffer, pH 7.0, with 20 % glycerol as stabilizer was placed in an electrophoresis tube. The tube was closed at both ends with a dialysis membrane which permits passage of substances of molec. wt. < 18,000. The tube was placed in a gel electrophoresis apparatus. Variable potential was applied over some 36 h until opalescence appeared at the bottom of the tube. When solution from the bottom of the tube was kept overnight at 4 °C, gross and microscopic examination revealed a heavy crop of crystals. The specific activity remained constant through three recrystallizations. The preparation displayed a single band in polyacrylamide and SDS gel analysis. The new technique should be applicable for crystallizing other labile enzymes and receptor proteins which have so far resisted crystallization by conventional methods. Further, availability of both the enzyme in crystalline form and 4-mercuri-estradiol-17β which we have previously synthesized permits ultimate elucidation of the topography of the steroid binding site by X-ray diffraction studies.
9.15 a.m. 50 Detection of Ovulation in the Pigtail Monkey with an Implantable Optical Transducer
Sheridan A. Halbert, Robert A. Steiner, Harvey S. Schiller, Pavel Illner, Charles C. Gale and Richard J. Blandau
Departments of Biology, Structure, Physiology and Biophysics, Obstetrics-Gynecology, Laboratory Medicine, and Regional Primate Research Center, University of Washington, Seattle, Wash.
Precise timing of ovulation in subhuman primate experimental models is crucial to fertility and contraception research. We now have a technique for detecting ovulation within minutes. In the pigtail monkey (M. nemestrina) the ovulated cumulus mass containing the egg is transported rapidly into and through the ampullar portion of the oviduct. The technique to be described detects the cumulus mass as it moves through the ampulla, thereby providing an accurate time of ovulation. An optical-electronic transducer is surgically implanted extraluminally on the oviduct near the infundibular ostium. It senses relative changes in light transmittance through the oviduct. The cumulus egg mass moving within the oviductal lumen causes an increase in light transmittance as it passes through the light path of the transducer. We have successfully recorded the passage of the cumulus egg mass in the chronically instrumented, intact, caged monkey by means of radiotelemetry. Serum LH and estradiol, measured by RIA, were estimated to have reached their peak concentrations at 36 and 60 h before ovulation, respectively, and a small preovulatory rise in serum progesterone was noted. This technology provides thus far unavailable information about the precise time of ovulation in relation to hormonal changes.
(Supported by NIH contract NOI-HD-2791 and grants NB-06622 and TI-HD-00272–10.)

9.30 a.m. 51 Catecholamine (CA) and Prolactin Secretion during Pregnancy of the Rat
TV. Ben-Jonathan, C. Oliver and J. C. Porter
Department of Obstetrics-Gynecology, Southwestern Medical School, Dallas, Tex.
Dopamine secretion by the hypothalamus into hypophysial portal blood and prolactin release by the pituitary during pregnancy were studied. Portal and arterial blood were collected from anesthetized pregnant rats, and dopamine, norepinephrine, and epinephrine were determined simultaneously in plasma by a radioenzymatic assay. In a parallel study, hypothalami and posterior pituitaries from pregnant rats were analyzed for CAs and systemic plasma and amniotic fluid were assayed for CAs and prolactin. The major CA in the hypothalamus was norepinephrine, whereas that in the posterior pituitary was dopamine. Dopamine was the only CA found in portal plasma, and was 5–30 times higher than in arterial plasma. During diestrus, dopamine in portal plasma was 0.6 ng/ml but was 6 ng/ml on day 1 of pregnancy. Dopamine in portal plasma reached 18 ng/ml on day 8, declined to 3–4 ng/ml on day 11, and then rose to 18–19 ng/ml on day 20. This was followed by a decline on day 22 – the day of parturition – and a further reduction after birth. During pregnancy, prolactin in systemic plasma was high on day 1 and day 22 but low during the rest of pregnancy. In systemic plasma of nonanesthetized pregnant rats, epinephrine levels were 10–15 ng/ml, norepinephrine 4–6 ng/ml, and dopamine 0.4–1 ng/ml. The major CA in amniotic fluid was dopamine, and its concentration rose from 2 ng/ml on day 15 to 20 ng/ml on day 22. Prolactin was not detectable in amniotic fluid. The data demonstrate a reciprocal relationship between dopamine levels in portal blood and prolactin levels in systemic blood during pregnancy and suggest a role for dopamine in regulating prolactin secretion.

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9.45 a.m. 52 Effect of Umbilical Vein Occlusion on Fetal EEG, Cardiovascular Parameters and Fetal Oxygenation
Wolfgang Kunzel, Leon I. Mann, Amrutha Bhakthavathsalan and John Ayromlooi Department of Obstetrics-Gynecology, State University of New York Medical School at Stony Brook, Nassau County Medical Center, East Meadow, N.Y.

In 9 fetal sheep experiments the BP in the fetal aorta (FA) and in the umbilical vein (UV), fetal heart rate (FHR), the pH, pCO2 and oxygen saturation (S02) in both fetal vessels and umbilical blood flow (Qumb) of the common UV were measured following umbilical vein occlusion (UVO). The fetal EEG was recorded continuously through the experiment. The results (n = 14) were grouped according to the response in FA S02 into moderate: (S02 > 40 %) (x 48.8, SD 6.5) and severe (S02 < 40 %) (x 18.6, SD 10.7). After 8–10 sec the fetal BP in FA increased. UV BP increased to 25 mm Hg (SD 8) and 35 mm Hg (SD 9) in the moderate and severe groups, respectively. As a result of the decreased perfusion pressure (FA UV BP) across the fetal side of the placenta the Qumb fell from 162 ml/kg/min (SD 65) and 134 ml/kg/min (SD 54) to 86 ml/kg/min (SD 52) and 39 ml/kg/min (SD 33), respectively. The fall in FA S02 was related to the decrease in Qumb: SC%fa = 30.1 X log Qumb – 12.4 (2a < 0.01). There was a mild decrease in S02 from 70 to 60 % when Qumb fell from 300 to 120 ml/kg/min. Below 80–120 ml/kg/min the fall in FA S02 was almost linear. The S02 in the UV remained constant so that arteriovenous difference for oxygen (AV D02) increased. Oxygen consumption decreased only when Qumb fell below 80–120 ml/kg/min. The fall in FHR was related to the fall in Qumb: FHR (% of control) = 66.1 ± 0.53 X Qumb (2< 0.01). The fetal EEG showed a slight decrease in voltage while the faster activities remained constant. From these observations it is concluded that a decrease in Qumb following UVO jeopardizes the fetus only if a critical Qumb (80–120 ml/kg/min) and S02FA (50–60 %) is achieved.

(Supported by UCPR&EF, MMERF, DFG-Germany.)

10 a.m. 53 Immunologic Benefits and Hazards of Milk in the Maternal–Perinatal Relationship
Judith R. Head and Alan E. Beer
Departments of Obstetrics and Gynecology and Cell Biology, University of Texas
Southwestern Medical School, Dallas, Tex.

Apart from its nutritional significance, milk affords infant mammals immunologic benefits; however, it is not without immunologically based hazards. Viable lymphocytes are normal ingredients of colostrum and milk. Controlled foster nursing and other experiments in inbred strains of rats and mice have been conducted to investigate the immunologic consequences of this maternal to neonatal cellular transaction. It has been found that: (1) milk is a neglected source of T lymphocytes in congenitally athymic nude mice. Nude mice allowed to suckle on their own syngeneic Balb/c mother live significantly longer than those transferred immediately after birth to unrelated C57 mothers. All fostered nude mice die of a wasting disease before weaning. (2) Milk lymphocytes from an allogeneic foster mother confer resistance to tumor growth in susceptible hosts. C57 perinates suckled on their own syngeneic mother and subsequently inoculated subcutaneously with a C57 Leydig cell tumor succumb to the tumor within 29 days; however, C57 animals suckled exclusively by an allogeneic A strain mother survive, showing only transient tumor growth. (3) Tolerance induction of FI tissue antigens in DA strain rat hosts by the neonatal intravenous inoculation of (FI × DA) F, marrow cells is facilitated both at low and high doses by foster nursing DA.
newborns on (FI X DA) F, mothers. In this circumstance any milk lymphocytes entering the
perinate are genetically tolerant of the tolerance conferring inoculum and incapable of reacting
against it. These findings indicate that milk-borne lymphocytes gain access to the tissues of
sucklings in a viable and immunologically reactive form and make an adoptive contribution to
the developing immunocompetence of the recipients.

10.15 to 10.45 a.m. Intermission
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Concurrent Session A
Friday, March 26, 1976
Grand Ball Room – Bellevue Stratford Hotel
10.45 to 12 noon Moderator: Pentti K. Siiteri
10.45 a.m. 54 Isolation of Human Chorionic Gonadotropin (HCG) mRNA
Tom Landefeld, Diana Mc Williams and Irving Boime
Department of Obstetrics-Gynecology, Washington University School of Medicine,
St. Louis, Mo.
Very little is known concerning the factors regulating the biosynthesis of HCG in placenta and
choriocarcinoma cells. One way to study this problem begins from the isolation of the mRNA
encoding for HCG. RNA was prepared from first trimester placentae and purified by oligo-dT-
cellulose chromatography and on sucrose gradients. This mRNA directed the synthesis of 2
major proteins with molecular weights (MW) of 20,000 and 18,000 in a wheat germ cell-free
system. The 20,000 MW protein was identified as containing the \( \alpha \)-subunit by tryptic
fingerprinting and amino acid analysis. Since the MW of the protein moiety of the \( \alpha \)-HCG is
about 11,000, this suggests that a precursor to the \( \alpha \)-subunit has been synthesized in the cell-free
system. The sedimentation rate of the \( \alpha \)-subunit mRNA, about 10S, is consistent with this. Since
the total MW of the protein portions of HCG is about 27,000, too large to be encoded by a single
10S mRNA molecule, these data suggest the subunits of HCG are synthesized from individual
mRNAs, rather than as a protein from one mRNA.
The radioactivity present in the tryptic peptides synthesized from first trimester RNA was 5
times greater than seen with term mRNA. This suggests that the higher in vivo blood levels of
HCG at first trimester results from increased synthesis rather than secretion.

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11 a.m. 55 Identification of Human Chorionic Somatomammotropin (HCS) – Synthesizing
Polysomes from the Placenta
David J. Gusseck, George M. Lessard and C. Raja Mohan Maisillamoni
Departments of Biochemistry and Perinatal Research, Loma Linda University School
of Medicine, Loma Linda, Calif.
Recently developed techniques which permit elucidation of mechanisms for regulating the
synthesis of specific proteins require the preparation of protein-specific messenger RNA
(mRNA). As an initial step in purifying the mRNA for HCS, we have optimized procedures for
isolating undegraded polysomes from the human placenta. Polysomes prepared by these
procedures were analyzed by centrifugation through a 10–50 % continuous sucrose density
gradient. HCS radioimmunoassays were performed on the fractions in order to identify the
polysomal region most active in the synthesis of HCS. While there was evidence of HCS
associated with polysomes throughout the entire polysomal region, peak binding (indicating
nascent HCS chains) was observed in fractions containing 9–14 ribosomes per message. Since the placenta is known not to synthesize insulin, radioimmunoassays for insulin which were negative ruled against nonspecific binding of antibody. The polysomes were active in directing HCS synthesis in an in vitro cell-free protein-synthesizing system utilizing wheat embryo components. Phenol extraction of RNA from the HCS-synthesizing polysomes revealed, in addition to the expected 5S, 18S and 28S ribosomal RNAs, an unexpected 20S RNA fraction. While alternative explanations have not yet been ruled out, it is possible that this represents a messenger RNA molecule. In conclusion, polysomes which are active in the synthesis of HCS have been partially purified for the first time. A distinctive size class of RNA associated with these polysomes may be the HCS message. (Supported by NIH grant No. HD 07036.)

11.15 a.m. 56 mRNA-Dependent Synthesis of an Authentic Precursor to Human Placental Lactogen (HPL)
Elzbieta Szczesna and Irving Boime
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.

Translation of term placental mRNA in a wheat germ cell-free system resulted in synthesis of a protein (MW 25,000) heavier than HPL, but containing HPL tryptic peptides. Instead, in the post-mitochondrial supernate (S-30) derived from ascites tumor cells, term mRNA directed the synthesis of HPL (MW 22,000). However, when the ascites S-30 was fractionated into ribosomal and cell-sap fractions, term mRNA primarily directed the synthesis of a larger protein (MW 25,000) that comigrates on SDS-polyacrylamide gels with the protein synthesized in the wheat germ system; this protein again contains HPL tryptic peptides. Only trace amounts of native HPL were synthesized in this fractionated system. We inferred that during fractionation a component responsible for cleavage might be lost, perhaps with the microsomal membranes. Addition of ascites microsomes to the homologous or to the wheat germ systems, resulted in the disappearance of the 25,000 MW protein and the appearance of native HPL. This conversion was further confirmed by tryptic mapping.

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Moreover, in partially purified placental homogenates, a prominent protein with a MW of 25,000, as well as HPL, was synthesized. It comigrated on SDS gels with the protein made in wheat germ and the fractionated ascites system, and it contained the same HPL tryptic peptides. These data are consistent with the notion that the 25,000 MW protein is an authentic physiologic precursor, and that it represents the primary gene product for HPL.

11.30 a.m. 57 A New Affinity Chromatography Approach to Isolation of Steroid Hormone Receptors
Frederick Sweet
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.

Estrogen or progesterone containing affinity chromatography columns were synthesized for purification of the corresponding uterine steroid receptor protein. 17-O-carboxy-methylestrone or 21-S-carboxyethylmercaptoprogesterone were first conjugated with di-2-aminoethyl disulfide (cystamine) to obtain the corresponding monoamide. The monoamide was reacted with CNBr-activated Sepharose 4B which in each case produced a stable disulfide containing affinity absorbent which had a 3 × 10^-3 M covalently bound steroid content. Immature sheep uterine
intact estrogen and progesterone ‘receptor’ proteins in a 105,000 E cytosol preparation were specifically adsorbed at 4 °C. After removing nonspecific protein from the adsorbent each of the receptor proteins were recovered by incubating the adsorbents with 2-mercaptoethanol. This treatment completely removed the adsorbent-bound steroid by breaking the disulfide linkage in the chain between the steroid and stationary matrix. Between 25- and 100-fold purifications of receptor protein were achieved. An estrogen-binding antibody from sheep was used as a model of the receptors to further improve this technique. With this model it was discovered that the disulfide containing affinity adsorbent-bound mercaptide-containing proteins which reduce the degree of purification of the high affinity proteins. This problem was overcome by preincubation of the antibody with 10-2 M cystamine, followed by dialysis which concealed any available mercaptide functions. Thus, the purification factor increased by a factor of 10 and 60% pure antibody was obtained by this procedure. Inclusion of cystamine during preparation of crude estrogen receptor increases the total amount of specific protein 2- to 5-fold; aggregation of protein is inhibited and receptor stability is enhanced.

11.45 a.m. 58 Progesterone Binding Protein in Human Chorion and Amnion
Barry E. Schwarz, John M. Johnston, Robert A they, Leon Milewich and Paul MacDonald
Department of Obstetrics-Gynecology, University of Texas Southwestern Medical School at Dallas, Dallas, Tex.
The progesterone binding protein found in the cytosols (105,000E supernatants) of human fetal membranes at term has been further characterized. The protein binds progesterone, cortisol, and 5α-pregnanedione but does not bind cortisone, 20α-hydroxyprogesterone, dexamethasone, or R5020. These properties suggest that the protein is unique and is not identical with the progesterone ‘receptor’ of decidua, transcortin as found in maternal serum or any previously demonstrated glucocorticoid receptor. The appearance of the progesterone binding capacity has been studied as a function of gestation. Prior to 37 weeks only low levels of progesterone binding capacity are demonstrable – 121 ± 36 (SEM) fmol/mg protein – however, high levels of progesterone binding capacity are present in fetal membranes at term – 476 ± 72 (SEM) fmol/mg protein. This difference is statistically significant, p < 0.005. Furthermore, the progesterone binding protein can be extracted from sheets of amnion with 0.4 M KCl whereas it is quantitatively recovered in cytosol following prior salt extraction of sheets of chorion. This apparent localization of a progesterone binding protein unique to gestation on the amnion, but in the chorion, may contribute to a local progesterone withdrawal which could initiate those biochemical events that eventuate in human labor.

12 noon to 1.45 p.m. Luncheon
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Concurrent Session B
Friday, March 26, 1976
Clover Room – Bellevue Stratford Hotel
10.45 a.m. to 12 noon Moderator: Chester B. Martin, jr.
10.45 a.m. 59 Fetal Insulin Response to Glucose: a Reexamination
W. Ann Reynolds and R.M. Pitkin
Department of Anatomy, University of Illinois Medical Center, Chicago, 111.
According to previous reports, the normal monkey fetus does not respond to a glucose challenge by secreting insulin. Because of incidental findings on other studies of nutrient metabolism which seemed to contradict these earlier reports, we recently had occasion to reexamine the issue of fetal insulin response. Normal rhesus monkeys of known gestational duration were studied acutely during the last third of pregnancy with access to maternal and fetal circulations provided by catheters in the maternal vena cava and the interplacental vessels, respectively. Glucose was administered as either a constant intravenous infusion (0.2 mg/min over 2–5 h) to the mother or a single bolus injection (500 mg) into the fetal circulation. Simultaneous maternal and fetal plasma samples taken at intervals were analyzed for glucose and immunoreactive insulin. Baseline insulin levels were lower (by approximately half) in fetus than in mother. Constant maternal glucose infusions induced maternal and fetal hyperglycemia (225–325 mg%) and, in response, a 2- to 4-fold increment in fetal insulin (to 50–240 µU/ml). The fetal insulin response was clearly evident within 30 min after glucose was begun, although it was proportionately smaller than the maternal response and the fetal peak lagged behind the maternal peak by 0.5–1 h. Fetal intravenous injection of a glucose bolus produced a prompt (within 15 min) 3- to 5-fold fetal insulin response. Thus, we found the normal monkey fetus to be capable of responding appropriately to hyperglycemia (induced with either continuous maternal infusion or single fetal injection) by releasing insulin.

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60 Effect of Thyroidectomy on Fetal Brain and Lung Development
Amrutha Bhakthavathsalan, Leon I. Mann and Maida Liu
Department of Obstetrics-Gynecology, State University of New York Medical School at Stony Brook, Nassau County Medical Center, East Meadow, N.Y.
The effect of ovine fetal thyroidectomy (Tx) on brain, lung and erythropoietic development and function was studied in 5 experiments. Tx was performed at gestational ages ranging from 104 to 111 days (106.8 ± 1.1 SEM) and indwelling catheters were placed into maternal and fetal circulation for chronic blood sampling. Fetal T4 levels decreased sharply 1 week postoperatively and remained low thereafter (18.3 ± 5.6 → 1.1 ± 0.4 µg %). Chronic observations of blood gases, pH, glucose, lactate, calcium and phosphorous were within normal limits. On approaching term (137.2 ± 1.1 days) the animals were studied acutely for the effects of Tx. Compared to age-matched controls, the body weight (Tx 2.8 ± 0.1; C 3.9 ± 0.2 kg) and brain weight (Tx 43.5 ± 1.4; C 48.5 ± 1.8 g) were significantly reduced in the Tx fetuses. While the lung weights were less in the Tx fetus, the difference was not significant. Cardiovascular and acid-base parameters, brain metabolism, morphological and histological studies of the brain did not show any significant difference between the experimental and control groups. All except one Tx fetus showed mature EEG consistent with the gestational age. Surfactant production was not significantly different as measured by tissue homogenate phospholipid (PL)/protein ratio and the total PL and protein levels in the fetal pulmonary fluid. Erythropoietic studies suggested immaturity in 2 Tx fetuses while erythropoietin levels were unaffected. The relative maturity of the sheep fetus in the third trimester probably explains the lack of disturbances of maturation in the brain and lungs of the Tx fetuses.
(Supported by UCPR&EF and MMERF.)
11.15 a.m.
Relationship between Oxygenation and Distribution of Fetal Cardiac Output
Louis L. Peeters, M. Douglas Jones, jr., Roger E. Sheldon, Giacomo Meschia, Frederick C. Battaglia and Edgar L. Makowski
Division of Perinatal Medicine, University of Colorado Medical Center, Denver, Colo.

Previous studies have shown that acute severe hypoxia alters the distribution of fetal cardiac output (Am. J. Obstet. Gynec. 120: 817, 1974). However, it is not known whether this effect is triggered by a decrease of paO2 below a critical level or is an expression of the fact that the distribution of fetal cardiac output is a continuous function of fetal oxygenation. In order to provide such evidence, blood flows to fetal organs were measured by means of the microsphere technique in 15 chronique fetal lamb preparations whose carotid arterial pO2 was varied from 30 to 14 mm Hg by changing maternal pI02. Under these experimental conditions, and contrary to what happens in severe hypoxia, the fetus maintained normal blood pressure and pH. Cerebral and coronary flows varied over a three- and fivefold range respectively, in inverse relation to arterial O2 content ([O2]a). The product [O2]a × coronary flow remained constant. Adrenal blood flow increased sixfold as the pO2 in the postductal arterial blood decreased from 26 to 14 mm Hg. Placental and renal flows did not vary significantly with oxygenation, whereas intestinal, pulmonary and skeletal muscle flows showed a positive correlation with O2 J.

In conclusion, the distribution of fetal cardiac output is O2-dependent in a range that encompasses the normal as well as the hypoxic state.

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Cardiovascular and Uterine Effects of Ritodrine HC1 in the Pregnant Sheep
Robert K. Creasy and Anja S.I. Siimes
Department of Obstetrics-Gynecology and Cardiovascular Research Institute, University of California, San Francisco, Calif.

There recently has been renewed interest in the use of \(\beta\)-adrenergic drugs for the inhibition of premature uterine activity, the management of fetal distress and the treatment of intrauterine growth retardation. We have studied the effects of one of these agents, ritodrine hydrochloride, in the chronically prepared pregnant ewe. Arterial and venous blood pressure, heart rate, cardiac output, uterine blood flow and its distribution, peripheral and uterine vascular resistances and uterine activity were measured or calculated before, during and after ritodrine infusions, and during concomitant \(\beta\)-adrenergic blockade and ritodrine infusions. Methodology used included the dye-dilution technique, radioactive microspheres, implanted blood flow transducers and various catheters to sample blood or record pressures.

Ritodrine caused (1) minimal changes in arterial pressure, (2) a significant increase in heart rate that was dose dependent, (3) an increase in cardiac output of over 2 l/min, (4) no significant change in uterine blood flow or its distribution, (5) a decrease in peripheral vascular resistance, and (6) no significant change in uterine vascular resistance. Ritodrine was an effective inhibitor of both spontaneous and oxytocin-induced uterine activity. (3-Blockade with propranolol reversed the ritodrine-induced uterine inhibition and maternal tachycardia whereas \(\beta\)-blockade with practolol reversed the tachycardia without interfering with uterine inhibition.

Intrauterine and/or Exchange Transfusion with the Development of Leukemia J.H. Turner and J. Petricciani Department of Obstetrics-Gynecology, University of Pittsburgh, Pittsburgh, Pa.
This paper reports evidence relating to the possibility that blood-borne viruses or other oncogenic agents might be transmitted by intrauterine or exchange transfusion to highly susceptible individuals at high risk. Highly susceptible because of their relative immune incompetence-high risk because the hypothetical agent(s) would have been received by direct inoculation were it present in the peripheral blood of the donor. Of 63 fetuses transfused in utero, one case of acute lymphatic leukemia was positively diagnosed in a male chimeric (46, XY/46, XX) child at the postnatal age of 4 years. The primary evolutionary features apparent in the karyotypic profile preceding and subsequent to remission, were an increasing frequency of 46, XX donor cells, relative to natural 46, XY cells, correlated with an increasing relative frequency of an aneuploid cell line characterized by significant non-random increases of C and G group autosomes. Other less striking deviations from normal expectations were also observed. Two cases of leukemia were identified, retrospectively, among 840 neonatal recipients of exchange transfusion(s). No cases were found among their nontransfused partner controls (matched by sex, race, parity, and birth weight).

12 noon to 1.45 p.m. Luncheon
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Concurrent Session C
Friday, March 26, 1976
Grand Ball Room – Bellevue Stratford Hotel
1.45 to 4 p.m.
Moderators: Alan Goldfier and T. Terry Hayashi
1.45 p.m. 64 Gonadotropin, Estrogen, and Androgen Dynamics Following Ovarian Wedge Resection (WR) in Poly cystic Ovary Syndrome (PCO)
Howard L. Judd, Lee A. Rigg, David C. Anderson and Samuel S.C. Yen Department of Reproductive Medicine, UCSD School of Medicine, La Jolla, Calif.
To evaluate the early hormonal effects of WR daily blood samples were obtained before and up to 35 days after surgery in 8 PCO patients. For controls, samples were also obtained for 10 days in 5 ovulatory women undergoing hysterectomy during the early follicular phase for nonovarian disease. Preoperatively, LH but not FSH, estrone (E1), but not estradiol (E2), and both androstenedione (Δ) and testosterone (T) were higher in the PCO patients than in the normal women. In the PCO patients, surgery had no discernible effect on FSH levels for the duration of the studies. In the 5 patients who ovulated after WR, LH levels were stable until midcycle LH peaks occurred 13–25 days after surgery. In the 3 nonovulators surgery had no effect on LH concentrations. For the estrogens, there was a small but significant fall of E1 (p < 0.05) and a decrease of E2 during the first 3 postoperative days. These were followed by preovulatory rises of both E1 and E2 in the ovulatory patients. Large decreases (p < 0.05) of both T and Δ were seen during the first 3 days. These were followed by steady increases of both androgens back to preoperative levels. This pattern was seen whether the patients did or did not ovulate. With the exception of a small transitory fall of androgens surgery had no effect on any of the hormones in the control subjects.
These results show that in PCO patients, WR is followed by a profound but temporary reduction of ovarian androgen secretion and a smaller but significant decrease of estrogen production. Ovulations occurred in 5 of the 8 patients after surgery even though gonadotropin secretion was stable (particularly FSH) and early follicular phase rises were not seen.
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2 p.m. 65 Androgen-Induced Ovarian Follicular Atresia in the Rat
Freddy Febres, Bernard Gondos and Pentti Siiteri
Departments of Obstetrics-Gynecology and Pathology, Reproductive Endocrinology
Center, University of California, San Francisco, Calif.

The direct effect of estrogens on granulosa cell proliferation and follicular maturation is well established. The mechanism(s) of follicular atresia, however, is poorly understood. We have studied the effect of dihydrotestosterone (DHT) on estrogen-stimulated ovaries in the immature hypophysectomized (Hpx) rat. Seven days post-Hpx groups of 6–8 rats were treated for 4 days with estradiol (E2), DHT, E2 + DHT, or E2 + DHT + progesterone (P) delivered by silastic implants. Another group was treated with E2 and HCG, 1 IU every 12 h s.c. (E2 + HCG). The average ovarian weights (mg ± SE) were, control, 6.8 ± 0.5; E2, ± 0.65; DHT, 4.5 ± 0.25; E2 + DHT, 9.3 ± 1.0; E2 + HCG, 11.8 ± 0.65; E2 + DHT + P, ± 1.8. In control- or E2-treated groups light- and electron-microscopic analysis revealed that DHT and HCG accelerated granulosa cell death and follicular atresia in medium-sized but not in primary or antral follicles. A significant DHT effect was observed at 8 h in controls and P significantly reduced DHT-induced atresia in E2-treated animals. Together with other data demonstrating (1) increased ovarian testosterone (T) and DHT production in response to LH, and (2) the presence of androgen receptors in granulosa cells, these findings suggest that follicular atresia may be induced by intraovarian androgens. Selective action may result from absence of androgen receptors in primordial follicles and critical E2 and/or P levels in antral and/or Graffian follicles.

2.15 p.m. 66 Differentiation of Androgen Dynamics in Rhesus Monkeys
Ken A. Burry, Toru Tabei, Philip H. Petra, Harvey S. Schiller, John Resko and W. LeRoy Heinrichs
Departments of Obstetrics-Gynecology, Biochemistry and Laboratory Medicine, University of Washington School of Medicine, Seattle, Wash, and Oregon Regional Primate Center, Beaverton, Oreg.

In primates, an obligate relation between prenatal androgen and differentiation of gonadotrophin regulation, and steroid metabolism is less certain than in rodents, although male sexual behavior does appear to be androgen-dependent in rhesus monkeys. We now report studies of androgen dynamics in female rhesus monkeys androgenized by prenatal testosterone (Nature 242: 119, 1973), and in male (M) and female (F) control animals from untreated pregnancies. All animals, 6/group, were castrated postpubertally.

Metabolic clearance rates (MCR-p), and production rates of testosterone (PRj) were small and showed no statistical difference among the groups. MCRj (1/day/kg) for M, F, and MF were 6.94 ± 1.39, 6.07 ± 0.47, and 7.59 ± 1.75 respectively, and PRT (µg/day/kg) were 2.24 ± 1.16, 2.87 ± 0.86, and 3.37 ± 2.19 (mean ± SD). Binding capacity (µg DHT-bound/100 ml serum) of the sex-steroid-binding protein (SBP) was significantly (p < 0.02) lower in M (3.95 ± 1.14) than in F (5.85 ± 0.98); MF values (4.88 ± 1.14) were intermediate. This sex difference of SBP appeared despite elevated concentrations compared to normals. Also, MCRj and SBP were inversely related (r/0.9).

The correlation of MCR·j· and SBP suggests that this protein participates in regulating androgen metabolism in castrated rhesus monkeys. The data also support the hypothesis

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that regulation of SBP rather than kinetics of various hepatic or peripheral metabolic pathways that determine MCRj, is set in this species by prenatal versus postpubertal determinants.

2.30 p.m. 67 Studies on the Activation and Transformation of the Estrogen Receptor of the Rat Uterus
Kaspar A. Buchi and Claude A. Villee
Laboratory of Human Reproduction and Reproductive Biology, Department of Biological Chemistry, Harvard Medical School. Boston, Mass.

Cytosol from uteri of ovariectomized rats was incubated at 0, 15 and 25 °C for various lengths of time before or after 3 H-estradiol was added. The influence of these treatments on the incorporation of estradiol receptor complex into uterine nuclei and on its sedimentation in sucrose density gradients was studied. Prolonged incubation of the cytosol at 0 °C resulted in an increased nuclear uptake whereas incubating the cytosol at 15 or 25 °C decreased nuclear uptake. Thus, the estradiol receptor complexes were first activated and then inactivated; both processes were accelerated with increasing temperature, but the inactivation process has a higher temperature coefficient than the activation process. The presence of estradiol has little influence on the activation rate, but enhances the rate of inactivation. Prolonged incubation of the cytosol resulted in transformation of the estradiol receptor complexes from 4S to 5S forms; this transformation was enhanced by increased temperature and by the presence of estradiol. At 15 °C the transformation process becomes dominant only after activation has ceased and inactivation has begun. Activation occurs rapidly and is only slightly estrogen dependent, hence it is distinctly different from transformation and inactivation which are estrogen dependent and occur later. An important effect of estradiol may be the liberation of the cytosol receptor so that it can undergo activation, which may or may not be estrogen dependent.

2.45 p.m. 68 Phosphatidylcholine Biosynthesis by Isolated Lamellar Bodies from Lung Type II Cells
Hugh L. Spitzer, Patricia Wallis and John M. Johnston
Departments of Obstetrics-Gynecology and Biochemistry, University of Texas Health Science Center at Dallas, Dallas, Tex.

Indirect evidence from autoradiographic and histochemical studies have suggested that surfactant phosphatidylcholine (PC) biosynthesis is associated with the lamellar bodies (LB) of the lung type II cell. This laboratory recently reported that LB, free from contamination by other subcellular particles, contain phosphatidic acid phosphohydrolase (PAPase) a key enzyme in lipid metabolism (BBRC 66: 17, 1975). The activity of CDP-choline: diglyceride choline phosphotransferase (CPTase), the requisite enzyme in PC biosynthesis, has now been demonstrated in LB. When the enzymatic activity of LB and whole lung microsomes are compared PAPase is 4 × higher and CPTase 2 × higher in the LB. We have also found phospholipase A2 activity associated with LB. These findings suggest that an important subcellular site for surfactant PC biosynthesis may reside with the LB. This conclusion is consistent with the demonstration that the LB have the highest specific activity of PAPase and CPTase. Both of these enzymes have been reported to have a regulatory function in the synthesis of PC. Furthermore, the presence of phospholipase A2 provides a mechanism in the LB for the remodeling of preexisting PC via the acylase cycle to form surfactant PC. (Supported, in part, by NIH grant POIHD 08672–01 and AM 03108.)
Placental Transfer of Aspartic Acid

R.M. Pitkin, L.D. Stegink and W. Ann Reynolds
Departments of Obstetrics-Gynecology, Pediatrics and Biochemistry, University of Iowa, Iowa City, Iowa and Department of Anatomy, University of Illinois Medical Center, Chicago, 111.

In general, amino acids are transported readily across the placenta, presumably by an active process. Maternal-fetal transfer of aspartic acid was studied in late-pregnant rhesus monkeys in which aspartate (with added tracer l4C-aspartate) was infused intravenously in doses of 100 or 400 mg/kg/h (4 experiments at each dosage level). Sequential maternal and fetal plasma and RBC samples were analyzed simultaneously for free amino acid composition and incorporation of radioactivity into amino acids and metabolites. Maternal infusions of 100 mg/kg/h produced maximal maternal aspartate levels 100–150 times baseline but negligible change in fetal values. Maternal infusions of 400 mg/kg/h raised maternal aspartate 1,000–1,500 times baseline and, at these markedly elevated levels, a rise in fetal values (to 150 times baseline) was noted.

Comparison of simultaneous maternal and fetal levels suggested a ‘threshold’ effect whereby some transfer occurred at or above maternal plasma levels of 200 µmol/dl (500 times baseline). Radioactivity profiles confirmed a relative placental impermeability to aspartate and indicated that the compound was metabolized in the mother to glucose and lactate which then crossed the placenta readily. The results demonstrate that the hemochorial placenta is virtually impermeable to aspartic acid at anything less than enormously elevated maternal levels. Thus, for aspartic acid (as we have previously demonstrated for glutamic acid, the other dicarboxylic acid normal present in plasma) fetal levels of this neurotransmitter substance normally arise from fetal synthesis de novo rather than from placental transfer.

90 Changing Characteristics of Placental Hexokinase and Tyrosine Aminotransferaseduring the Course of Gestation

D.J. Gusseck, J.C. Dean and R.S. Wade
Departments of Biochemistry and Perinatal Research, Loma Linda University, Loma Linda, Calif.

Since enzymic complements frequently reflect the metabolic responsibilities of tissues, studies of the composition and characteristics of placental enzymes have been undertaken. Hexose phosphorylation is regulated by an array of four hexokinase isozymes, each having a characteristic tissue distribution and distinctive kinetic and physical properties. We have examined the population of hexokinase isozymes in rabbit and human placentas of different gestational ages. The placentas of both possess all four isozymes but in relative proportions which differ from liver and other differentiated tissues. During the course of gestation in both the human and rabbit, there is a substantial decrease in the relative amount of type III hexokinase and an increase in type I while types II and IV (which is also called glucokinase) remain unchanged. Because of correlations derived from studies in other tissues, certain implications are implicit in these findings. For example, the increase in type I relative to type II suggests that the insulin responsiveness of the placenta may decrease with gestational age. Other studies carried out by us support this. Tyrosine aminotransferase is an enzyme which participates in the redistribution of amino acid nitrogen and the shunting of amino acid carbon atoms into gluconeogenesis. We have found that, while it is present only in low levels in the rabbit placenta, its activity can be enhanced substantially by administering either insulin or hydrocortisone to the
mother. This ability of rabbit placental tissue to respond to these two hormones decreases markedly with gestational age. (Supported by NIH grant No. HD 07036.)

3.30 p.m. 71 Antagonistic Effects of Testosterone and Estradiol on the Synthesis of Adult Hemoglobin in Cultures of Human Fetal Liver Cells L.F. Congote and S. Solomon
Departments of Biochemistry, Experimental Medicine and Obstetrics-Gynecology, McGill University, Montreal, P.Q.
The synthesis of adult hemoglobin in short-term cultures of liver cells prepared from human midterm fetuses was monitored by two methods. First, we measured 59Fe-incorporation into adult hemoglobin, which was separated from fetal hemoglobin by chromatography on Biorex-70; and second, we followed the incorporation of radioactive leucine into α-chains which were separated from α- and 7-chains by chromatography on carboxymethyl cellulose. Cells were incubated with 5 × 10^-7 M testosterone for 6 h, followed by an 18 h pulse with radioactive iron or radioactive leucine. The ratios of adult to fetal hemoglobin (HbA/Hbf) were very similar in controls and testosterone-treated cells. The radioiron incorporation into adult hemoglobin was significantly higher in testosterone-treated cells than in controls. Estradiol had the opposite effect, but only at a concentration of 10^-6 M. It is interesting that the leucine incorporation into α-, β- and γ-chains did not change after treatment with the hormones mentioned above. This could be interpreted as a hormone action on iron incorporation independent of globin chain synthesis, or by a very early increase (or decrease) of β-chain synthesis which would be leveled off during the 18 h pulse. The effects of testosterone and estradiol in fetal cell described here are consistent with the ratios HbF/HbA reported in the literature in male and female adolescents with sickle cell anemia.

3.45 p.m. 72 Alternate Precursors of Steroid Biosynthesis in the Pregnant Mare Bhagu R. Bhavnani and Robert D. Baker
Departments of Obstetrics-Gynecology and Clinical Biochemistry, University of Toronto, St. Michael’s Hospital, Toronto, Ont. and Department of Animal Science, MacDonald College of McGill University, Montreal, P.Q.
We have shown that the fetoplacental unit of the mare can produce ring B unsaturated estrogens equilin (Eq) and equilenin (Eqn) from acetate, mevalonate and isopentenyl pyro-phosphate but the pathway then bypasses squalene and cholesterol. The conversion of these labelled precursors to estrone and 17α-estradiol was consistently greater than that to Eq and Society for Gynecologic Investigation

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Eqn. In order to rule out the possibility that preformed benzenoid compound might act as a precursor for Eq and Eqn, we injected 2 mCi of 14C (U) tyrosine and 7 µCi of 3H-dehydroisoandrosterone (3HD) into the muscle of a horse fetus at approximately 9 9’/2 months of pregnancy. Maternal urine was collected for 5 days and the following compounds were isolated and recrystallized to constant specific activity before and after derivative formation: estrone; equilin; 3/3-hydroxy-5α-pregnane-20-one, 5α-pregnane-3β, 20/3-diol, and 5α-pregnane-3β, 20α-diol. Each of these steroids contained easily measurable amounts of 14C indicating that the aromatic acid tyrosine (or one or more of its breakdown products) can act as a precursor for these steroids in this species. Tritium was found only in the estrone fraction which confirmed the previous results that 3 HD is not a precursor for the ring B unsaturated estrogens Eq and Eqn. The physiological significance of this finding is not yet clear.

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1.45 p.m. 73 Effect of Atropine Blockade on the Fetal Cardiovascular Response to Hypoxemia
Herbert E. Cohn, George J. Piasecki and Benjamin T. Jackson
Department of Surgery, Boston University School of Medicine and Department of Pediatrics, New England Medical Center Hospital, Mass.

We studied the effect of atropine on the cardiovascular response to hypoxemia in 7 fetal lambs of 121–130 days gestation. We placed catheters in fetal and maternal vessels and placed an electromagnetic flowprobe on the fetal-descending aorta. The fetuses were studied 4–5 days postoperatively. Fetal cardiac output (CO) and its distribution were measured with labelled microspheres during the control state, atropine blockade, and hypoxemia with atropine blockade (standing ewe breathing 8 % O2 and 3 % CO2). Fetal and maternal arterial pressures, O2 contents, and pH were measured repeatedly and fetal descending aortic blood flow (DABF) was measured continuously during the studies. During hypoxemia with atropine blockade, mean fetal heart rate increased from 188 to 206, fetal arterial pressure remained constant, fetal CO decreased from 513 to 316 ml/min/kg, and DABF decreased by 45 %. There was an 83 % decrease in flow to the lower body and a 17 % decrease in umbilical blood flow (UBF), while the proportion of fetal CO to the placenta increased from 40 to 53 %.

Conclusions: (1) atropine blockade prevents the fetal bradycardia seen during hypoxemia in late-gestation fetal lambs; (2) despite the prevention of fetal bradycardia, CO falls significantly; (3) the fall in CO is associated with a small but significant decrease in UBF; (4) the decrease in UBF occurs despite a major redistribution of fetal CO which favors the umbilical circulation.

(Supported by the John A. Hartford Foundation, Inc. N.Y. and HD 07681.)

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2 p.m. 74 Stimulation of Active Transport across Porcine and Human Placentae by Human Placental Lactogen
M.H. Goldstein, F.W. Bazer, W.N. Spillacy and W.C. Buhi
Departments of Physiology, Animal Science, and Obstetrics-Gynecology, University of Florida, Gainesville, Fla.

Dynamic changes occur in allantoic fluid volume and electrolyte composition during gestation of the pig. Allantoic fluid volume (x ± SE) at days 30, 40, 60 and 90 of gestation were 209.4 ± 6.9; 65.9 ± 3.9; 322.6 ± 38.9; and 76.4 ± 10.3 ml. Measurements (x ± SE) of Na+ and K+ concentration at similar times were 16.6 ± 1.0 and 8.6 ± 0.3; 6.4 ± 0.9 and 27.3 ± 2.7; 10.5 ± 5.7 and 3.5 ± 0.5; 12.4 ± 2.7 and 44.0 ± 2.3 mEq/l respectively. Human placental lactogen on days 24 and 30 stimulated active transport when applied to the fetal (allantoic) side of the porcine placenta, but had little or no effect when added to the maternal surface (chorion). Mean short-circuit current (SCC) and potential difference (PD) before treatment were 21.33 µA/cm² and 3.5 mV; within 4–5 min after addition of hormone, maximal stimulation was observed, 244 µA/cm² and 40.5 mV. Late in gestation (day 90) HPL added to the fetal surface had little or no stimulatory effect on active transport. However, HPL added to the maternal surface stimulated the SCC and PD. Mean control SCC and PD were 26.5 µA/cm² and 5.67 mV and after treatment, within 1 min, maximal values were 124 µA/cm² and 25.7 mV. HPL added to the fetal (amnion) side of term human
placenta had no effect on SCC or PD, but HPL added to the maternal (chorion) side stimulated and maintained elevated SCC and PD values for several hours. Mean SCC and PD prior to HPL were 5 µA/cm² and 1 mV; while after addition maximal values were 224 µA/cm² and 7.2 mV. These data suggest that HPL may be involved in regulating water and electrolyte balance between maternal tissue and the fetal-placental unit.

2.15 p.m. 75 Effect of Progesterone Antiserum in Pregnant Rats
T. Erdos and A. Csapo
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.
The elegant and precise immunological technique of controlling hormone levels in vivo with highly specific antisera offered a new approach to the study of the regulatory mechanism of pregnancy. In the rat ‘model’, antiprogesterone (A-P) alone (without supplemental treatment with uterine stimulants) predictably terminated pregnancy over a broad gestational range. A-P treatment was effective whenever the biologically active unbound P (Pu) was reduced to and sustained below a critical level.

After establishing the relationship between A-P, total P (Pt), bound P (Pb) and Pu, a computer simulation study was performed to estimate the gestational dependence of the dose of A-P which predictably tips the regulatory balance and terminates pregnancy. Subsequent experiments verified this estimate; four times more A-P was needed for the termination of pregnancy in the rat at day 6 of gestation than at day 10.

These computer-simulated experiments also revealed a novel action of P-withdrawal (Pw). They showed that unless Pw (provoked by A-P) rapidly suspends P-genesis, A-P becomes saturated by Pj, and Pu quickly returns to the pretreatment value. The experiments documented that effective A-P treatment provokes sustained (rather than transient) reduction in Pu, indicating that critical Pw suppresses P-genesis. This relationship has been confirmed by protecting P-genesis from the effect of A-P-induced Pw, through P substitution therapy.

These experiments further increased confidence in the immunological approach to the exploration of basic relationships in the regulatory mechanism of pregnancy.

2.30 p.m. 76 The Development of a Model for the Destruction of Erythrocytes in ErythroblastosisFetalis
Daniel B. Whitesides, Euripides Ferreira, D. Bernard Amos, Wendell F. Rosse and Stanley A. Gall
Duke University Medical Center, Duke Hospital, Departments of Immunology and Obstetrics-Gynecology, Durham, N.C.
The objective of this work is to present a model for the noncomplement-mediated lysis of erythrocytes in erythroblastosis fetalis. The antibody-dependent lymphocyte-mediated lytic (LDA) system can provide this mechanism. In the LDA system a target cell, coated with a specific IgG antibody, is destroyed by a circulating lymphocyte. In erythroblastosis fetalis the target cell is the fetal erythrocyte, the antibody is the maternal anti-Rh antibody and the effector cell is the fetal lymphocyte.

The presence in neonate cord blood of lymphocytes capable of effecting lysis in the LDA system has been demonstrated using adult lymphocytes as targets and a specific anti-HLA antibody. In this system 27 of 28 neonate lymphocytes were effective in lysing the adult lymphocyte.
Neonate lymphocytes and Rh- and Rh+ neonate erythrocytes have been collected from cord bloods at birth. Using maternal serum from 3 isoimmunized patients as the source of antibody, the neonate lymphocytes have been demonstrated to lyse Rh+ but not Rh- neonate erythrocytes regardless of ABO type. The attack of anti-Rh antibody-coated erythrocytes by lymphocytes has been demonstrated using time-lapse microcinematography in an in vitro system.

2.45 p.m.

77 Erythropoiesis in the Rhesus Monkey Fetus
Benjamin T. Jackson, Herbert C. Cohn and George J. Piasecki Department of Surgery, Boston University Medical Center, Boston, Mass.

This study was undertaken to define the course of erythropoiesis with progress of gestation in the normal monkey fetus and the erythropoietic response of the fetus in utero to a blood-loss anemia. Methods. Fetal jugular vein and carotid artery catheters were chronically implanted. In 4 normal fetuses Hgb, Hct, red cells (RBC) and reticulocytes were quantitated at 2-day intervals for 4–21 days. Six fetuses (anemia group) were bled at 2-day intervals and studied as above and with determination of erythropoietin (EP) by the plethoric mouse assay for 8–20 days. Results. Normal: Hgb, Hct and RBC remained stable in individual fetuses and among fetuses ranged from 11–14.5 g%, 35–44 % and 3.20–4.75 X 106/mm3, respectively. Reticulocytes were 7–9 % at 127 136 days gestation and fell from 5.5 to 3.5 % over days 136–149. Anemia: After start of bleeding, Hct was reduced to 20–25 % within 5 days; reticulocyte percentages increased by 0.5 at 2 days and reached maximum levels of 15 30 % at 7- 8 days; EP, undetectable initially, showed a response of 0.05–0.1 U/ml at 5–7 days and a sustained maximum response of 0.6 U/ml at 10 12 days.

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Conclusions. (1) The monkey fetus experiences gradually declining erythropoietic activity in late gestation. (2) The fetus in this species responds rapidly to anaemic hypoxia with increased erythropoiesis. (3) Initial and maximal fetal erythropoietic (reticulocyte) responses to hypoxia precede the equivalent EP responses. This paradoxical temporal relation of fetal reticulocytosis and EP elevation may indicate either effective changes in EP at undetectable levels or a possible functional erythropoietic control mechanism in the fetus other than EP. In addition it is clear that EP is not the rate-limiting factor in determining the maximum capacity of the fetal erythropoietic response to hypoxia.

3 p.m. 78 Changes in Fetal Red Cell Oxygen Affinity in Relation to Gestational Age: the Role of Diphosphoglyceric Acid (DPG) and Adult Hemoglobin
H. Bard, M.A. Soukini, A. Comet, J.-C. Fouron and J. Robillard
Centre de Recherche, Hôpital Sainte-Justine, Université de Montreal, Montreal, P.Q.

In order to evaluate changes in oxygen affinity in fetal red cells the following study was carried out on 14 different fetal sheep whose gestational ages varied from 70 to 148 days. The older fetuses were sampled via chronic indwelling catheters while those less than 100 days were sampled once at hysterotomy. The following analysis were done: (1) the percentage of adult hemoglobin by column chromatography; (2) DPG by method of Kiett; (3) oxygen affinity (P50) by gas-mixing tonometry. We observed that the oxygen hemoglobin affinity remains constant from 70 to 120 days of gestation (P50 = 14.1 ± 0.1 mm Hg; n = 4), this being before any adult hemoglobin was detected. But once adult hemoglobin appeared in red cells, there was a decrease in 02 affinity which correlated with the increase in adult hemoglobin (r = 0.7, p < 0.025, n= 9).
Also noted was that oxygen hemoglobin affinity decreases in relation to gestational age after 120 days of gestation. P50 rose from 14 to 18.5 mm Hg (r = 0.62, p < 0.025, n = 11). We also demonstrated that the level of DPG remains constant throughout the interval of gestation that was studied (3.5 ± 1.5 µmol/ g Hb). We can conclude that in the fetal lamb the red cell oxygen hemoglobin affinity is dependent upon the levels of adult hemoglobin and PDG has a very minor role in modifying red cell oxygen affinity in utero. Also suggested from this study is that the postnatal response to hypoxemia that increases DPG levels may be non-functional in utero.

3.15 p.m. 79 Comparison of Neural Tone of Resting Cardiovascular Functions in Neonate and Adult Sheep

J.R. Woods, jr., A. Dandavino, K. Murayama, C.R. Brinkman, III and N.S. Assali Department of Obstetrics-Gynecology, UCLA School of Medicine, Los Angeles, Calif.

The magnitude of resting neural tone of given circulatory function may be assessed by blocking specific components of controlling arc reflex and observing respective circulatory changes. Previous studies using this technique in the fetus (Am. J. Physiol. 1975) have shown progressive maturation of adrenergic and cholinergic tone of cardiovascular functions between 60 days term gestation. The present report deals with data obtained from chronically-instrumented newborn lambs (3–70 days) and adult nonpregnant sheep. Specific blockers used were: arfonad (Ar) autonomic ganglia; dibenzyline (Db) α-adrenergic receptor; propraolol (Pp) β-receptor, and atropine (At) cholinergic receptor. Results show: (1) throughout the neonatal period, ganglionic blockade produced moderate systemic hypotension and tachycardia similar to the adult; (2) in a 1-week-old neonate, α-receptor blockade produced marked systemic hypotension similar to term fetus; hypotensive action decreased progressively and by 5 weeks it approached nonpregnant adult level; (3) β-adrenergic blockade elicited the same degree of bradycardia in neonate and adult; (4) cholinergic blockade produced marked tachycardia in both neonate and adult which was much greater than term fetus.

Conclusions: (1) the cholinergic system is developed at birth and exerts primary control over resting HR; (2) β-adrenergic receptor activity, although functional at birth, has little influence on resting state; (3) role of autonomic ganglia in maintenance of systemic vascular tone is the same for neonate and adult and is in contrast to declining influence of α-adrenergic receptor activity during neonatal development.

3.30 p.m. 80 Analysis of the Immunocompetence of Human Milk Lymphocytes

Michael J. Parmely, H. Paul Stiefel and Alan E. Beer
Department of Obstetrics and Gynecology and Cell Biology, University of Texas Southwestern Medical School, Dallas, Tex.

Immunological transactions between a mother and her offspring may continue beyond birth. Recent studies in rats and mice in our own laboratories have documented that during suckling the perinate receives a dowry of maternal immunities in the form of viable lymphocytes in the mammary exocrine. Human colostrum and milk contain large numbers of macrophages and lymphocytes, 1.3 X 106 and 1.45 × 105/ml respectively. Purified human milk lymphocytes (ML) were cultured in microtiter plates with appropriate mitogens or antigens and were labelled with tritiated thymidine to assess the extent of DNA synthesis. Peripheral blood lymphocytes (PBL) from the same patient were cultured under identical conditions in order to compare the reactivity of both cell populations. It was found that (1) ML are as viable and long-lived as PBL in culture; (2) the mitogenic response of ML following PHA stimulation is inferior to the response of PBL;
mixed lymphocyte reactive lymphocytes (MLC) reside in milk; however, their reactivity is somewhat muted when compared with MLC-reactive PBL; (4) ML from tetanus or Candida-positive patients are usually unresponsive in culture; however, the reverse may apply for responses to the KL antigen of E. coli; (5) this selective reactivity of ML is not due to suppressive factors, antigen specific populations of suppressor cells, or lack of adherent cells in milk. The data suggest that milk may lack certain antigen reactive lymphocytes and may contain others. Mammary tissue and its exosecretion appear to be a depot for certain selected clones of reactive maternal lymphocytes.

3.45 p.m. 81 The Relationship of Mammary Temperature to Parturition in Humans
Laurence Burd, James A. Lemons, Edgar Makowski and Giacomo Meschia Division of Perinatal Medicine, University of Colorado, Boulder, Colo.

Previous studies in pregnant sheep using electromagnetic flow probes demonstrated a 100–300 % increase in mammary blood flow (MBF) 7–10 days prior to delivery. This study attempted to detect similar physiologic changes in humans using an indirect measurement of MBF, mammary temperature (MT). Infrared radiation from the mammary gland was measured by thermography using an indium antimonide detector cooled to −196 °C. A thermal reference standard set at 34 °C was used in all studies. Sternal temperature (ST) measured by the same technique was used as a control. There were 470 examinations performed in 14 nonpregnant, 196 pregnant patients at various gestational ages and in 6 postpartum patients. MT increased from nonpregnant values until 30 weeks gestation (y = 0.05, x + 33.38, r= 0.75) and then decreased until the time of delivery, remaining, however, significantly above the mean nonpregnant MT. On the first postpartum day, MT increased and reached the highest value. In nonpregnant patients, ST (34.1 ± 0.10 SEM °C) was higher than MT (33.3 ± 0.13 SEM °C). At 18 weeks gestation, MT exceeded and remained higher than ST until term. These results suggest that in humans, unlike sheep, an increase in mammary circulation appears to occur early in pregnancy, but there is no further increase preceding labor and delivery. A further increase in MBF seems to occur following parturition.

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82 Effect of Oral Thyrotropin-Releasing Hormone (TRH) on Lactation
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The present investigation attempts to elucidate the effect of enhancing endogenous prolactin (PRL) secretion on milk production in 8 puerperal women using synthetic TRH (60 mg/day) during 4 weeks. Another 8 lactating women received placebo in a double-blind trial. Serum PRL determined at 8 a.m. was notably elevated in all postpartum women and abruptly decreased 48 h after delivery in the group of controls. This decrease persisted in these cases despite lactation. On the contrary, the gradual decline in serum PRL was markedly retarded in women receiving TRH. Moreover, women receiving TRH exhibited higher PRL increments in response to suckling. Milk samples taken before and after nursing showed that TRH had no significant effect on the milk composition. The weight gain in the infants before and after each breast feeding showed no significant difference when the mother received TRH or placebo. In a complementary study
where TRH was administered to 8 women who had been nursing for 2 weeks but showing a
decrease in milk yield, no improvement in milk production was observed. Basal FSH and LH
levels were not different in either group and they exhibited no significant changes after suckling.
It is concluded that although TRH produced a marked increment in PRL concentration, no
significant augmentation of milk production was observed. Colaterally, gonadotropin
concentration was not affected by TRH or nursing.

83  Prenatal Diagnosis of Neural Tube Defects Using Maternal Serum and Amniotic Fluid α-Fetoprotein
Robert R. Weiss, James N. Macri and Leon I. Mann
Department of Obstetrics-Gynecology and Animal Research, State University of New
York Medical School at Stony Brook, Nassau County Medical Center, East Meadow,
N.Y.

The prenatal diagnosis of neural tube defects (NTD) through measurement of α-feto-protein (α-FP) in amniotic fluid has gradually gained clinical recognition. A retrospective and prospective study was conducted at our NTD center. The retrospective analysis involved the determination of α-FP in 237 amniotic fluids from normal pregnancies ranging between 7 and 42 weeks of gestation. Based on these data a normal curve of α-FP content in amniotic fluid throughout pregnancy was established. The curve demonstrated a steady decline in α-FP from 26 µg/ml at 9 weeks to 155 µg/ml at term. α-FP was determined in 35 amniotic fluids from 33 confirmed NTD pregnancies. With few exceptions occurring only late in gestation the α-FP content of amniotic fluid was markedly elevated in the NTD pregnancies when compared to the normal curve, thus confirming its prognostic significance. α-FP was determined by radioimmunoassay in over 400 sera of normal gravidas at all stages of gestation. A normal curve of maternal serum α-FP has been constructed based on these data. Utilizing these normal curves a clinical plan of management for women at high risk for NTD has been formulated. A prospective study of 25 patients with previous NTD was conducted. Each patient underwent prenatal diagnostic procedures including sonography, amniocentesis and the determination of α-FP in amniotic fluid and maternal serum. Using this approach, two prospective diagnoses of NTD were made and confirmed after selective abortion. (Supported by Nat. Found. – March of Dimes, NICHD.)

84 Cardiovascular, Metabolic and Fetal Brain Function Observation following Total Cord Occlusion
Wolfgang Kunzel, Leon I. Mann, Amrutha Bhakthavathsalan and John Ayromlooj Department of Obstetrics-Gynecology, State University of New York Medical School at Stony Brook, Nassau County Medical Center, East Meadow, N.Y.

In 12 fetal sheep preparations (gestational age 126–137 days) the influence of total cord occlusion (TCO) on fetal systolic (S) and diastolic (D) BP, fetal heart rate (FHR), the pH, pCO2 and oxygen saturation (S02) in the fetal arterial (FA) blood and the fetal electroencephalogram (FEEG) was studied. With TCO pulse pressure increase within 60 sec (n = 9) as a result of a greater increase in the systolic [53 mm Hg (SD 7) to 86 mm Hg (SD 10)] than the diastolic pressure [39 mm Hg (SD 5) to 59 mm Hg (SD 7)]. FHR fell from 174 beats/min (SD 36) to 86
beats/min (SD 23). The cardiovascular alteration was paralleled by a linear fall in oxygen saturation: S02 = 49.7 – 0.71 •t (2α < 0.001), demonstrating that after 60 sec the FA blood was saturated with 7 % oxygen. There was only a small fall in pH and base excess during 1 min. The
alteration in the fetal EEC showed a decrease in voltage and a dropout of faster frequencies prior to the appearance of an isoelectric EEG after 60–80 sec. To identify the pressoreceptor-response to TCO the first 10 sec following occlusion were analyzed (n = 27). The increase in systolic BP during the first 3 sec was found to be related to the preocclusion p, the FA pH, and S02 and to the umbilical blood flow (Qumb) before occlusion [(Qumb): p occ. syst. =25.7·log Qumb – 38.6 (2α < 0.001)]. From these observations it is concluded that the sudden fall in FHR following TCO is initiated by a pressoreceptor response to an increase in BP due to an increased resistance in the umbilical circulation. After 8 sec a further increase in fetal BP occurs which was then due to the fall in fetal oxygenation.

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85 Rectal Colonization with Group B Streptococci
Anorectal carriage as a possible primary source for vaginal colonization of women by group B streptococci was investigated. The study included 260 third trimester gravid women

86 Rectal Colonization with Group B Streptococci

and 45 neonates. Nasal, pharyngeal, vaginal and rectal cultures were obtained on all parturients and ear canal, nose, umbilical and rectal cultures were obtained on all infants. The culture swabs obtained were transported in nutrient broth, then streaked into selective media plates consisting of blood agar base, 5 % sheep blood, 8 µg/ml of gentamicin sulfate and 15 µg/ml of nalidixic acid. Serological identification of group B streptococci was performed by the Lancefield capillary precipitin technique.

Cultures positive for group B streptococci were obtained from 56 of 260 parturients (21.6 %). Vaginal cultures were positive in 27 (10.5 %) while rectal cultures were positive in 46 (17.7 %). Of the 46 women with positive rectal cultures 19 had positive vaginal cultures; the remaining 27 had positive rectal cultures only. Among the 45 neonates cultured, 8 yielded positive cultures. The highest incidence of positive cultures (15.5 %) was obtained equally from rectum and umbilical stump. Serotyping of 55 isolates from mothers yielded 6 type la, 23 each of type II and type III, and 3 nontypeable strains. Of the 14 isolates from neonates, 4 were type la and 10 were type III. The finding that the highest colonization rate by group B streptococci occurred in the rectum of both mothers and infants, suggests that the gastrointestinal tract may act as the reservoir for this organism and that vaginal colonization in women is secondary to contamination from this source. The absence of type II from neonates is noted with interest.

86 Quantitative Analysis of Phosphorylated Metabolic Intermediates in Human TermPlacenta
Steven G. Gabbe, Shunwoo Ahn, Samuel P. Bessman and Edward J. Quilligan Departments of Obstetrics-Gynecology and Pharmacology, Los Angeles County-University of Southern California Medical Center, Los Angeles, Calif.
Almost all ATP production in the human placenta depends upon the controlled degradation of glucose by glycolysis. Quantitative analysis of this process has not previously been performed. An automated analyzer which permits the colorimetric measurement of 20 organic phosphate compounds in the nanomole range has been developed in this laboratory and applied to the collection of such data. Homogenates of 10 human term placentas have been studied. Placental levels of glycolytic intermediates such as G 1-P (0.32 nA/mg protein), F 6-P (0.65 nA/mg), and F 1,6-diP (1.55 nA/mg) are 3 times higher than those in rat hamstring muscle. Placental creatine
phosphate was found in relatively large amounts (1.47 nA/mg). ATP levels were low (2.77 nA/mg) in normal placentas and were decreased 50–75 % in specimens from deliveries of low Apgar infants or stillbirths. These studies demonstrate that (1) human term placenta has a very active glycolytic cycle, (2) placental ATP levels and energy charge are low, (3) placental ATP levels may be correlated with the status of the newborn.

87 Prolactin Production by Term Human Decidua
Daniel H. Riddick
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The source of prolactin in term amniotic fluid is unknown. Prolactin does not enter the amniotic fluid from the maternal circulation or the fetal circulation in significant quantities in the monkey (Endocrinology 94: 1364, 1974). Thus, fetal membranes have been suggested as a possible source of prolactin. This study was designed to demonstrate the site of production of prolactin. Amnion, chorion free of decidua, and decidua were incubated for 24 h

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and prolactin released into the medium was determined at various timed intervals. 20–30 ng prolactin/mg decidual protein was released into Gey’s buffer at 6 h of incubation and remained unchanged through 24 h. Amnion, chorion, and placenta released < 3 ng prolactin/mg protein over 24 h. Incubation of decidua in 10 % fetal calf serum released a similar quantity of prolactin as decidua in Gey’s buffer at 6 h, but by 24 h 100–120 ng prolactin/ml protein was released. Incubation of amnion, chorion, and placenta in 10 % fetal calf serum produced results similar to that in Gey’s buffer. N2 inhibited the stimulation of prolactin production from decidua in fetal calf serum and had no effect on the release in Gey’s buffer. Decidua contains 50–60 ng prolactin/mg protein. It is concluded that the decidua may be a major source of prolactin in the amniotic fluid of term human gestation, and synthesis of new prolactin occurs during incubation in fetal calf serum.

88 The Response of the Reproductive Tissues in the Postpartum Ewe to Estradiol-17\beta (E2)
Charles R. Rosenfeld
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Systemic infusions of E2 cause significant vasodilation in the vascular beds of reproductive tissues of nonpregnant ewes. This response is maintained throughout the ungulate pregnancy, but is altered during the last two thirds of gestation. It is obvious that these alterations are not permanent, and the vasodilatory response to E2 seen in the nonpregnant ewe should return following parturition. Utilizing a chronic sheep preparation with flow probes around the uterine arteries and a left ventricular catheter for microsphere infusions, 8 ewes were prepared prior to lambing. 1–10 days following parturition a systemic infusion of 1.0µg/kg of E2 was given over 2 min. Tissue blood flows were measured with micro-spheres. Total uterine blood flow increased 0.609 ml/min·g (306 %) on day 1 and 3.640 ml/min·g (1,578 %) on day 10 (r = 0.85), with a mean increase of 872 % ± 249 SE (p < 0.0005) by 90 min. Similar responses were seen in individual uterine tissues: (a) cotyledons: 0.154–10.357 ml/min·g (r = 0.94); (b) endometrium: 2.223–14.587 ml/min·g (r = 0.77); (c) myometrium: 0.326–2.088 ml/min·g (r = 0.83). Increases in blood flow also occurred in vagina, cervix, tubes, mammary gland, ovaries, and thyroid gland (p < 0.05). Cardiac output increased a mean of 24.6 % ± 10.7 SE (p < 0.025). When these data are compared to those obtained from near-term and nonpregnant ewes, there is a gradual return in the puerperium to the nonpregnant vasodilatory response to E2 by 10–14 days. This gradual
increase in vasodilation by the reproductive tissues to exogenous estrogen would further support
the hypothesis that the vascular beds of these tissues may be under the influence of endogenous
estrogen during pregnancy.

89 Placental Accumulation of Cadmium
Robert A. Ahokas, Wesley K. Herman and Preston V. Dilts, Jr.
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Memphis, Tenn. and University of North Dakota School of Medicine, Grand Forks, N.Dak.
Placental transfer and accumulation of cadmium (Cd), a known toxic trace element, was
investigated following a single oral dose of 10 µg-10 mg Cd/rat as CdCl2 containing 109 Cd on
day 17 of gestation. At 24 and 96 h the rats were killed and the fetuses, placentas, and maternal
tissues removed for Cd determination. At subtoxic dosages (10 µg-1 mg) 24 h
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67 fetal Cd levels were very low (0.00006–0.00020 % dose/g) and did not increase in 96 h fetuses.
The mean total fetal weight/rat at 24 h (18 days gestation) was 16.5 g while at 96 h (21 days
gestation) it was 53.4 g. Placental Cd levels ranged from 0.025–0.092 % dose/g at 24 h, and were
slightly lower, 0.013 0.071 % dose/g, at 96 h. The placental to maternal blood Cd ratio was high
(66.77–90.43 at 24 h and 29.52–45.88 at 96 h) while the fetal to placental Cd ratio was very low
(0.0023–0.0055 at 24 h and 0.0025 0.0054 at 96 h). The placenta apparently protects the fetus
from this element by accumulating Cd, at least at these dosages and this stage of gestation. A
dose of 10 mg Cd caused maternal gastric edema and loss of appetite, fetal death in 2 rats, and
maternal convulsions, and death within 24 h in 3 rats. Fetal Cd was not increased in the live
fetuses, but was higher in the dead ones (0.00236 % dose/g). It is not known whether fetal death
was a result of high Cd concentration or the Cd increase occurred after placental damage which
resulted in fetal death.

90 The Relationship between Maternal Urinary Estrogens, Pregnandiol Excretion and Neonatal
Respiratory Instability
Raja W. Abdul Karim, Alfred Steinschneider, Michael Pavy and Samir N. Beydoun Department
of Obstetrics-Gynecology, State University of New York, Upstate Medical Center, Syracuse,
N.Y.
Maternal 24 h urinary total estrogens and pregnandiol levels were determined serially on 23
normal pregnant women from the 28th week of pregnancy till term. Estrogens and pregnandiol
were expressed as a ratio of the amount of creatinine in the urine (E/C and P/C, respectively) and
their relationship with gestational age were determined for each mother. All ratios were within
the normal range. Respiratory instability in the newborn was assessed as the risk status for
prolonged sleep apnea during the first and fourth week of life. A previous study had resulted in
the development of a score which discriminated infants with prolonged sleep apnea from those
who were normal. This score obtained during a standard nap is based on the frequency and
duration of brief apneic pauses. Based on the latter results, 10 neonates were classified at high
risk for prolonged apnea (unstable respirations) and 13 at low risk.

The slope (b) of the regression line describing the relationship between E/C ratio and gestational
age was significantly less (p < 0.05) for the mothers of the high-risk infants (b = 0.93) when
compared to mothers of low-risk infants (b = 1.26). This finding was independent of birth
weight. No relationship was identified between the pregnandiol level and the infants’ risk status.
These results suggest that maternal urinary estrogens, within the ‘normal range’, are related to
respiratory control in the neonatal period.
91 Chronic Measurements of Respiratory Gases in Uterine Circulation of Pregnant Pigs D. Caton and F. W. Bazer
Departments of Obstetrics-Gynecology, Anesthesiology and Animal Science, University of Florida, Gainesville, Fla.

There are no chronic studies of respiratory gases in uterine circulation of pregnant pigs, a species with an epitheliochorial placenta. For this reason gilts and sows with known breeding dates were prepared with polyvinyl catheters implanted in main vein draining each uterine horn and in the femoral artery. Blood was collected anaerobically and analyzed for pH and O2 and CO2 contents and partial pressures with standard techniques until catheters ceased to function or animals delivered. Composition of arterial blood tended to be constant throughout gestation but there was a systematic change in venous blood; mean pO2 fell from 69.6 ± 0.71 (SEM) (30–60 days) to 57.0 ± 0.94 (80–110 days) and a-vO2 and a-vCO2 widened. Venous pO2 at term appears to be higher in pigs than in any other species studied with similar methods, a point of interest considering the pig has an epitheliochorial placenta. In addition, in 4 of 8 animals there appeared to be an inverse relationship between pvO2 and paCO2 which suggests there may be circumstances in awake animals in which the latter participates in regulation of uterine circulation.

Departments of Obstetrics-Gynecology, Anesthesiology and Dairy Science, University of Florida, Gainesville, Fla.

Uterine blood flow (UBF) of sheep varies in relation to cyclical changes in the ovary and in response to administration of a variety of hormones. Presumably, these hormones also participate in the regulation of UBF during pregnancy. However, to date no correlations have been observed between spontaneous variations in UBF and levels of endogenous hormones. For this reason, sheep (100–115 days pregnant) were ovariectomized and studied for 2–4 weeks with chronically implanted polyvinyl catheters. UBF (cm³/kg/min) was estimated with antipyrine and an indirect Fick method; plasma concentrations of free unconjugated estrone (E₁), estradiol (E₂) and progestins (P) by radioimmunoassay. In 5 of 6 animals there appeared to be a high correlation between the ratio of E₂/P in the uterine vein and UBF. However, UBF did not correlate with absolute concentration of any hormone either in arterial or venous blood. The observations suggest that UBF may change in relation to endogenous hormones. They also confirm earlier work which suggests that the ratio of hormones may be more closely related to the rate of UBF than their absolute concentrations.

93 Anaerobic Superinfection in Patients with Gonococcal Salpingitis/Peritonitis Gilles R. G. Monif, Susan L·. Welkos, Herman Baer and Robert J. Thompson Department of Obstetrics-Gynecology, University of Florida College of Medicine, Gainesville, and University Hospital, Jacksonville, Fla.

22 patients with salpingitis/peritonitis were selected by virtue of the isolation of one or more species of bacteria from exudate obtained by culdocentesis. 12 of the 22 patients had demonstrable endocervical gonococcal infection. In these 12 patients, Neisseria gonorrhoeae was the sole bacteria recovered from the cul-de-sac in three instances. Delayed plating of cultures demonstrated the presence of predominantly aerobic organisms in two instances and anaerobic
dominance in 3 other patients (concomitantly with the recovery of TV. gonorrhoeae). The 4 remaining patients with endocervical gonorrhea had obligatory anaerobic infection in the cul-de-sac. The 10 patients without demonstrable endocervical gonococcal infection in terms of their cul-de-sac isolates had a pattern of anaerobic dominance. 5 of these 10 patients had underlying structural alterations of the Fallopian tubes. The data is interpreted as supporting the concept of anaerobic superinfection following initial infection with TV. gonorrhoea to explain the polymicrobial infection observed in a significant percentage of patients with gonococcal salpingitis/peritonitis of the female genital tract.

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94 Effects of Hydrogen Bonding on Solute Permeability in the Placenta
John M. Bissonnette, Lauretta L. Richard and Walter K. Wickham
Department of Obstetrics-Gynecology, University of Oregon Health Sciences Center, Portland, Oreg.

Trace amounts of tritiated water and/or a 14C-labeled solute were injected into the carotid artery of unanesthetized guinea pigs. Transplacental flux was determined from the number of counts in the fetus and placental permeability (P) calculated by dividing flux by the time-weighted concentration gradient between maternal artery (MA) and fetal umbilical vein (FV). In separate experiments simultaneous sampling of FV showed an FV/MV ratio of 1.27 ± 0.17 (mean ± SE) for water (n = 8) and 1.38 ± 0.19 for antipyrine – 14C (n = 5). This is consistent with a counter-current or cross-current pattern of exchange and justifies the use of MA-FV as a concentration gradient. Results:

<table>
<thead>
<tr>
<th>Solute</th>
<th>Molecular K weight ether bonds fetuses (mean ± SD)</th>
<th>Hydro- Number P, ml/min/cm²/g of placental weight</th>
<th>( \text{Molecular K weight ether} )</th>
<th>( \text{Hydro- Number P, ml/min/cm²/g} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>20</td>
<td>0.003</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Antipyrine</td>
<td>188</td>
<td>0.073</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>1,7-Heptanediol</td>
<td>132</td>
<td>0.25</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Urea</td>
<td>60</td>
<td>0.00047</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

In additional experiments we calculated a placental transfer index by dividing 14C-solute/3H₂H₁₆₀ in FV by 14C-solute/3H₂H₁₆₀ in MA. For antipyrine this was 0.98 ± 0.06 (n = 8) while for 1,7-heptanediol 0.69 ± 0.05 (p < 0.05). Despite its similar size and greater lipid solubility 1,7-heptanediol is retarded relative to antipyrine which indicates the placental membranes include polar structures as well as lipid bilayers.

(Supported by HL-17150 and Ore. Heart Association.)

95 Human Uterine Artery Response to Lidocaine
Charles P. Gibbs and Stephen C. Noel
Departments of Obstetrics-Gynecology and Anesthesiology, University of Florida, Gainesville, Fla.

Local anesthetics are widely used for obstetrical analgesia. In some instances they have been held responsible for fetal distress. Although these drugs are usually considered vasodilators, their effects on the human uterine artery have not been studied. This work investigated the in vitro responses of the human uterine artery to a single dose of lidocaine hydrochloride. Six pregnant and 7 nonpregnant patients were studied. Arterial segments were taken from hysterectomy specimens and 3- to 4-mm tubular rings fashioned from each segment. The isometric contractions produced by these rings were measured in a manner similar to that reported by Faye.
and Cook (Am. J. Physiol. 222: 841, 1972). 1,000 µg/ml lidocaine caused both the pregnant and
the nonpregnant arteries to contract. The mean tension produced by the gravid arteries was
2,758.3 mg ± 591.4 while that produced by the non-gravid was 696.4 ± 324.0 (± = SE), p = <
0.01. It should be pointed out that although fetal or maternal systemic blood levels of a local
anesthetic agent would not be expected to reach 1,000 µg/ml, the uterine artery is exposed to
quantities well above that range during the
administration of a paracervical block. These in vitro results suggest that uterine blood flow
could be decreased and the fetus compromised upon exposure of the uterine arteries to high
concentrations of local agents during anesthetic procedures such as the paracervical block.
Finally, the fetal bradycardia often associated with that procedure may represent this vessel
spasm effect.

96 Possible Risk Factors for Endometritis following Elective Abortion
Ronald T. Burkman, James A. Tonascia, Theodore M. King, Milagros F. Atienza and Lonnie S.
Burnett
The Johns Hopkins University School of Medicine, Department Obstetrics-Gynecology,
Baltimore, Md.
A matched pair analysis of 228 cases of endometritis occurring over a 2-year period in 4,823
elective abortion patients was carried out. The overall incidence of endometritis was 4.7 % while
for first and second trimester cases the incidence was 3.3 and 8.1 % respectively. The risk factors
studied were positive cervical gonococcal cultures untreated preabortion, and IUD insertions
immediately after postabortal abortion. Cases of endometritis were matched with other elective
abortion patients for age, parity, race, pay status, time of performance and type of abortion
procedure. The incidence of cervical gonorrhea was 2.7 % in the entire group seeking abortion
with 14.7 % of patients with gonorrhea subsequently developing endometritis. Results indicate a
threefold increased risk for endometritis in patients with untreated gonococcal cervicitis when
compared with matched controls (p < 0.05). Similar analysis of postabortal IUD insertions
reveals a reduced risk for endometritis in those patients when compared with matched controls (p
< 0.05). This data suggests that in populations at high risk for cervical gonorrhea, the diagnosis
and treatment of the disorder prior to an abortion procedure may reduce the incidence of
subsequent endometritis. Furthermore, IUD insertions following suction abortions do not appear
to increase the risk for endometritis within a 4-week interval following the procedure as has been
shown in other studies. An explanation for the reduced risk in IUD users seen in this study may
be bias in assigning a diagnosis of endometritis to these patients.

97 Studies of Lymphocyte Populations in Preeclampsia-Eclampsia
John P. Gusdon, Jr., E.R. Heise and G.A. Herbst
Department of Obstetrics-Gynecology, Bowman Gray School of Medicine of Wake Forest
University, Winston-Salem, N.C.
The possibility that the etiology of toxemia might be immunological has been held for over 50
years. In the past decade, numerous studies have been instituted in attempts to verify the possible
role of the immune system in this disease. The present study was undertaken as a probe to
determine if a gross difference in the numbers of T and B cell lymphocyte populations might
exist between preeclamptic and normally pregnant patients. T and B cell determinations were
performed in 20 normal nonpregnant women as well as 25 normally pregnant women in the third
trimester and compared to 25 preeclamptic women. No significant differences were noted
between these groups. If indeed there is an immunological basis for preeclampsia, it is more subtle than the methodology used in this study is capable of detecting.

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98 A Simple and Reliable Assay for Corticosteroid-Binding Globulin to Correlate with Estrogen Therapy
Donald E. Moore, Shinnosuke Kawagoe, Daniel R. Mishell, Jr. and Robert M. Nakamura
Department of Obstetrics-Gynecology, University of Southern California School of Medicine and the Los Angeles County-University of Southern California Medical Center, Los Angeles, Calif.

The measurement of corticosteroid-binding globulin (CBG) as an in vivo response to exogenous estrogens has been demonstrated by many investigators. In order to evaluate this phenomenon, a simple, reliable and rapid assay for CBG was required. The assay utilizes the affinity of CBG for tritiated cortisol (3H-F). Dextran-coated charcoal (DCC) is initially used to remove all endogenous steroids. A known quantity of 3H-F is added to the sample and after equilibration, the free 3H-F is removed by DCC. An additional replicate is assayed for nonspecific binding of 3H-F. The replicate is heated to 60 °C for 30 min and subsequently incubated with 3H-F. The free is removed by DCC and the 3H-F remaining in the medium is designated as the nonspecific binding. CBG is expressed as micrograms of 3H-F bound per 100 ml serum. In 8 h 25 serum samples can be assayed in triplicate (total volume of serum required is 0.4 ml). The interassay coefficient of variation is 9%.

By this assay, the effect of estrogens was measured by the increase in circulating CBG. Women taking oral contraceptives all had CBG levels greater than 45 µg%. CBG levels in men and women without exogenous estrogens were 18–22 µg%. Pregnant women did not show an increase in CBG until the tenth gestational week and by term CBG had attained values of 46–52 µg%. Six women taking 300–500 µg of norgestrel plus 30–50 µg ethinyl estradiol began to show an increase in CBG during the twelfth hour of ingestion and by the fifth day levels had reached 35–41 µg%.

99 Quantitative and Qualitative Effects of Bolus Antibiotic in Patients Undergoing Elective Vaginal and Abdominal Hysterectomy Gilles R.G. Monif, John Rieder, Joan Thompson and Herman Baer Departments of Micro, and Obstetrics-Gynecology, University of Florida, College of Medicine, Gainesville, Fla.

The prophylactic administration of antibiotics altered postoperative infectious morbidity. The exact mechanism by which this reduction in infection is achieved has not been delineated by quantitative and qualitative bacteriological studies. The posterior vaginal pool of 20 women undergoing either vaginal or abdominal hysterectomy was sampled in a double-blind testing situation using oxygen-free premoistened cotton swabs preoperatively and then again 36 h after surgery. The swabs were transferred to a tube containing 5 ml diluent and vortexed for 30 sec. Serial tenfold dilutions were plated prepared for inoculation onto anaerobic and aerobic media. The procedure was such that 23 plates were cultured anaerobically and 20 aerobically for each vaginal swab. Aerobic isolates were identified by using a standard classification scheme. Anaerobic isolates were identified using the methods of the Virginia Polytechnic Institute of Anaerobic Laboratory. Bolus antibiotics act by radically altering the vaginal flora. Sensitive bacteria which are potential facilitating organisms in the anaerobic progression syndrome are eliminated and replaced by bacteria resistant to antibiotic administered. Local alterations in the
microbiological environment result in the significant replication of other bacteria not originally present.

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100 Correlation between Urinary 17-Ketosteroids and Serum Androgens Before and After Dexamethasone Suppression in Hirsute Patients George B. Maroulis and Guy E. Abraham
Department of Obstetrics-Gynecology, UCLA School of Medicine, Harbor General Hospital Campus, Torrance, Calif.

Although widely used, the value of urinary 17-ketosteroids (17-KS) remains in doubt in the study of hirsutism. 29 paired determinations of 17-KS and serum androgens (SA) were done in 27 hirsute women before (control) and after 7 days of dexamethasone (Dex). Upper normal levels in ng/ml serum or mg/24 h urine before and after Dex are: 17-KS 15, 5; dehydroepiandrosterone sulfate (D-S) 2,500, 400; testosterone (T) 0.5, 0.3; dihydrotestosterone (DHT) 0.35, 0.2; androstenediol (Δ5-diol) 1.6, 0.4; androstenedione (A) 2.3, 1.6; and cortisol 140, 40. All 5 women with elevated control 17-KS had elevated control SA (5 D-S, 1 T, 3 DHT, 1 Δ5-diol, 3 A). However, 19 of 24 with normal control 17-KS had elevated control SA (10 D-S, 10 T, 6 DHT, 4 A); D-S was the only steroid elevated in 7 of these, T in 2, and DHT in 1. Following Dex all 9 patients with inadequate suppression of 17-KS had also inadequate SA suppression (7 D-S, 3 T, 3 DHT, 5 A, 1 Δ5-diol). However, 15 of 20 with adequate 17-KS suppression had inadequate SA suppression (7 D-S, 6 T, 2 DHT, 7 A); D-S was the only steroid elevated in 3 of these, T in 3, DHT in 1, and A in 2. Conclusion: (1) 17-KS alone are unable to identify most patients with elevated SA. (2) Dex suppression of 17-KS correlates poorly with SA suppression. (3) In the evaluation of hirsute patients, measurement of serum D-S, T, DHT, and A gives a better understanding of the pathophysiology involved.

101 Serum Levels of Cortisol and 11-Desoxycortisol in Normal and Hirsute Women George B. Maroulis and Guy E. Abraham
Department of Obstetrics-Gynecology, UCLA School of Medicine, Harbor General Hospital Campus, Torrance, Calif.

It has been postulated that hirsute patients may have a relative deficiency in 110-hydroxylase activity of the adrenal cortex. In order to test this postulate, we have measured the serum levels of cortisol (Cp F) and 11-desoxycortisol (Cp S) and estimated the Cp S/Cp F ratio in 9 nonhirsute and 34 hirsute premenopausal women. The following levels (ng/ml) and Cp S/Cp F ratios were observed: (1) Normal women: Cp F = 105 ± 9 (x ± SE), Cp S = 0.72 ± 0.09, Cp S/Cp F ratio = 0.0070 ± 0.0006. (2) Hirsute women: Cp F = 156 ± 10, Cp S = 1.0 ± 0.07, Cp S/Cp F ratio = 0.0071 ± 0.0008. As a group, the hirsute patients had significantly elevated (p < 0.05) mean Cp F and Cp S levels but the mean Cp S/Cp F ratio was not significantly different from normal. Considered individually, only 3 hirsute patients had a Cp S/Cp F ratio greater than 2 SD above the mean normal levels. These ratios were 0.0218, 0.0139, and 0.023. If there is indeed an 11/3-hydroxylase deficiency in these 3 patients, it must be relatively minor, since a patient with documented 11/3-hydroxylase deficiency had Cp S levels of 218 ng/ml and a Cp S/Cp F ratio of 0.7. Our data suggest that 11/3-hydroxylase deficiency is not a common cause of hirsutism.

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102 Ovarian and Adrenal Contributions to Serum Steroids in Postmenopausal Women George B. Maroulis and Guy E. Abraham
Department of Obstetrics-Gynecology, UCLA School of Medicine, Harbor General
Hospital Campus, Torrance, Calif.

Serum levels (ng/ml) of cortisol (F), pregnenolone (Δ5-P), 17-hydroxypregnenolone (17-Δ5-P), dehydroepiandrosterone (D), dehydroepiandrosterone sulfate (D-S), progesterone (P), 17-hydroxyprogesterone (17-P), androstenedione (A), testosterone (T), dihydro-testosterone (DHT), androstenediol (Δ5-diol), estrone (E1) and estradiol-[Δ]ø (E2) were measured in 10 post- (Post) and 5 premenopausal (Pre) women before (control) and after 7 days of dexamethasone (Dex). Control and Dex levels of Δ5-P, P, DHT, T and F were not different (p > 0.05) in Pre vs. Post.

The control levels of 17-P, D, D-S, A, Δ5-diol, and E2 were lower in Post (p < 0.05). Assuming Dex levels equal ovarian contribution (Ov), the Ov of 17-ΔS-P, 17-P, D, Δ5-diol, A, E, and E2 (p < 0.05) and the adrenal contribution (control-Dex) to D, D-S, 17-P, A, and ΔS-diol was lower in Post (p < 0.05). Conclusion: menopause affects ovarian and adrenal steroidogenesis.

103 Rapid Detection of Endotoxin in Amniotic Fluid by the Limulus Test
John W. Larsen and John L. Sever
Department of Obstetrics-Gynecology, George Washington University School of Medicine, Washington, D.C. and Infectious Diseases Branch, NINCDS, NIH, Bethesda, Md.

Chorioamnionitis can be caused by endotoxin-producing bacteria. The newly developed limulus assay, a rapid simple means for detection of endotoxin in cerebrospinal fluid, has been examined for diagnostic use with human amniotic fluid specimens. E. coli added to human amniotic fluid reached a maximal colony count (108 organisms/ml) and maximal endotoxin content (10s ng/ml) after 10 h incubation at 37 °C. Viable colony counts and endotoxin levels remained stable during an additional 50 h incubation. The limulus assay involves the addition of 0.2 ml of amniotic fluid to premeasured limulus lysate. A positive test was formation of a firm gel after incubation at 37 °C for 1 h. The lower limit of sensitivity to endotoxin was 0.1 ng/ml saline. Using viable colony count dilutions of human clinical pathogenic isolates of E. coli, B. fragilis, Bacteroides species, Proteus species, and Enterobacter cloacae limulus assays were negative at 103 colonies/ml and positive at 106 colonies/ml. In a series of 50 human amniotic fluid specimens, the lower limit of assay sensitivity was 0.1 ng/ml in 37, 2.0 ng/ml in 6, and 4.0 ng/ml in 7. A decrease of assay sensitivity was frequently associated with meconium appearance in the fluid. Further studies are directed at measurement of endotoxin in naturally occurring amniotic infections as a means of diagnosing intrauterine infection.

104 Management of Nulliparas with Pregnancy-Induced Hypertension Remote from Term
John C. Hauth, Peggy J. Whalley and F. Gary Cunningham
Department of Obstetrics-Gynecology, University of Texas Southwestern Medical School, Dallas, Tex.

From 10/71 through 4/75, 372 nulliparous women with pregnancy-induced hypertension were admitted to the High Risk Pregnancy Unit. 62 % were admitted before 37 weeks yet 91 % were delivered after 37 weeks. Management included: hospitalization; regular diet; blood pressure 4 times daily; weight and urine protein 3 times weekly; creatinine clearance once weekly, sonography every 3 weeks. Delivery was delayed until term unless hypertension persisted or recurred following an initial salutary response. Factors other than hypertension that contributed
to delivery were (1) rapid weight gain, (2) decreasing GFR, (3) significant proteinuria, (4) fetal growth retardation, (5) severe headache or scotomata. 31% of the women had severe hypertension (> 110 mm Hg diastolic), 42% moderate (100–109 mm Hg) and 27% mild (90–99 mm Hg). 85% of patients had a good response (normotensive in 3–5 days), 9% a moderate response (intermittent mild hypertension not severe enough to warrant delivery), and 6% had a poor response which demanded delivery.

346 women remained on the Unit until delivery (mean antepartum hospitalization 24 days). Placental abruption occurred in 3 and prompt C/S was performed with delivery of healthy infants. Five infants developed RDS; all did well. Three infants were lost; perinatal mortality 9/1,000. Of the 26 who left the Unit against medical advice 4 returned with severe hypertension and dead fetuses; perinatal mortality 154/1,000.

Management of the nulliparous patient with pregnancy-induced hypertension by hospitalization and close observation is a viable alternative to delivery.

105 Effects of Naturally Occurring Steroids on the Placental Biogenesis of Progesterone S.C. Chattoraj, J.L Pinkus, A.K. Turner, D. Charles and E.W. Lowe Boston University School of Medicine, Department of Obstetrics-Gynecology, Boston, Mass. and Memorial University of Newfoundland, St. John’s, Nfld.

The biogenesis of progesterone is an important biosynthetic event occurring in the placenta. The mechanism(s) regulating the process in the placenta is poorly defined. We have investigated the effect of estriol, 17/3-estradiol, estrone, dehydroepiandrosterone (DHA), 16/α-hydroxy DHA, cortisol and prostaglandin F2α on the enzymic activity of the 30-hydroxysteroid dehydrogenase-isomerase involved in the placental conversion of pregnenolone to progesterone. Studies were carried out in vitro using 10,000 g supernatants prepared from full-term placenta. No evidence for inhibition by estriol, 16/α-hydroxy DHA, cortisol or prostaglandin F2α was found. While at high concentrations (6.67 × 10^-5 M) of

estrone, 17(3-estradiol and DHA, all were effective inhibitors, at the lowest concentrations (1.67 X 10^-5 M) only estrone and 17/3-estradiol showed significant inhibition. This in vitro finding may have some relevance to the literature report that 17/3-estradiol/progesterone ratio rises during the 5 weeks preceding labor in humans and the onset of labor occurs after the withdrawal of an inhibitory effect of progesterone on the myometrium and at a time of relative estrogen dominance. (Supported by HD-06799 and HL-15157.)

106 Immunofluorescent Studies of Liver Biopsies in Preeclampsia Fernando Arias and Raul Mancilla Departments of Obstetrics-Gynecology and Pathology, Washington University School of Medicine, St. Louis, Mo.

Seeking evidence which might resolve the existing controversy about the role of disseminated intravascular coagulation (DIC) in toxemia of pregnancy we have examined needle liver biopsies from ten patients by immunofluorescence and correlated the histologic findings with hematologic studies. Six patients with mild preeclampsia showed bright staining of sinusoids with antiserum to fibrinogen in the absence of detectable lesions by light microscopy. Two patients with severe preeclampsia exhibited by light microscopy focal areas of cell necrosis with no special topographic distribution, while immunofluorescence detected large amorphous deposits of fibrinogen in the areas of tissue destruction. Further, weak deposits of IgG and C3
were found in the areas of fibrinogen deposition and in one case IgM and C3 were found in the walls of portal vessels. Control liver biopsies of two term pregnant women studies similarly were negative.

Plasma fibrinogen, fibrin-split products and fibrin monomer were within normal limits in all patients, but four of those with toxemia exhibited thrombocytopenia. All toxemic patients showed decreased fibrinolysis and at least mild elevation of SGOT and LDH values. These findings indicate that fibrinogen deposition in liver capillaries is an early lesion in toxemia and are suggestive of an immunological basis for the disease. This study also suggests that fibrin deposition could be secondary to cell damage rather than to DIC.

107 Novel Features in the Secretion of Prolactin (PRL) during Pregnancy L·A. Rigg and S.S.C. Yen Department of Reproductive Medicine, UCSD, La Jolla, Calif.

Due to the presence of marked individual variabilities, a meaningful secretory pattern of PRL during pregnancy has yet to be established. In addition, the pattern of PRL secretion during labor and delivery has not been previously investigated. Serum PRL, estradiol (E2), estriol (E1), and progesterone (P) levels were measured by RIA in serial samples collected from 4 patients at weekly intervals throughout pregnancy. PRL levels showed a linear increase from 8 weeks to term in all 4 individuals. The increase in E2, E1, and P levels exhibited a curvilinear pattern. Thus, the correlation between pituitary PRL and placental steroid hormones is apparent only if one considers estrogen augmentation of PRL secretion.

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108 Delineation of Hypothalamic (H), versus Pituitary (P) Lesions in Hypopituitarism (Hypopit) J.S. Rakoff and S.S.C. Yen Department of Reproductive Medicine, UCSD, La Jolla, Calif.

Low basal levels of E2, LH, FSH, GH and TSH and their impairment of release in response of LRF, TRF and arginine infusion were observed in all 13 patients with hypopit studied. The basal PRL levels were highly variable but were positively correlated with responses to TRF. Since PRL is the only P hormone regulated in a reverse fashion by the H, the use of basal levels of PRL should facilitate the differentiation of H vs. P sites of defect. Accordingly, patients (n = 6) with elevated basal PRL levels had impaired release of several but not all tropic hormones and many shared in common (1) head trauma with shock or unconsciousness, (2) diabetes insipidus, (3) appropriate PRL release to TRF. From the neurophysiological point of view, the hypopit in this group of patients is secondary to H defects. In contrast is a group of patients (n = 3) with low basal PRL levels in whom response to stimuli of all P hormones including PRL were uniformly absent. It is assumed that in this group a primary P defect accounts for the hypopit. A third group of patients (n = 4) with basal PRL levels in an intermediate-normal range had partially impaired
release of all tropic hormones, including PRL. They share in common (1) large intrasellar lesion with suprasellar extension, (2) no diabetes insipidus, (3) none required full replacement therapy. A combined H-P defect appears to account for their partial hypopit. Thus, integrated analyses of PRL dynamics, degree of tropic hormone impairment and clinical correlates have provided important clues in the delineation of hypopituitarism.

109 Delineation of Abnormal Adrenal Function in Polycystic Ovary Syndrome (PCO) Howard L. Judd, David C. Anderson and Samuel S. C. Yen
Department of Reproductive Medicine, University of California at San Diego, School of Medicine, La Jolla, Calif.
The role of the adrenal gland in PCO was examined by administering dexamethasone (Dex) (1 mg Q6H x 4 days) to 13 adult and 5 young (age 13–15 years) PCO patients, and 10 regularly ovulating women. 8 a.m. blood samples were obtained and listed below are the means ± SE levels (pg/ml) found before and on the last day of Dex.

Scientific Abstracts

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<tr>
<th>Hormone</th>
<th>PCO-adult</th>
<th>PCO-young</th>
<th>Normal</th>
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<tr>
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<tr>
<td>Dex</td>
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<tr>
<td>pregnenolone</td>
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2.3 ± 0.2
10.9 ± 20* 
2.4 ± 0.5 
7.1 ± 1.0 
1.9 ± 13 
Androstenediol 
2,076 ± 217* 
563 ± 96 
1,600 ± 342* 
816 ± 102* 
890 ± 204 
309 ± 57 
Progesterone 
420 ± 62 
470 ± 81 
464 ± 112 
398 ± 72 
344 ± 171 
202 ± 63 
ΠΟΗ-Prog 
898 ± 129* 
848 ± 129* 
: 857 ± 299* 
697 ± 92* 
325 ± 32 
293 ± 42 
Androstenedione (Δ) 
2,786 ± 349* 
2,272 ± 351* 
: 2,782 ± 384* 
1,703 ± 231* 
1,080 ± 130 
684 ± 124 
Testosterone (T) 
632 ± 90* 
526 ± 85* 
719 ± 332* 
498 ± 222* 
334 ± 34 
160 ± 21 
Cortisol, ng/ml 
168 ± 9 
22 ± 3 
181 ± 15 
25 ± 3 
202 ± 23
16 ± 13
* Significantly higher than normal p < 0.05.

In summary: (1) in adult PCOs all Δ5 hormones were significantly elevated and these increases appeared to be adrenal in origin since Dex resulted in suppression to normal levels; (2) 17-OH-Prog, Δ, T were also significantly elevated but these increases appeared to be ovarian since Dex did not result in normal suppression; (3) in young PCOs similar findings were present and suggested that abnormal adrenal function may be of etiological importance in this syndrome.

110 Anterior Pituitary (P) Function in Patients with Hyperprolactinemia and Amenorrhea (PRL-A)

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Comprehensive analyses of basal P hormone (except ACTH) levels, E, and E2, and their release (Δm) following either sequential stimulation with arginine, and a single bolus of TRF (500 µg) and LRF (150 µg), or repeated stimulation with alternating doses of TRF (200 µg) and LRF (10 µg) at hourly intervals for 6 h were made in PRL-A patients (n = 22) – none of whom were receiving CNS-acting agents. When compared with values obtained in normal women during the early follicular phase (n = 11), mean basal levels of PRL, TSH and GH were elevated and E2 was reduced (p < 0.01). LH, FSH and E, were comparable. A greater Δm for LH (NS), FSH (p < 0.02) and TSH (p < 0.05), a diminished GH (NS) and an absent PRL response to sequential stimuli were discerned. When P sensitivity (S) and reserve (R) were quantitated during alternate TRF-LRF stimulation, a normal (S) and reduced (R) (NS) for LH, a greater (S) (p < 0.01) and (R) (p < 0.05) for FSH, a normal (S) and (R) for TSH, an absence of PRL response to TRF and a reduction of GH fluctuations were found. Separate analyses of PRL-A patients according to absence (n = 13) or presence (n = 9) of clinical evidence of a tumor disclosed a progressive trend of aberration for LH, GH, TSH and PRL, but a reversed situation for FSH. There was a negative correlation between (S) and (R) for FSH (but not LH) and E2 (p < 0.05). A reversal of LH, FSH and PRL but not GH abnormalities was demonstrated in 3 patients after adenoma removal. The lack of PRL release to TRF in PRL-A patients was associated with a prompt inhibition of PRL release in response to dopamine infusion and dopamine agonists (β-dopa and CB-154). These findings suggest that in patients with PRL-A, multiple P hormone derangements and low ovarian activity exist.

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111 Plasma Cortisol, Progesterone and the Renin-Angiotensin System in Mother and Fetus at Cesarean Section

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Most studies comparing neonatal and maternal renin-angiotensin-corticoid systems have been in women delivering vaginally. To obviate effects of hormonal alterations which initiate labor we...
obtained blood from umbilical artery (UA) and vein (UV) and maternal vein (M) of 29 multigravid women undergoing elective cesarean sections. All patients were normotensive, consumed unrestricted diets and had received neither diuretics nor antihypertensive drugs. Plasma renin activity (PRA), angiotensin converting enzyme activity (ACE) and cortisol (F), progesterone (P), renin substrate (RS) and angiotensin II (AI) concentration were measured by specific radioimmunoassays. Plasma protein binding of F and P were also measured. ACE was similar in mother and fetus. Other results (mean ± SEM):

Our results demonstrate that ACE is similar in mother and fetus. Data differ from others in that PRA and AI are greater in maternal blood. This discrepancy may relate to factors which initiate labor.

112 Hemodynamic Action of Histamine and Its H, Receptor Blocker in Fetal and Neonatal Lamb
JR. Woods, Jr., C.R. Brinkman, III and N.S. Assali
Department of Obstetrics and Gynecology, UCLA School of Medicine, Los Angeles, Calif.

In nonpregnant ewes, i.v. histamine decreases arterial pressure and some regional flows, whereas i.a. injections increase these same blood flows. These results have been attributed to different distribution of H, and H2 receptors in heart and peripheral circulation on the basis of blockade with specific blockers, Benadryl and metiamide. The present report deals with effects of histamine and its receptor blocker in near-term fetuses studied acutely (spinal anesthesia) and chronically (unanesthetized) and in neonates (chronically instrumented)

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79 between 3 and 70 days of age. Fetuses were tested before and after ductus occlusion. Results show: (a) in fetus, i.v. histamine produced marked fall in ductus flow and increase in pulmonary and ascending aortic blood flows; arterial and pulmonary pressures decreased; pulmonary response was blocked by Benadryl; (b) in neonate, i.v. histamine produced pulmonary hypertension and systemic hypotension, both of which increase as a function of age; (c) when neonatal pulmonary vascular resistance was raised by hypoxia, histamine produced first pulmonary vasodilatation followed by constriction which was blocked by Benadryl. Conclusion: (1) As in adult, H, receptors are dominant in pulmonary vascular bed of fetus and neonate; the different response to histamine of this bed in fetus and neonate is related to difference in the status of its resistance in the resting state. (2) The histamine-induced ductus constriction in fetus may or may not be secondary to pulmonary vasodilatation. (3) Neonatal response to i.v. histamine, although incomplete at birth, is fully developed by 3–8 weeks of life.

113 Changes in Reactivity of the Vascular Neuroeffector System after BirthC.R. Brinkman, HI, J.R. Woods, Jr. and N.S. Assali
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Previous studies in fetal lambs (60 days and term gestation) showed increasing nemo-dynamic response to autonomic agonists with fetal age mostly because of maturation of neuroeffector system. The present data deal with changes in response to norepinephrine (NE), isoproterenol (IS) and acetylcholine (ACH) in the neonatal period. Newborn lambs 3–4 days old were chronically instrumented for measurements of systemic and pulmonary pressures, and main pulmonary artery flow. The same lamb was tested at regular intervals until 60–70 days old and response compared to adult. Results show: (1) the profound pulmonary vasodilatation produced by ACH in fetus was absent in neonate and adult; when neonatal pulmonary vascular resistance
was raised by hypoxia, ACH exerted vasodilatation; ACH produced systemic hypotension and ‘paradoxical’ tachycardia in neonate and adult which were not observed in fetus; (2) in neonate, NE produced systemic hypertension and baroreceptor-induced bradycardia (contrast to tachycardia in fetus) without effects on pulmonary pressure; such response increased with age approaching adult at 5–8 weeks of age; (3) IS produced tachycardia similar to adult throughout neonatal period. Conclusions: (A) α-adrenergic neuroeffector system in peripheral circulation does not reach adult behavior until 5 weeks after birth, but β-adrenergic cardioaccelerator mechanisms are fully developed after birth; (B) cholinergic receptor stimulation in neonate produced systemic hypotension similar to adult; its negligible effects on pulmonary circulation is related to status of pulmonary vascular resistance in resting condition.

114 Placental Integrity and the Fetal Contribution to Initiation of Labor in Goats
W. Bruce Currie
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Labor is initiated in goats by PGF-provoked luteolysis and progesterone withdrawal (Pw). The release of PGF into the uterine vein ipsilateral to the fetus serves as a signal between the fetoplacental unit and the maternal ovary and is provoked by chronically elevated fetal plasma corticosteroids which have already guaranteed respiratory competence.

115 Fluorometric Studies of Uterine Bioenergetics
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The fluorometric technique of Chance, as applied by Kovach and his associates, opened up a new approach to the examination of uterine bioenergetics. This method provides continuous information about energy production of structurally intact tissues during several hours. Using this technique, the fluorescence of reduced pyridine nucleotide (366–460 nm), reflectance (366–366 nm) and corrected fluorescence were measured in the isolated rabbit myometrium under the experimental conditions described by Csapo. The fluorescence of the resting uterus in oxygenated mammalian Krebs’ solution, at 37 °C, was called 100 %. In anoxia (N2), the fluorescence of the postpartum uterus increased (reduction). Replacement of dextrose by 10 mM pyruvate decreased fluorescence (oxidation) when IAA (0.2 mM) was not present, while it increased fluorescence when IAA was present. The removal of Ca2+ from Krebs’ solution reversibly reduced pyridine nucleotide, indicating the significance of Ca2+ in the...
regulation of mitochondrial function. Electric stimulation caused oxidation in the postpartum and reduction in the pregnant uteri, a qualitative rather than quantitative difference in uterine response which illustrates the potential of the fluorometric technique in the exploration of uterine bioenergetics.

116 Metabolism of Oral Contraceptive Drugs: the Accumulation and Identity of Metabolites of Norethindrone (NOR) and Mestranol (MEST)

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Previously reported studies from this laboratory have demonstrated that 3H NOR and 3H MEST are very rapidly cleared from the plasma of subjects receiving a single i.v. injection of the drugs. However, apparent metabolites and conjugates of these drugs remain elevated in the blood for 24 h after this single injection (Am. J. Obstet. Gynec. 120: 764–778, 1974). The nature and identity of these metabolites are of interest because they are present in high concentration and over an extended period of time. In the present study, 3H NOR and 3H MEST were given by both intravenous injection and oral administration. Following injection of either drug, metabolites remain elevated for 5 days, disappearing with half-lives of 50 60 h (NOR) or 30 40 h (MEST). Oral administration of the drugs yields measurable levels of both the native drugs and their metabolites within 15 min of ingestion. While native NOR and MEST are cleared within 24 h of this oral ingestion, the metabolites remain elevated over 5 days. Further studies with NOR reveal that when 3H NOR is taken orally over several consecutive days, the metabolites accumulate in the plasma in stepwise fashion. Some blood-borne metabolites of NOR present 3 h after oral ingestion have been identified by gas chromatography and mass spectrometry and found to include predominantly NOR in the free and glucuronide fractions, while the 3α,5(3 metabolite dominates the sulfate fraction. Lesser amounts of other metabolites including 3α,5α; 3(3,5/3 and 5/3 NOR have also been documented. (Supported by NIH contract No. NOI-HD-1-2297.)

117 Ultrasonic Placental Localization and Bloody Taps in Mid-Trimester Amniocentesis

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Many prenatal diagnosis centers employ ultrasonic placental localization routinely before mid-trimester amniocentesis, hoping thereby to minimize the incidence of bloody taps and subsequent complications. The efficacy of this practice, however, is still uncertain.

In the present prospective study, amniocentesis was performed concurrently on 32 patients after ultrasound and on 50 patients without prior ultrasound. The two patient groups were homogeneous with regard to gestational length and uterine size. A single small team of obstetricians performed all the taps in a random manner. After amniocentesis, the fluids were classed as clear, transiently blood-stained, blood-tinged without clearing, and grossly bloody. Then, a different set of examiners recorded the number of red blood cells per 40 X microscopic field in the uncentrifuged fluids. A general correlation was established between these numbers and the macroscopic classifications.
No significant difference was found between the two patient groups in percentage of bloody taps, or in average fluid red cell count. Moreover, when the fluids were arranged in subgroups according to the number of red cells present, there was remarkable similarity, subgroup by subgroup, between the two series of fluids. There were no post-amniocentesis complications in the entire patient population.

These results suggest that (1) ultrasonic placental localization is not helpful in avoiding bloody taps, and (2) bloody taps are not necessarily disadvantageous. Therefore, it would seem appropriate at present to use pre-amniocentesis ultrasound selectively, based upon individual considerations in each case.

118 Pregnancy Outcome with Sickle Hemoglobinopathies. II. Evaluation of Systematic Transfusion
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Pregnancy wastage as well as maternal morbidity and mortality have been intolerably high in women with sickle hemoglobinopathies, yet low among those with sickle trait. From these observations the question is raised: ‘Will systematic RBC transfusions to increase circulating HGB A > 50 % (as normally exists with sickle trait) reduce perinatal and maternal morbidity and mortality in women with sickle hemoglobinopathies?’

To date, normal donor RBC have been transfused during 18 pregnancies (9-SS, 6-SC, 3-S-Ø-Thal) at frequencies and in amounts to maintain hemoglobin A > 50 % and sickling RBC < 50 %.

15 infants have been delivered and are healthy. One pregnancy (SS) is not yet delivered. One (SS) terminated in spontaneous abortion. One woman (SS) withdrew from the study at 20 weeks and at 31 weeks returned moribund in labor. She survived but her infant succumbed. Transfusions were terminated in one woman (S-Ø-Thal) at 27 weeks because of a rare antibody. Serious maternal morbidity developed at 36 weeks but the infant survived.

Pregnancy wastage has been reduced remarkably by this transfusion regimen. Although there were no perinatal deaths, inexplicable perinatal morbidity has been manifested by fetal growth retardation, meconium staining of amniotic fluid and fetal bradycardia. These factors, as well as transfusion-related maternal morbidity, detract from the favorable results. All of these complications must be considered if transfusion therapy is contemplated in the management of such pregnancies.

119 Effect of Cupric Ions on Progesterone-Binding Protein
Peter CM. Young, Robert E. Geary and Clarence E. Ehrlich
Department of Obstetrics-Gynecology, Indiana University School of Medicine, Indianapolis, Ind.

The effectiveness of copper-containing intrauterine device as a contraceptive was first demonstrated by Zipper in 1969, but the exact mechanism by which copper produces its effect still remains unknown. Kontula’s description of the effect of metal ions on the progesterone-binding protein of human myometrium (J. clin. Endocrin. Metab. 38: 500, 1974), prompted us to investigate the effect of cupric ions and other heavy metal ions on the progesterone-binding protein in human endometrium. When compared at a concentration of 50 µM, Hg2+ was the most potent inhibitor, followed by Cu2+, Zn2+, Cd2+ and Ag+. Fe2\ Pb2+ and Mn2+ had little
or no effect. The addition of Cu2+ to the incubation mixture decreased the apparent association constant (Ka) from $1.8 \times 10^9$ M$^{-1}$ to $4 \times 10^5$ M$^{-1}$, but the concentration of binding sites appeared to be the same. Cu2+ and Zn2+ probably exert their effect by interacting with the free sulfhydryl groups at the progesterone-binding sites of the binding protein, since dithiothreitol and thioglycerol could partially reverse the inhibition. Addition of equimolar concentrations of dithiothreitol and thioglycerol without the addition of Cu2+ had no appreciable effect on binding, but EDTA in the same concentration decreased the binding activity of the cytosol drastically. These data suggest that one possible mode of action of Cu2+ released by the Cu-IUD is the interference of progesterone action at its target sites.

120 Adequacy of Vitamin B6 Supplementation during Pregnancy

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The effects of 2.5, 4 and 10 mg of pyridoxine (PN) supplementation on maternal and fetal vitamin B6 nutritional status were compared in a prospective study by measuring the levels of pyridoxal 5'-phosphate (PLP) in maternal and cord plasma. The amount of dietary intake was assessed by dietary record. With 2.5 mg PN supplementation, 7 out of 10 subjects in the latter half of their third trimester and at the time of delivery exhibited plasma PLP levels below 4.7 ng/ml, the lower limit of normal for nonpregnant subjects. With 4 mg PN supplementation, 4 of 6 subjects at term had abnormal plasma PLP levels. With 10 mg PN supplementation, only 1 of 10 subjects exhibited abnormally low plasma PLP. Supplementation with 10 mg PN daily also significantly altered the plasma PLP concentrations in cord blood: mean PLP value in cord plasma from subjects supplemented with 10 mg PN was twice that for subjects supplemented with 2.5 mg ($p < 0.02$). In addition, a significant correlation ($p < 0.001$) was also observed between maternal and cord plasma PLP levels. The dietary records of the patients in this study revealed that only one of the 26 subjects consumed the daily ‘recommended dietary allowance’ of 2.5 mg PN. The results indicate that more than 4 mg PN supplement daily is required for most pregnancies to restore normal vitamin B6 nutrition.

121 Effect of Th1165 a Infusion on Uterine and Umbilical Blood Flow in Pregnant Sheep

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Th1165a, a /3-adrenergic agonist, has been shown to be effective in the inhibition of premature labor. Since the response of the uteroplacental circulation to the agent is unknown, we have studied its effects in chronically instrumented Dorset sheep. At 116 – 121 days gestation, electromagnetic flow transducers were applied to the main uterine artery of the pregnant horn and the intraabdominal common umbilical vein; catheters were placed in maternal and fetal vessels and the amniotic cavity. At 3–15 days postoperation, drugs were infused intravenously to the ewe for 120 min; uterine contractions were not present. Uterine blood flow (UtBF) and umbilical blood flow (UmBF) did not change during either incremental doses of Th1165 a from 0.025 to 0.200 µg/kg/min (n = 4) or single infusions of 0.025 (n = 4) or 0.200 µg/kg/min (n = 4). However, during the 120 min post-infusion recovery period, UtBF did increase 15 ± 3 % (mean ± SE) ($p < 0.001$) at 60 min and remained elevated; UmBF did not change. Dose-related elevations of maternal heart rate (MHR) ranging from 24–65 % ($p < 0.01$) occurred during both
regimens with return to control levels by 60 min after infusion. During all of these experiments, mean maternal and fetal arterial pressures and fetal heart rate did not change significantly, and maternal and fetal arterial pH, pCO2 and pO2 also remained normal.

Thus, in contrast to other clinically utilized α-adrenergic agonists we have examined in this sheep preparation, Thl 165 a does not impair uterine-umbilical blood flow nor fetal acid-base status.

122 Effect of Uterine Vascular Insufficiency on the Near-Term Sheep Fetus John H. G. Rankin and Terrance M. Phernetton
Departments of Physiology and Obstetrics-Gynecology, University of Wisconsin School of Medicine, Madison, Wise.

The late fetal bradycardia in response to some uterine contractions is thought to be caused by hypoxic depression of the fetal myocardium. We have compared the fetal responses to hypoxia caused by norepinephrine in the maternal circulation with the fetal responses to hypoxia caused by norepinephrine in the maternal circulation with the fetal.

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responses to hypoxia caused by a PGE2-induced uterine contraction in 8 near-term sheep. With these 2 drugs the uterine blood flow as measured in one middle uterine artery fell to 41 and 40 % of its control value respectively. The fetal responses to PGE2 were a bradycardia which was apparent within 10 sec (p 0.05) and a hypertension which was also apparent within 10 sec (p 0.03). Both of these changes were at a maximum at about 150 sec. The fetal heart rate and arterial pressure were still different from the control value 4 min after the injection of the drug. The fetal responses to the injection of norepinephrine to the mother were different from those that were observed with PGE2. After norepinephrine was injected into the mother there was no observable change in the fetal arterial pressure. The fetal heart rate started to fall after 30–60 sec and started to return to the control value within 90 sec. The fetal responses to uterine vascular insufficiency induced by PGE2 may not be caused by hypoxia alone as these responses were more rapid in onset than the fetal responses observed subsequent to uterine vascular insufficiency induced by norepinephrine. We postulate that some uterine contractions may be associated with strong vasoconstriction in the fetal peripheral circulation which accentuates the fetal hypoxia due to uterine vascular insufficiency.

(Supported by grant HD-06333.)

123 Plasma 11-Deoxycortisol (S) in Normal and Hirsute Women
James R. Givens, Richard N. Andersen, Winfred L. Wiser and Edward S. Urnott Division of Reproductive Medicine, Department of Obstetrics-Gynecology, University of Tennessee, Memphis, Tenn.

Ten of 20 hyperandrogenic hirsute women studied in our laboratory had an exaggerated diurnal swing of plasma androstenedione (A) synchronous with cortisol (F) and/or hyperresponsiveness of A to ACTH and were termed hirsute I women (J. clin. Endocr. Metab. 40: 988). Those with a normal A response were termed hirsute II women. Nine of the hirsute I women also had ACTH-independent hypersecretion of A; 5 had enlarged or poly cystic ovaries. Four hirsute I women had an exaggerated 17-hydroxyprogesterone response to ACTH. Since androgens inhibit 11-hydroxylase (ll(S-HOR)′ in vitro, the hypothesis was examined that there might be induced deficiency of this enzyme in hyperandro-genism. Diurnal S and/or S response to 0.5 U ACTH were measured. Mean (range) S values in ng/100 ml are shown below.

<table>
<thead>
<tr>
<th>Normal</th>
<th>Hirsute I</th>
<th>Hirsute II</th>
</tr>
</thead>
<tbody>
<tr>
<td>S at diurnal F peak, (S)fp</td>
<td>162(95–256)</td>
<td>207(85–287)</td>
</tr>
</tbody>
</table>
S at diurnal F nadir, (S)fn 68(39–98) 42(17–82) 65(34–94)
(S)fp-(S)fn, Δ(S)d 94(1–200) 166(38–253) 106(42–192)
(S) before ACTH, (S)o 95(20–283) 77(39–120) 64(34–120)
(S)maxF 273(113–452) 289(196–389) 302(222–438)
(S)maxF-(S)o, Δ(S)ACTH 178(81–324) 213(113–298) 238(171–390)

Means of the 3 groups were not different. Although 2 hirsute I women had greater than normal Δ(S)d, deficiency of 11/3-HOR is uncommon in hyperandrogenism. Apparent deficiency of 21-hydroxylase was more common. Factor(s) other than deficiency of these 2 enzymes are operative in some cases of ACTH-dependent hyperandrogenism.

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124 Effects of Denervation and Nerve Stimulation on Contractility of the Rabbit Ovary
Stuart Weiner, Karen H. Wright and Edward E. Wallach
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Sympathetic neural mechanisms have been described in the smooth muscle of the uterus and Fallopian tube. Although ovarian smooth muscle activity also responds to adren-ergic drugs, the role of the ovarian nerves in this mechanism has not been fully described. The neuromuscular mechanism of the rabbit ovary was studied using 2 approaches. In one group of 9 rabbits, the in vivo contractility of one ovary was measured 3 weeks after surgical ovarian denervation. Six of 9 ovaries demonstrated spontaneous contractions, and all of these responded to α- and β-receptor blocking and stimulating agents. In a second group of 12 rabbits, ovarian contractility and the effects of electrical stimulation of the ovarian nerve were studied in an isolated perfused organ system. All 12 ovaries demonstrated spontaneous contractility. Electrical stimulation of the ovarian nerves had a β-stimulating effect, inhibiting ovarian contractility, but this effect varied with the hormonal state of the rabbit at the time the ovary was excised. These studies suggest that ovarian smooth muscle contains α-and β-receptors which can act independently of the ovarian nerves, but that neural and hormonal influences may alter receptor dominance and muscular activity. This neural modulation of ovarian contractility may alter the known adrenergic effect on ovulation in the rabbit.

125 Apparent Free Testosterone Concentration in the Management of Androgenicity
Walter G. Wiest, John D. Paulson, David W. Keller and James C. Warren Department of Obstetrics-Gynecology, Washington University Medical School, St. Louis, Mo.

Physiologically effective levels of testosterone (T) are represented by circulating non-protein-bound T. We report use of a method for evaluating androgenicity which measures T-binding activity (TBA) and estimates the apparent free T concentration (AFTC) of diluted serum. 3H-dihydrotestosterone (DHT) is used to measure steroid-binding activity. After equilibration with diluted serum, unbound steroid is removed by adsorption to dextran-coated charcoal. Serum is diluted serially over a range at which bound and unbound DHT are equal (TBA). Serum AFTC is calculated from total T concentration (determined by radioimmunoassay) and from TBA (Karolinska Symp. No. 2, Geneva, 1970, p. 225). Normal values (mean ± SD) for total T and AFTC were: 0.48 ± 0.18 ng/ml and 4.2 ± 2.5 pg/ml respectively. Total T and AFTC for a group of 22 hirsute females were: 0.73 ± 0.28 ng/ml and 13.4 ± 6.9 pg/ml. Decadron suppression lowered total T and AFTC in 42 % of patients studied; however, 19 % responded with lowered total T and no reduction in AFTC. Enovid-E (1 tablet/day × 18 days + 1 mg Decadron at bedtime) administered following Decadron was uniformly effective in lowering AFTC; however,
33% of patients had increased total T during Enovid therapy. Proper clinical management could
not have been achieved by reliance on the total T assessment; on the other hand, evaluation of
AFTC provided a reliable monitor of effective drug suppression.
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126 Sulfatase Activity in Human Fetal Membranes
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Tex.
By virtue of the proximity of the human fetal membranes to both decidua and the amniotic fluid-
fetal compartment, the fetal membranes may play a central role in the initiation of labor.
Therefore, we sought to define if these nonvascularized extensions of the placenta might be
capable of steroid hormone synthesis in situ. Since most of the Δ5–3/3-hydroxy steroids found in
the fetal component are conjugated as sulfatases, we initially looked for sulfatase activity in
these membranes. The chorion, but not the amnion was found to have this activity. Additionally,
after cell fractionation, the highest specific activity was concentrated in the endoplasmic
reticulum.
Using (7–3H)-dehydroisoandrosterone sulfate as the substrate we found the following
Tissue preparation Dehydroisoandrosterone, pmol·mg⁻¹ protein·h⁻¹
chorion + amnion
Homogenate 661
0.7
187
800 g pellet
77
25
50
20,000 g pellet
1,710
3
272
157,000 g supernatant
258
0
84
The kinetics of the chorion sulfatase were studied using tissue minces, homogenates and
microsomal preparations. Using microsomes, the sulfatase reaction is linear up to 1 h and the pH
optimum is 6.8–7.0.
127 Angiotensin II Pressor Responsiveness in Normal and Hypertensive Gravidas Before and
After Progesterone
Normotensive gravidas are resistant to the pressor effects of angiotensin II (ATI). Conversely, gravidas with pregnancy-induced hypertension (PIH) exhibit increased sensitivity to ATI. Because recent evidence suggests that pressor responsiveness to A-II during pregnancy is not controlled by circulating levels of A-II as in nonpregnant subjects, the present study was conducted to ascertain if progesterone (Prog) might have an effect on the control of pressor responsiveness to A-II (ng of A-II·kg⁻¹·min⁻¹ required to ↑ diastolic BP 20 mm Hg) was measured before 200 mg of i.m. Prog and 15 min, 1, 2, 3, and 4 h after Prog. Plasma levels of Prog and 5α-pregnan-3,20-dione (5α-DHP) were measured before each A-II infusion. In both groups of women exogenous Prog increased plasma levels of Prog and 5α-DHP. In women with PIH, increased amounts of A-II were required to elicit a pressor response following Prog administration; however, in normotensive gravidas, decreasing amounts of ATI were required. After an initial increase or decrease, 5α-DHP levels paralleled ATI pressor responsiveness in both groups.

128 A Rapid Screening Technique for Detection of Y Chromosomes in Human Leukocytes
John D. Paulson, David W. Keller, Kenneth I. Muhlendorf and Connie fatherly
Division of Reproductive Endocrinology, Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.
The diagnosis of gonadal dysgenesis necessitates the exclusion of the Y chromosome which, if present, is associated with a high incidence of ovarian neoplasm. This paper describes a simple, rapid, inexpensive technique for determining the presence of Y chromosomes in peripheral blood smears. Using a fluorescent staining technique which identifies the Y chromosome in the leukocyte, 16 normal patients and 7 patients with detectable chromosomal or anatomical abnormalities were analyzed for the Y body. The correlation between predicted sex and actual sex of the individual in the normal patients studied was 100%. Predicted sex in the patients with abnormalities corresponded to the chromosomal sex as determined by blood karyotyping. The correlation with actual sex, using probability tables from Baye’s formula, was shown to be accurate when used with a 99% confidence limit. This procedure can be utilized in the investigation of primary amenorrhea as a screening method prior to more expensive and time-consuming karyotyping procedures.

129 Hormonal Control of Genital Microflora
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The role of bacteria in the pathogenesis of nonspecific vaginitis is poorly understood, due to a paucity of knowledge concerning the interactions of the vaginal microflora with the mucosa of the genital tract. An animal model is described which demonstrates changes in the bacteriology of the vagina in relation to hormonal fluctuations. Quantitative estimation Society for Gynecologic Investigation
of vaginal bacterial counts based on microscopic examination of gram-stained vaginal smears and viable plate counts of bacteria recovered by vaginal lavage from mature, virgin, randomly-bred, albino rats, showed that the number of bacteria colonizing the genital tract increases during proestrus and estrus phases of the sex cycle to levels as much as 100,000 times those observed during diestrus. Transmission and scanning electron microscopy of the vaginal epithelium at various stages of the estrus cycle corroborated the finding of cyclically varying bacterial counts in the rat vaginal tract and demonstrated the ultra-structural relationship between the microflora and its supporting tissue. Following ovariec-tomy, vaginal bacterial counts fell to levels comparable to those found during diestrus, while estradiol treatment of ovariectomized rats raised bacterial counts to levels characteristic of estrus in intact rats. The enhancement of vaginal colonization by estrogen in ovariectomized animals was antagonized, but not abolished, by progesterone. Light microscopy of vaginal contents demonstrated an affinity of vaginal bacteria for the cornified cells resulting in forms similar to those described as ‘clue cells’ in humans. These findings suggest clinically applicable manipulation of vaginal colonization might be possible with specific hormonal therapy.

130 Hormonal, Histochemical, and Autoradiographic Studies in Luteal Phase Insufficiency (LPI)
Hans D. Taubert, Gunter Bastert and Josef Geisz
Division of Gynecologic Endocrinology, Department of Obstetrics-Gynecology, J.W. Goethe University, Frankfurt am Main
The characterization of LPI by hormonal and histological parameters has remained an unsatisfactorily solved diagnostic problem. As a consequence, we studied 20 presumably ovulatory women with no known cause of primary infertility. LH and progesterone were measured daily beginning 4–5 days prior to the assumed day of ovulation and continued until menstruation ensued. An endometrial biopsy was taken between day 22 and 25 of the cycle. In addition to conventional histologic techniques, the specimens were subjected to autoradiography and the histochemical determination of 16 enzyme activities. On the basis of the biopsy results and the progesterone determinations, only 10 of the 20 cases were considered as having LPI. In 5 of those 10 patients, serum progesterone was found to be lower than normal, and shortened luteal phases in another 3. Decreased LH peaks were also seen in 5 cases. The histochemical studies did not reveal any differences between either group. Contrary to this, there was a significantly lower number of marked cells in the LPI group (p < 0.05), particularly in stromal cells. This was interpreted as meaning that stromal alterations could play a considerable role in the genesis of LPI.

131 Placental Clearance of Dehydroisoandrosterone Sulfate before, during and after Indomethacin Administration in Pregnant Women
John C. Hauth, Normal F. Gant and Peggy J. Whalley
Department of Obstetrics-Gynecology, University of Texas Southwestern Medical School, Dallas, Tex.
It is likely that the prostaglandins play an integral role in the initiation of labor. Blocking production of these compounds by the prostaglandin synthetase inhibitor indomethacin has been reported to arrest uterine contractions in pregnant women by Wiqvist and in a prospective study of premature labor by Zuckerman. However, it also has been demonstrated that prostaglandins are necessary for the maintenance of uterine blood flow.
flow in gravid rabbits, dogs and monkeys. In addition, the animals became hypertensive when
these inhibitors were used. A provocative question must now be raised! Is the use of a
prostaglandin synthetase inhibitor safe in pregnancy?
The placental clearance of DS to estradiol (E2) (PC_{\gamma jse}) has been measured to date in 5 normal
pregnant volunteers. Studies were done before, during and after indomethacin administration (25
mg p.o. t.i.d. or q.i.d.). None of the women became hypertensive and all infants were normal at
delivery.
If pretreatment P%SE values are compared to treatment measurements, 3 of 5 women had an
average decrease of 14% (9.4–8.1 ml/min) and 2 women an average increase of 18% (12.6–14.9
ml/min). If the pre- and posttreatment values are averaged and compared to the treatment values,
4 of the women had values decreased 18% (10.2–8.4 ml/min) and one woman had an increase of
16% (17.8–20.7 ml/min).
The present study must be expanded but suggests along with animal data that indomethacin
might decrease uterine perfusion.
132 Quantitation of Proacrosin and Acrosin in Human Spermatozoa Kenneth L. Polakoski
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis,
Mo.
During the fertilization process, mammalian sperm use an acrosomal proteinase (acrosin EN
3.4.21.10) to penetrate the ovum’s zona pellucida. At the time of ejaculation, acrosin is inactive
and is activated during the capacitation process. The objective of this study was to determine the
amount of proacrosin (an inactive acrosin precursor) and total acrosin in freshly ejaculated
human spermatozoa. The sperm from eight individual ejaculates were removed from the seminal
plasma after liquefaction via centrifugation through a sucrose gradient. Acrosomal extracts were
prepared from the sperm and assayed for proacrosin and acrosin with N-\(\alpha\)-benzoyl-Z-arginine
ethyl ester (BAEE) at 253 nm. The total acrosin content per 106 sperm was between 5.22 and
8.90 U with a mean of 6.91 U (1 U = 1 nmol of BAEE hydrolyzed per minute at 25 °C at pH
8.0). Shortly after ejaculation, more than 90% of the total acrosin present is in the proacrosin
form. These data indicate that human spermatozoa may undergo the process of capacitation prior
to the act of fertilization.
(Supported by a grant from the Rockefeller Foundation and by grant HD 09422–01 from NIH.)
133 Indomethacin Prevention of Death Following Intravenous Injection of Placental Material
Ernest J. Ewaschuk, Richard S. Childs, Kenneth P. Satin, Burton V. Caldwell and Leon
Speroff
Department of Obstetrics-Gynecology, Yale University School of Medicine, New
Haven, Conn.
An animal experimental model was devised to study the mechanism of shock and death in
amniotic fluid embolism, utilizing intravenous infusion of material prepared from human
placental tissue. The supernatant of a human placental homogenate produced rapid shock, with
no survivors, in 8 virgin and 4 pregnant white New Zealand rabbits. Pretreatment with
indomethacin prevented death in 6 of 7 virgin females, but failed to prevent death in
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6 pregnant animals. Differential ultracentrifugation of the placental homogenate produced Pellet-
II, rich in mitochondria, ER derivatives, and free ribosomes (as verified by EM). As suspension
of Pellet-II in saline was infused intravenously, rapidly causing shock and death in 3 virgin and 3
pregnant rabbits. Indomethacin pretreatment prevented death following Pellet-II in 3 virgin and
in 2 of 3 pregnant rabbits. Prostaglandin blood levels were measured by radioimmunoassay; PGE and PGF increased immediately after injection of Pellet-II, and prior to death, in the virgin animals. In the pregnant animals, infusion of the Pellet-II suspension was immediately followed by a decrease in PGE and an increase in PGF. Pretreatment of virgin and pregnant animals with indomethacin was associated with lower prostaglandin levels before and after infusion of Pellet-II.

These results suggest that prostaglandins are instrumental in the shock and death induced by the entry of placental tissue components into the vascular system.

134 Shake Test: Graded Prediction of Risk of Respiratory Distress Syndrome (RDS) and Association of Neonatal Asphyxia and Shock
Departments of Obstetrics-Gynecology and Pediatrics, and Cardiovascular Research Institute, University of California, San Francisco, Calif.
This investigation examined the associations between fetal pulmonary lung maturity, as predicted antenatally with the shake test, birth asphyxia, cardiovascular shock, and development of RDS in the newborn. The accuracy of the shake test was assessed in 196 patients that delivered within 24 h of amniocentesis. 1 of 103 positive tests was associated with neonatal RDS.

In the 93 cases wherein the shake test was less than positive there were three levels of test reactivity, each level indicating different pulmonary maturity and a risk of developing RDS of either 70, 33, or 7%. In 60 of these 93 patients, detailed studies of blood pH, PaO2, PaCO2, hematocrit and blood pressure were made within minutes of delivery. No infant excluded from these latter studies developed RDS. 32 of 60 infants had asphyxia and 16 of these newborns were in shock. 3 of 60 infants exhibited shock without asphyxia. RDS developed in 17 of 19 newborns with shock and in 6 of 16 newborns with only asphyxia. Only 2 of 28 newborns without shock or asphyxia developed RDS. Within each shake test risk category the incidence of RDS decreased as birth weight increased. Severity of RDS was similar in the three different shake test groups at risk.

135 Differences in Serum Progesterone (P) and Estradiol (E2) between Normal Pregnancies and Those Complicated by Various Types of Premature Labor
Larry Cousins, R. Jeffrey Chang, Calvin J. Hobel and John R. Marshall Harbor General Hospital, UCLA School of Medicine, Department of Obstetrics-Gynecology, Torrance, Calif.
Serum P and E2 levels were measured serially by radioimmunoassay in 19 normal pregnancies, in single samples in 60 pregnancies with premature labor, and serially in 5 pregnancies prior to the onset of premature labor. In normal pregnancies E2 values steadily increase to term, while P values steadily rise between 26 and 32 weeks then the rate signifi-

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antly (p < 0.02) increases between 32 and 34 weeks followed again by a steady rise to term. No significant change in P or E2 occurs immediately prior to term labor. Premature labor patients have significantly lower P and E2 levels than controls. Pregnancies complicated by idiopathic premature labor (IPL) (p < 0.001), abruptio (A) (p < 0.01), marginal separation (MS) (p < 0.05) and premature rupture of membranes (PROM) (p < 0.01) have significantly lower P levels than controls. Patients with IPL and A-MS have significantly lower P levels (p < 0.05) than PROM patients. Of the premature patients followed serially, 3 with IPL had persistently low P levels
prior to the onset of labor, whereas one with A and one with PROM had normal P levels until they became symptomatic at which time the levels fell. Conclusions: (1) serum P levels significantly increase in normal patients between 32 and 34 weeks; (2) premature labor patients have significantly lower P and E2 levels than controls; (3) the degree and onset of P depression varies according to the type of premature labor, and (4) IPL is characterized by premature labor with no predisposing cause except persistently low P levels.

136 Metabolism of Progesterone by the Human Fetal Membranes
Leon Milewich, Normal F. Gant, Barry Schwarz, Russell A. Prough, Grace Chen, Bob A they and Paul C. MacDonald
Departments of Obstetrics-Gynecology, and Biochemistry, University of Texas Southwestern Medical School, Dallas, Tex.

Considerable evidence has accrued that suggests the human fetal membranes participate in key metabolic events that culminate in the initiation of parturition. An important mediator of these biochemical signals appears to be the metabolic action of progesterone in the amnion and chorion laeve. For this reason, we studied the metabolism of progesterone by the two components of the human fetal membrane form various stages of pregnancy. After dissection, chorion and amnion preparations were incubated with (1,2,6,7-3H)-progesterone in the presence of added NADPH. Conversion rates into the metabolites 5α-pregane-3,20-dione (5α-DHP), 20α-hydroxy-4-pregnen-3-one (20α-DHP) and 3β-hydroxy-5α-pregnan-20-one (3/3-30H-5α-P) were calculated taking into consideration the initial velocities and the endogenous levels of progesterone, measured by RIA. It was found that the conversion rates are higher prior to 17 weeks of gestation and that these rates fall towards the end of gestation.

<table>
<thead>
<tr>
<th>Tissue preparation</th>
<th>Metabolite, pmol·mg-1 protein·h-1</th>
<th>14-17 weeks</th>
<th>36-40 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorion laeve</td>
<td>Sot-3/3-OH-5α-20α-30-OH-5α-P DHP DHP</td>
<td>1.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Amnion homogenate</td>
<td></td>
<td>2.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>

These results are consistent with the view that a decreasing catabolism of progesterone with advancing gestation occurs and may be the consequence of a metabolic removal of progesterone from its active metabolic sites within the membrane cells.

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137 Ø-Adrenergic Stimulation and Fetal Oxygenation in the Primate
/. Joelsson, R.E. Myers and K. Adamsons
Departments of Obstetrics and Gynecology, Sabbatsberg Hospital, Stockholm; Women and Infants Hospital of Rhode Island, Brown University, Providence, R.I., and Laboratory of Perinatal Physiology, NINCDS, NIH, Bethesda, Md.

Infusion of isoproterenol (1 µg/kg/min i.v.) into the anesthetized, pregnant rhesus monkey near-term impaired fetal oxygenation despite diminishing myometrial activity. The decline in pO2 of the fetal arterial blood (mean = 4.3 ± 2.3 mm Hg SD) was accompanied by a rise in pCO2 (mean = 4.6 ± 2.7 mm Hg) and a decline in pH (mean = 0.04 ± 0.02 SD), and was limited to the period of infusion. Similar changes, but of greater magnitude, were observed in the composition of fetal blood when the corresponding dose of isoproterenol was administered directly to the fetus. Evidence was obtained of transfer of isoproterenol from mother to fetus. The present findings point out that Ø-adrenergic agents whether used in the presence or absence of labor may cause
reduction in oxygen supply to the fetus; they also emphasize the need for the development of compounds which inhibit myometrial activity without altering adversely the blood flow to the uterus.

138 Demonstration of a Bacterial Sperm Immobilization Factor
John D. Paulson and Kenneth L. Polakoski
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.

Treatment of ‘sperm toxic bacteria’ in subclinical prostatic and cervical infections often aids in achieving pregnancies. Escherichia coli have previously been implicated in some cases of infertility due to the immobilization and/or agglutination of spermatozoa. This report describes our attempts at investigating the mechanism by which bacteria immobilize spermatozoa. An immobilizing factor (IF) was obtained from E. coli cultures by filtration through a 0.22 µm Millipore filter. The test system consisted of adding 10 µl of the filtrate to 100 µl of the sperm suspension (40–100 X 10^6/ml) and incubating the samples for various time intervals from 15 to 60 min. Aliquots were removed, examined microscopically, and the percentage of spermatozoa demonstrating progressive motility, nonprogressive motility, and no motility was recorded. Controls of sperm diluted with either saline or growth medium were performed. The IF was stable to boiling for 15 min, and could be lypholized. It was dialyzable which indicates a molecular weight of less than 6,000 daltons. This is the first report of a low molecular weight bacterial sperm immobilization factor.

(Supported by a grant from the Rockefeller Foundation and by grant HD 09422–01 from NIH.)

139 Removal of Dead and Agglutinated Spermatozoa from the Ejaculate
John D. Paulson and Kenneth L. Polakoski
Department of Obstetrics-Gynecology, Washington University School of Medicine, St. Louis, Mo.

The human ejaculate contains a mixture of motile, nonmotile, dead, and agglutinated spermatozoa as well as various types of debris. A glass column has been devised which removes the majority of the debris, dead, and agglutinated spermatozoa from the semen sample. The use of the column on semen samples possessing increased viscosity accompanied by poor progressive motility yields a sample with apparent normal viscosity and an increased percentage of forward progressing sperm. The treated samples also undergo better in vitro cervical mucus penetration and maintain a higher percentage of motile sperm after freezing in liquid nitrogen. Since a serious limitation to the clinical diagnosis of both the immobilizing and agglutinating sperm antibodies is the quality of the ejaculate being tested, it is suggested that the above technique can be useful in such analysis.

(Supported by a grant from the Rockefeller Foundation and by grant HD 09422–01 from NIH.)

140 Pituitary-Adrenal Axis in Pregnancy
C.R. Parker, jr., B.D. Carr, J.D. Madden, PC. MacDonald and J.C. Porter
Department of Obstetrics-Gynecology, Southwestern Medical School, Dallas, Tex.

The function of the pituitary-adrenal axis was evaluated throughout gestation in 9 women, of whom 7 had uneventful pregnancies, one developed preeclampsia, and one bore a growth-retarded fetus which eventually died in utero. The plasma concentration of ACTH, cortisol, and prolactin were determined at weekly intervals and at the time of delivery. The mean plasma concentration of these hormones in the women with normal pregnancies tended to rise.
throughout the period of gestation. Their values (mean ± SE) for each trimester and delivery are as follows:

<table>
<thead>
<tr>
<th></th>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>3rd trimester</th>
<th>Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol, ng/ml</td>
<td>242 ± 45</td>
<td>315 ± 50</td>
<td>519 ± 136</td>
<td>937 ± 165</td>
</tr>
<tr>
<td>ACTH, pg/ml</td>
<td>31 ± 7</td>
<td>38 ± 9</td>
<td>48 ± 10</td>
<td>257 ± 114</td>
</tr>
<tr>
<td>Proiactin, ng/ml</td>
<td>88 ± 6</td>
<td>169 ± 13</td>
<td>250 ± 9</td>
<td>239 ± 27</td>
</tr>
</tbody>
</table>

In the woman with preeclampsia, plasma ACTH and cortisol levels were generally higher than those in normal women. Following hospitalization and bedrest, her cortisol levels fell appreciably. However, her ACTH levels remained elevated, attaining a value of 116 pg/ml during the 38th gestational week. In the patient bearing a growth-retarded fetus, the ACTH levels rose steadily until the 26th gestational week, the time when intrauterine growth retardation was diagnosed. After the 26th week, the ACTH levels fell by 50 %, whereas the cortisol levels continued to rise through the 36th week. After the 36th week, cortisol levels declined sharply, coincident with diagnosis of intrauterine fetal death. In 24 h studies conducted in 2 patients during each trimester, the circadian rhythm of cortisol was obvious while that of ACTH was less apparent. Additionally, the diurnal variations in plasma cortisol became more pronounced as pregnancy progressed.

141 A Study of Histocompatibility between Recipient and Donor Lymphocytes in Human Chimerism
Mechanisms accounting for the persistence of donor lymphocytes in fetal recipients for years following intrauterine transfusions were investigated. The phenomenon of this tolerance can be best explained by the presence of defects in the stimulating and/or responding capabilities of the recipient and/or donor (as revealed by one-way mixed lymphocyte reactions), thereby either rendering the recipient incapable of rejecting the transfused donor lymphocytes or rendering the donor lymphocytes incapable of providing sufficient antigen stimuli to elicit
rejection in the recipient. Although there was partial HL-A identity between the recipient-donor pairs (using lymphocytotoxicity tests) which may have been integrally involved as a contributing factor in the long-term persistence of donor lymphocytes. As indicated by the strength of response to the plant mitogens, PHA and PWM, it is evident that the degree of tolerance observed cannot be attributed primarily to the lack of immuno-logical competency of the recipient and/or donor lymphocytes. Blocking factors which are identifiable in recipient plasma must therefore be considered as likely contributors to the resulting tolerance. And other factors, e.g., strong versus weak antigenic combinations probably play important but as yet undefined functions in the elicitation of graft acceptance.

142 Assessment of Fetal Pulmonic Maturity by Measurement of the Surface Tension of Amniotic Fluid Lipid Extract.
Chandra M. Tiwary and John W. Goldkrand
Departments of Pediatrics and Obstetrics-Gynecology, University of Nebraska College of Medicine, Omaha, Nebr.
Fetal pulmonic maturity is currently predicted by the L/S (lecithin/sphingomyelin) ratio in amniotic fluid which correlates with changes in the lecithin component of ‘surfactant’ within the fetal lung. The present study was undertaken to determine whether or not changes in ‘surfactant’ found in amniotic fluid could be measured directly. The surface tension (7) of various aliquots of a lipid extract from the amniotic fluid of 45 patients was measured by a modification of the Wilhelmy plate method. The lipids were quickly extracted using a chloroform:methanol solvent (2:1, v/v) and concentrated to a final volume of a quarter of the original amniotic fluid volume. Analysis of the 7 imparted by 80 µl (λ) of the lipid extract indicated that values of < 67 dyn/cm correlated with pulmonic maturity (as verified by the L/S ratio), while values of > 67 dyn/cm suggested further by determining the 7 imparted by a 200-λ aliquot of the extract: if > 67 dyn/cm at 80-λ but < 56 dyn/cm at 200-λ were considered ‘transitional’, but values > 56 dyn/cm at 200-λ were clearly immature. Compared to the L/S ratio, assignment of mature, immature or transitional surface tension status to each patient yielded no false-positives (mature 7 with immature L/S) and only 13.6% false-negatives (transitional or immature 7 with a mature L/S). In a preliminary clinical correlation, two patients with immature 7 had babies who developed respiratory distress syndrome. These results suggest that direct measurement of the surface tension of an amniotic fluid lipid extract may yield a more rapid and, perhaps, more reliable method of predicting, antenatally, the state of fetal pulmonic maturity.

143 Intrauterine Endoscopy and Sampling the Fetoplacental Circulation in the Pregnant Sheep
Ezra C. Davidson, Jack E. Maidman, Jerry E. Brown and John A. Morris
Department of Obstetrics-Gynecology, Chas. R. Drew PG Medical School, Los Angeles, Calif.
The present effort, still in progress, entails the development of a suitable experimental animal model for intrauterine endoscopy (fetoscopy) and sampling the fetoplacental circula-

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Postendoscopy abortion ensued within a week in 8 of 34 animals (24%) in which the pregnancy was allowed to continue. Despite the obvious differences in placentation and uterine morphology which distinguish the ewe from the subhuman primate and the human model, we conclude that both methods provide the endoscopist with a useful experimental animal model to develop and to test intrauterine endoscopic devices and techniques.

(Supported by DHEW-HL grant 15997.)

144 The Enigmatic Centric Segments of the Human X Chromosome
Gloria E. Sarto and Eeva Therman
Departments of Obstetrics-Gynecology and Genetics, University of Wisconsin Center for Health Sciences, Madison, Wis.
The Q-dark region next to the centromere on Xq is presumed to contain the X inactivation center. Without it the chromosome cannot form a Barr body and the cell—or possibly the chromosome itself—is inviable. If the X chromosome has two inactivation centers, a proportion of the Barr bodies are bipartite. The incidence of bipartite bodies and the distance between the two parts seem to be positively correlated with the distance between the inactivation centers on the chromosome. However, if the Q-dark region next to the centromere on Xp lies between the inactivation centers, the incidence of bipartite bodies is greatly increased and the distance between the two parts is longer and shows a greater variance. On the basis of this observation and the results of length measurements of the Q-region, we have put forward a hypothesis that this region on Xp stays active on the inactive X.

145 Effect of Cortisone Administration on Fetal Lung Surfactant Activity
John W.C. Johnson, Henry S. Lim, Kevin C. Kearney, Norman H. Daikoku and Rachel E. Scott
Department of Obstetrics-Gynecology, Johns Hopkins University School of Medicine, Baltimore, Md.
Previous studies have indicated that glucocorticoids may accelerate surfactant production in the lung of the premature fetus and its prenatal administration has been advocated as a means of preventing the idiopathic respiratory distress syndrome.

The objective of this sheep study was to determine the effects of fetal intraperitoneal hydrocortisone sodium succinate administration (50 mg daily for 3–5 days) on multiple parameters of fetal lung surfactant. 30 fetuses (singleton or twin) of known gestational ages were used for these studies. The correlation coefficients for gestational age and each of the following lung values: extract surface tensions ($7m\Pi$; $\%a\chi$); maximum inflation volumes ($V_{\text{max}}$); residual deflation volumes ($V_{15D}$); phospholipid concentrations (PL/DNA) and lecithin concentrations (L/DNA) were highly significant ($r = \pm 0.7$; $p < 0.005$); indicating all of these parameters are acceptable indices of lung maturation. Although plasma cortisol values in the treated fetuses (100–130 days gestational age) were 5–20 times those of untreated lambs, curvilinear covariance analyses demonstrated no significant differences between the two groups for $7m\Pi$, $7m\chi > V_{\text{max}}$, $V_{15D}$, PL/DNA or L/DNA. These negative findings raise important questions regarding species differences, mechanisms of action, and efficacy.

146 Secretion of Progesterone during Pregnancy in the Rat
Mrinal K. Sanyal and Claude A. Villee
Laboratory of Human Reproduction and Reproductive Biology, Department of Biological Chemistry, Harvard Medical School, Boston, Mass.
The concentration of progesterone and 5α-pregnane-3,20-dione in ovarian and uterine venous plasma and in the systemic circulation was measured during gestation in the rat. The steroids were quantified by radioimmunoassays after separation on silicic acid micro-columns. Throughout gestation the concentration of 5α-pregnane-3,20-dione was small relative to that of progesterone and showed no marked change as gestation proceeded. The concentration of progesterone in ovarian venous effluents was 10–20 times higher than that in the uterine vein and 20–50 times greater than that in the systemic circulation. The rate of secretion of progesterone by the ovary was also markedly elevated and reached its maximum on days 13–15. The rate of secretion of progesterone by the placenta was elevated on days 7–9. These observations indicate that the rat placenta in vivo synthesizes progesterone and secretes it into the maternal circulation. Ovariectomy on day 13 markedly reduced the concentration of progesterone in systemic plasma as well as in the uterine venous effluent collected on day 15. During midpregnancy the ovary is the primary source of progesterone and the placental contribution is of secondary importance.

147 Altered Zinc and Copper Metabolism Secondary to OCA use
Earl Dawson and William McGanity
Department of Obstetrics-Gynecology, University of Texas Medical Branch, Galveston, Tex.

The effect of 3 types of combined and/or sequential estrogen/progestin ovulatory control agents (OCA) on zinc and copper metabolism have been studied serially in over 100 young women. Serum and urinary zinc and copper levels and serum electrophoretic patterns were determined in each subject immediately prior to the initiation of OCA use at successive 3-month intervals for the next 12–18 months. Serum zinc levels remained constant for 6 months and then increased. In contrast the serum copper levels rose during 6 months, and then returned to pre-OCA levels. The urine copper levels dropped immediately and remained at fairly low levels throughout the year.

The albumin and α-1-globulin fractions which bind or contain the zinc and copper were altered in both directions throughout the study period. The significance of these changes and interactions will be presented.

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148 Hematologic Alterations Secondary to OCA Use
Earl Dawson and William McGanity
Department of Obstetrics-Gynecology, University of Texas Medical Branch, Galveston, Tex.

Three varieties of combined and/or sequential ovulatory control agents (OCA) were evaluated in over 100 young women as to their effect on 7 hematologic factors. Each subject was studied at 3-month intervals for over 1 year commencing just prior to their commencing OCA use. Serial measurements of hemoglobin, hematocrit, serum and urinary iron, RBC and serum folacin and serum B 12 were performed. Simultaneous alterations were observed for each factor. Increases occurred with hematocrit, serum and urinary iron. Decreases were found in the folacins while B 12 had a cyclic pattern. These changes, their interactions, and variations dependent on which OCA was used will be discussed.

149 Quantitative Assessment of the Incompetent Uterine Cervix
Michael R. Neuman, Mostafa A. Selim, Michael T. Gyves and Irwin R. Merkatz Department of Reproductive Biology, Case Western Reserve University, Cleveland, Ohio
The elastance of the uterine cervix has been measured from the pressure-volume characteristics of a compliant balloon inflated while in the cervical canal. A latex balloon measuring 1.5 cm in diameter and either 3–4 cm in length with its ends constrained located at the tip of a modified endocervical aspirator is introduced into the cervical canal while collapsed. The balloon is then infused with sterile water at a constant rate and the pressure-volume curve is recorded on a X-Y recorder. Infusion is terminated when the pressure reaches 150 mm Hg or a volume of 5 cm$^3$ has been infused. The cervical elastance is then determined from the slope of the curve.

Seven patients having a clinical diagnosis of incompetent cervix based upon a history of one or more painless, bloodless, midtrimester spontaneous abortions were found to have a mean elastance of 13.8 ± 5.2 (SE) mm Hg/cm$^3$ with values ranging from 0 to 29.8 mm Hg/cm$^3$. This data was compared to a group of 85 patients of parities ranging from zero to five or more who had not experienced abortion, prematurity or severe cervical laceration during delivery. The mean elastance for these patients was 280 ± 30.4 (SE) mm Hg/cm$^3$ with the lowest value observed being 40.0 mm Hg/cm$^3$. These patients were not screened in terms of menstrual history, contraception, time since delivery, or delivery complications, and this is no doubt responsible for the wide spread in the data. Nevertheless, it is seen that there is a significant difference between these patients and those with an incompetent cervix thereby suggesting that this technique may be used to aid in the diagnosis of this obstetrical problem.

Comparison of Methods for Quantitating Fetal Heart Rate (FHR) Variability

W.S. Wong, J.R. Butler, D.C. Heilbron, R.K. Laws, Jr. and J.T. Parer

Department of Obstetrics-Gynecology, UCSF, San Francisco, Calif.

FHR variability is increasingly being recognized as an important index of fetal health. It has been implied that lack of beat-to-beat variability may be associated with fetal compromise. However, a distinction between the implications of short-term variability (STV), a simple oscillation in beat-to-beat interval, and long-term variability (LTV), and all other oscillation and usually occurring at 3–5 cpm, has not been made to date. In this study we attempt to define these phenomena. We have developed computer programs to analyze both STV and LTV. Using only FHR data between contractions we compared 4 indices (Is) of FHR variability: deHaan’s Is, Yen’s Is, the visual template method of Hon, and an I developed by us. In a test program (artificially generated FHR patterns) cross-correlations of the various Is showed that: (a) deHaan’s Is discriminated between STV and LTV best; (b) Yeh’s STI did not delineate STV and LTV delineated LTV much less accurately than deHaan’s; (c) our STI was also poor at delineating STV accurately while our LTI discriminated better than Yeh’s but not as well as deHaan’s. With actual FHR records: (a) as would be desired, there was not consistent correlation between STV and LTV with deHaan’s Is; (b) there was always a correlation between STV and LTV with both Yeh’s Is and ours; (c) the visual method of Hon correlated best with deHaan’s Is of LTV.

We conclude that: (1) deHaan’s Is are the most valid for separating STV and LTV; (2) neither Yeh’s Is nor ours discriminate well between STV and LTV; (3) in visually evaluating variability, one is actually detecting LTV and not STV.
Estrogen-induced uterine hyperemia has been found, in this laboratory, to require intact α-adrenergic receptors, but not adrenergic nerves. Cyclic changes in uterine nor-epinephrine (NE) and epinephrine (E) have been reported by other laboratories using fluorometric assays. This laboratory employed the more sensitive isotopic-enzymatic assay and found: (1) no variation in uterine NE during the estrus cycle or estradiol-induced hyperemia, and (2) no detectable uterine E under any conditions. The paracervical ganglion was examined as a source of α-receptor stimulant during estradiol-induced hyperemia since it has many NE-containing small intensely fluorescent (SIF) cells adjacent to fenestrated capillaries. To test the hypothesis that these SIF cells might be a steroid-sensitive NE source, analogous to their role in other ganglia, the uterine vascular response to estradiol was studied in rats following paracervical ganglionectomy. Ovariectomized, estradiol benzoate-maintained rats were subjected to paracervical ganglionectomy (Gx) or sham operation (Sh) 1 day prior to the experiment. 2 h after estradiol-17β, 0.5 µg/kg, i.v., uterine blood volume was increased 50% in unoperated controls, 25% in Sh animals, and unchanged in Gx animals. Uterine NE content was 32 ng/horn in Gx animals and 57 ng/horn in Sh and control animals, and did not change in any group during estradiol hyperemia. The alpha stimulant active in the estradiol-induced hyperemia appears to be NE from the paracervical ganglion SIF cells, transported via the bloodstream. Static measurements of uterine NE do not reflect contributions from this source.

152 Uterine Activity and Impedance Measurement
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Department of Obstetrics-Gynecology, Hôtel-Dieu de Montreal et Ste-Justine, Groupe Génie Biomédical, Université de Montreal, Montreal, P.Q.
We have evaluated the clinical usefulness of impedance measurement techniques for the study of uterine activity during labor. Impedance, fetal heart rate and uterine pressure was recorded simultaneously in 20 patients. Impedance (Z) was measured by injecting a current of 400 µA at 20 kHz between two electrodes located 1 cm below umbilicus and 15–20 cm apart across the abdomen and measuring the voltage difference between them; the fetal heart rate was derived from a spiral scalp electrode signal and the uterine pressure measured by a catheter or a strain gauge. Of the 1,737 uterine contractions detected, 85% were accompanied by impedance changes. It was also observed that 435 impedance changes occurred in the absence of significant uterine pressure modification. In one third of these cases concomitant fetal heart rate variations were observed. A correlation between the first-time derivative of the impedance signal (dZ/dt) and the evolution of the labor being suspected, a signal-to-noise (S/N) ratio was defined as the mean amplitude of the dZ/dt signal during and after a contraction. Such ratios were calculated for each patient at 24-min intervals and a mean S/N established. It was found that normal labors have statistically higher S/N ratios than the abnormal ones and that evolution of S/N ratios can be related to labor progression. In conclusion, this demonstrates that the impedance signal recorded over the abdomen during labor is indicative of uterine activity. It is also suggested that this signal provides clinically useful information.

153 Influence of Estrogen and Progesterone on Uterine Motility Reassessed
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This investigation was prompted by observations in pregnant rats, in which frequent uterine contractions were present through most of gestation in spite of high progesterone levels, while near term when progesterone drops and estrogens rise a sharp decrease in uterine activity occurred (Biol. Reprod. 1: 344, 1969). Nonpregnant rats were fitted with indwelling ballon-tipped catheters for chronic intrauterine pressure recordings. Some were ovariectomized and given exogenous hormone treatments, others were studied during normal cycles as verified by vaginal smears. 17/3-Estradiol 17-phosphate Na2 salt (E) was given as a slow i.v. infusion, 1 µg/h for 5 h. Progesterone (P) was given i.m. in oil, mg/rat/day. After ovariectomy, strong rhythmic contractions were present for at least days. E infusions caused a marked reduction of uterine contractions and led to complete relaxation of the uterus within 5–6 h. Withdrawal of E resulted in reappearance of contractions in 24 h. P increased the frequency of contractions and induced an irregular pattern. P given together with E abolished the uterine relaxation observed with E alone and led to strong rhythmic contractions. In intact rats at proestrus the uterus exhibited little or no activity. Contractions appeared at estrus which become frequent and rhythmic in diestrus. At next proestrus uterus again became quiescent. Recordings from two separate sites indicated rapid conduction of contraction waves at proestrus, estrus and under E treatment; at diestrus, after ovariectomy and P treatment conduction was slower and after prolonged P treatment conduction appeared completely abolished with contractions randomly generated at all parts of the uterus.

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Cortisol concentrations in amniotic fluid and maternal plasma were determined by competitive protein-binding assay in 11 midtrimester pregnant patients following the intra-amniotic administration of prostaglandin F2α. Samples were obtained at 3-hour intervals until abortion or fetal heartbeat ceased. The plasma levels of cortisol increased from 216 ± 125 ng/ml at 0 h to 455 ± 255 ng/ml at 6 h post-PGF2α, infusion. In amniotic fluid, the mean cortisol levels increased from 3.4 ± 2.0 ng/ml at 0 h to 6.8 ± 2.4 ng/ml at 6 h. The results obtained indicate that the fetus at 16–20 weeks gestation is capable of responding in utero to a stress situation i.e., the PGF2α induced uterine contractions and their sequelae, by a rise in cortisol levels.

We measured fetal umbilical (UBF) and maternal placental (MPBF) blood flows in 12 near term pregnant baboons at 160–170 days gestation in acute experiments and demonstrated significant differences when compared to data available for the sheep. UBF was measured by the Fick principle using antipyrine and cardiac output (CO) and its regional distribution using radioactive microspheres.

Maternal cardiac output Maternal placental blood flow Umbilical blood flow Antipyrine clearance (APC) APC/MPBF
= 949 ± 499 ml/min or 67 = 53 ± 25 ml/min = 118 ± 49 ml/min = 48 ± 27 ml/min = 0.94 ± 0.39 ml/min
Published data on the sheep indicate that uterine blood flow is greater than UBF, that the APC/UBF ratio is approximately 0.75 and that the uterine blood flow is approximately 20–25% of cardiac output. In contrast, out data in the baboon show that UBF is greater than MPBF, that the APC/UBF ratio is approximately 0.36 ± 0.12 and that the MPBF is 4.6 ± 3.0% of CO.

In each model the major modifier of APC is the lesser placental flow. Therefore, modifications in uterine blood flow in the nonhuman primate, and by implication in the human, may significantly influence the well-being of the fetus through effects on placental transfer. All numerical values presented represent the mean ± 1 SD.

156 Electrolyte Composition of the Human Follicular Fluid
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Follicular fluid samples were obtained by puncturing follicles of ovaries in situ from patients undergoing laparotomy. The follicular fluid concentration of sodium, potassium, chloride, magnesium, calcium, phosphorus and sulfur measured by a new method, electron probe microanalysis, in picoliter volumes of fluid were similar to those found in blood with minimal differences. This work presents the first report of the analysis of the human follicular fluid concentration of these seven elements of biological importance. This suggests that culture media in which these electrolytes are added in concentrations similar to serum are appropriate for culture of the human oocyte.

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157 Metabolism of Palmitic Acid (PA) in the Postmature (PM) Rabbit Fetus
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Antuitrin-injected pregnant rabbits were delivered by cesarean section 3 days after term. Lipid metabolism of the PM fetus, near term fetus (NT), and 3-day-old newborn (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 turnover rate of FFA in mother and fetus was calculated following a single maternal injection of 1–14C-PA (18µCi). Tissue lipids were further analyzed by TLC. Body and organ weights of PM animals were higher than those of the NT but similar to those of the NB. Placental lipid concentration in the NT and PM models was comparable. Lipid deposition in the brain and lung was similar in the PM and the NB. Liver lipid concentration in the PM fetus was higher than in that of the NB. FFA turnover in the NT and PM mother was 93 and 123 µEq/min respectively, whereas the FFA turnover in the NT and PM fetus was 0.09 and 0.18 µEq/min. These numbers do not differ statistically. PA incorporation into tissue lipids was 2–3 times lower in liver and brain of the PM fetus. Incorporation by lung and adipose tissue was similar in the two models. Peak FFA radioactivity in fetal serum was reached in between 2 and 4 min. Based on its turnover rate, PA could serve as a source of 40% of the lipid present in the PM fetus. Although placental weight is static between 27 and 34 days of gestation, FFA transport appears unimpaired and the PM fetus thrives in a manner indistinguishable from that of the NB.
(Supported by MRC grant No. DGIII.)
158 Maternal Steroid Levels Following Intraamniotic Cortisol Instillation in Human Pregnancy
Six gravidas with postterm pregnancy were given cortisol 500 mg intraamniotically. Free E₁, E₂ and P were measured in samples of maternal plasma obtained sequentially from the time of cortisol instillation until spontaneous onset of labor. The values obtained were compared with those of 6 gravidas who did not receive intraamniotic cortisol prior to onset of labor. A progressive decline in E₁ and E₂ levels was noted during the instillation-to-labor interval in the cortisol group but not the control. P levels were not significantly changed in either group. Mean E₁, E₂ and P concentrations (ng/ml ± SE) at the onset of labor are summarized for both groups.

<table>
<thead>
<tr>
<th>E₁</th>
<th>E₂</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>1.7 ± 0.05</td>
<td>5.6 ± 1.3</td>
</tr>
<tr>
<td>Control</td>
<td>4.2 ± 0.08</td>
<td>13.5 ± 1.8</td>
</tr>
</tbody>
</table>

p < 0.05  p < 0.01  p > 0.01

The diminishing E₁ and E₂ levels in the cortisol group is regarded as a result of a suppression of estrogen precursors by the exogenous cortisol in the fetal compartment. Spontaneous onset of labor in the face of progressive decline in estrogens as well as emergent P dominance raises some question as to the role of E₂ in the initiation of labor in the human.

The diminishing E₁ and E₂ levels in the cortisol group is regarded as a result of a suppression of estrogen precursors by the exogenous cortisol in the fetal compartment. Spontaneous onset of labor in the face of progressive decline in estrogens as well as emergent P dominance raises some question as to the role of E₂ in the initiation of labor in the human.

Effect of Ethinyl Estradiol and Mestranol on Estrogen-Binding in the Human Fallopian Tube
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The action of contraceptive steroids on human oviductal tissue was studied in vitro. The comparative affinity of ethinyl estradiol and mestranol for estrogen-binding sites in human Fallopian tubes was determined by dextran-coated charcoal adsorption and sucrose density ultracentrifugation. The equilibrium dissociation constant for 3 H-estradiol binding was 1.5 X 10⁻⁹ M in oviductal cytosol. Lineweaver-Burk plots resulted in calculation of dissociation constants for the inhibitors ethinyl estradiol and mestranol. The Kᵣ values for ethinyl estradiol and mestranol were 0.7 X 10⁻⁹ M and 3.2 X 10⁻⁷ M, respectively. Sucrose-density ultracentrifugation showed similar quantitative relationships. Preparation of cytosol in Tris-EDTA-dithiotreitol buffer showed a single 4 S value, which was displaced by excess ethinyl estradiol or mestranol. Incubation with comparable concentrations of inhibitor resulted in a more potent displacement by ethinyl estradiol. The addition of DFP (diiso-propylfluorophosphate) to the homogenization buffer produced sedimentation coefficients of 8S and 4S in cytosol. The nuclear estrogen-receptor was extracted by addition of 0.4 M KC1 to the buffer solution. The results demonstrate a higher affinity of oviductal estrogen-binding proteins for ethinyl estradiol than for mestranol. The addition of the protease inhibitor DFP leads to 8S and 4S sedimentation coefficients, which is similar to human uterus. Both ethinyl estradiol and mestranol may exert antifertility action on the oviduct by interaction with estrogen-binding macromolecules.

Plasma Cyclic AMP in Normal and Hypertensive Pregnancies
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(Supported by GRSG No. 5–27123.)
In our continued studies on the changes of cyclic AMP (cA) in normal and pathological pregnancies, we have measured the plasma concentrations of cA in nonpregnant women; in 239 specimens from women in the 7–41 week of normal pregnancy (NP); in women during labor and 5–7 h postpartum. The cA levels in NP showed an initial peak value at 13–15 weeks. After falling to a nadir at 18 weeks, the level began to rise steadily and reached a second peak of equal magnitude at about 34 weeks. A gradual decline was then followed until labor. It decreased significantly to nonpregnant level after delivery. A similar pattern was found in serial studies in 4 NP. Sequential cA in 5 hypertensive pregnancies (HP) was markedly elevated during 16–26 weeks, but became comparable to NP values thereafter. In the only preeclamptic patient studied, cA was elevated in the 16–27 week.

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although no clinical symptom was found until the 31st week. It seems that cA in HP does not exhibit the biphasic pattern of NP and may be predictive of impending preeclampsia. cA in matched samples of umbilical and maternal plasma (M) from NP and HP showed that the levels were significantly lower in M, except in severe forms of HP where it was elevated to cord plasma level. The results indicate that the fctoplacental unit may be a source of plasma cA during NP and that the pattern is modified in HP by maternal factors. (NIH HL-14141, HD-05866, HD-03142, Ford Foundation 0338.)

161 Fetal-Maternal Dynamics of 14C-Uric Acid in the Pregnant Rhesus Monkey

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Information on placental transfer and dynamics of uric acid and other purine metabolites in man is not easily obtained. Therefore, this study was designed to assess the fetal-maternal dynamics of 14 C-uric acid in the rhesus monkey. In monkeys of 120–140 days gestation catheters were introduced into an interplacental vein and the maternal vena cava. In separate experiments, 14C-uric acid with an activity of 100µCi/ml was injected into one of the following compartments: fetal blood (FB), maternal blood (MB), or amniotic fluid (AF). Following injection of the isotope these compartments and maternal urine were sampled at frequent and predetermined intervals. Samples were submitted to a previously described method of high pressure liquid chromatography, which allows exact localization of the radioactivity on the chromatogram and subsequent counting in a liquid scintillation counter. Uric acid clearances (C, in ml/min) were calculated on the basis of a five-compartment system: FB, MB, AF and fetal and maternal interstitial spaces. CFB to MB appeared to be almost equal to CMB to FB (0.6–0.9). CFB to AF was 0.03–0.06, and CAF to MB was 0.6–0.7. The maternal renal uric acid clearance was calculated to be 13 ml/min, which figure could be confirmed in two additional experiments. During the experiments the maternal uric acid level remained constant, whereas uric acid levels in fetal plasma and amniotic fluid showed a gradual and concomitant rise of approximately 300 %. This phenomenon cannot be explained on the basis of the observed concentrations and clearances of uric acid in our model. Despite quantitative and qualitative differences between uric acid concentrations in rhesus and man, data from this experimental model could be extrapolated to man.

162 Assessment of the Electric and Mechanical Activity of the Nonpregnant Human Uterus in vivo
This study was designed to assess the relationship between electric myometrial activity and intrauterine pressure in different phases of the human menstrual cycle. Five nulliparous volunteers were selected on the basis of a normal ovulatory cycle as judged from their basal temperature record and regular determinations of plasma estrogen, progesterone, FSH and LH levels. Electric myometrial activity was recorded on the 1st, 8th, 14th and 24th day of the cycle during 3 cycles by means of a pair of needle electrodes. The electrodes were mounted on a small plastic cylinder and inserted into the fundal myometrium through a specially constructed guide tube. Intrauterine pressure was simultaneously measured through a fluid-filled open-tip catheter, connected with a pressure transducer. Uterine potentials and pressure were amplified and recorded on paper and magnetic tape. Electric potentials and variations in intrauterine pressure were demonstrated in all phases of the menstrual cycle, but different patterns were observed. During the first day of menstruation groups of high-frequency potentials (‘bursts’) occurred, with a duration of approximately 30 sec and amplitudes of 300 mV or more. These ‘bursts’ concurred with intrauterine pressure waves with amplitudes of 30–50 mm Hg. Both uterine pressure and electric activity decreased in the course of the menstrual cycle and increased again on the 24th day, when intermittent ‘bursts’ reappeared. The demonstrated relationship between ‘bursts’ of electric activity and intrauterine pressure during menstruation might be of importance for a better understanding of the underlying factors of dysmenorrhea.

163 Fetal Renal Function and in Relation to Amniotic Fluid Volume
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The object of this study was to assess the role of fetal urine production in the determination of amniotic fluid volume (AFV). Hourly fetal urine production rate (HFUPR) was measured by means of ultrasound, AFV was estimated using the p-amino-hippuric acid technique.

Results: (a) 60 normal pregnancies (36–41 weeks of gestation) were studied. For each week of gestation no relationship between HFUPR and AFV could be demonstrated, indicating that fetal urine is not the main factor in the determination of AFV at this stage of normal pregnancy. The mean HFUPR and AFV varied from 17.9 and 695 ml, respectively, at 36 weeks to 25.0 and 845 ml at 40 weeks. At 41 weeks the mean HFUPR was 21.9 ml, the mean AFV was only 350 ml. (b) In 13 preeclamptic patients associated with fetal growth retardation (36–39 weeks), HFUPR was always reduced as compared with our normal curve. AFV was reduced in 11 out of 13 cases (< 400 ml). These findings suggest a relationship between reduced fetal urine production and oligohydramnios. In 5 cases of preeclampsia associated with normal fetal growth (36–40 weeks), HFUPR was reduced in only one case, AFV varied from 430 to 1,130 ml (normal values), (c) In 18 patients with polyhydramnios (diabetes mellitus 9 × , anencephaly 4 × , fetal hydrops 2 X , congenital deformations 2 × and preeclampsia 1 × ) AFV varied from 1,500 to 6,900 ml, but HFUPR was never found above the normal range. This suggests that fetal urine production did not play an important part in the formation of polyhydramnios in these cases.

164 Metabolism of Dihydrotestosterone (DHT) by the Gut Flora of the Mature Rat under Aerobic and Anaerobic Conditions
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Morishita et al. (submitted for publication) have shown that dihydrotestosterone propionate significantly suppressed serum LH in weaned intact male rats as well as in weaned castrated male and female rats but failed to do so in suckling rats. They have suggested that DHT may require metabolism by intestinal bacterial for its action. We have investigated the metabolism of DHT by the gut tissues and gut flora to centrally ‘active’, metabolites by the gut flora. Under aerobic conditions of incubation, gut metabolism was

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more than 80% in 2–6 h of which between 55 and 65% were due to formation of 5α, 3α-androstanediol, 5α,3β-androstanediol and very small amounts of 5β,3α-androstanediol. Their identity was confirmed by reverse isotope dilution. Approximately 90% of DHT is metabolized by gut contents in 2–6 h incubation of which 80% were accounted for by the androstanediols in 2–6 h. Phenolic steroids were looked for but were not identified. Under anaerobic conditions, gut homogenate metabolize 86% of DHT of which 75% constitute the androstanediol fraction in contrast to the gut flora which metabolize 79% of DHT of which 69% constitutes the androstanediol fraction. It is of interest to note that small amounts of 5ti,3α-androstanediol are formed. Conversion of DHT to the 5(3)-metabolite implies formation of small amounts of testosterone. Furthermore, Eckstein (J. Steroid Biochem. 6: 873, 1975) has shown that the 5α-androstane-3α,17β-diol and the 3β-epimer are implicated in onset of puberty in the female rat. Whether these steroids are ‘active’ metabolites, is currently under investigation.

165 Transport and Metabolism of 3H-Epinephrine in the Rabbit Fetal Tissues
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In order to study the effects of B sympathomimetic drugs on fetal lung maturation, experiments were designed to determine the placental transport and metabolism of catechol-amines in fetal rabbit tissues. Pregnant rabbits (day 26) were laparotomized under local anesthesia; 3H-epinephrine (E) (5 μCi/100 ng/fetus) was infected through the uterine wall into the flank of 5 fetuses. After 30 min, less than 0.1% of the injected 3H was found within the maternal circulation and the tissues of uninjected littermates. Uptake of 3H was very rapid, with blood levels constant at 5 and 30 min, but decreased by 50% after 60 min. 76% of the 3H-E found in the blood was metabolized after 30 min, with 50% present as free metanephrine (MN). Liver, kidney and intestine show the greatest uptake (dpm/g), while only the liver retains accumulated 3H up to 60 min. 3H-metabolites found within the liver after 30 min are: E – 1%, free MN – 45%, MN-glucuronide – 35%, and an unidentified fraction – 15%. Thus, 3H-E is rapidly metabolized by fetal tissues and O-methylation is the predominant metabolic route in the liver, followed by rapid glucuronide conjugation.

In some experiments promethazine-HCl (Phenergan) was administered to the mother prior to laparotomy. 3H uptake in lung, liver, kidney and intestine was depressed by 50–60% after 30 min. As Phenergan has been shown to potentiate the actions of catecholamines in nonpregnant animals, this drug may also potentiate the actions of E on fetal cardiovascular tissues by inhibition of uptake and subsequent metabolic processes.

166 Estrogen Replacement Therapy in Peri- and Postmenopausal Women
Ronald C. Strickler and C. Allan Woolever St. Michael’s Hospital, Toronto, Ont.
A double-blind placebo controlled cross-over study evaluated estrogen replacement therapy for climacteric symptoms and quantitated the psychological response to treatment 20 women with complaints consistent with the climacteric syndrome were followed during 15 months. During the initial 3 months, examinations by a gynecologist recorded symptoms, excluded organic disease, and confirmed estrogen deficiency. Patients were interviewed by a psychiatrist and psychologist, at which time the Minnesota Multiphasic Personality Inventory (MMPI) and 16 Personality Factor (16PF) tests were administered. During the next 12 months each woman received alternating 3-month courses of Premarin 1.25 mg t.i.d. or placebo. At follow-up visits, patients were interviewed by different gynecologists and the MMPI of 16PF tests were administered.

In 16 women, placebo therapy was as effective or more effective than Premarin for subjective symptomatic relief. Only 2 women could distinguish by their sense of well-being the placebo from the estrogen tablets. Mood and energy ratings, recorded by the patients, varied little during all phases of the study. The average scores from psychological tests before and during the study were not changed on Premarin or placebo. 10 women experienced symptoms directly related to estrogen therapy: bleeding in 7 was the most common problem.

Estrogen replacement therapy which has been so strongly applauded in medical and lay literature and pharmaceutical advertising requires reevaluation, and perhaps de-emphasis, lest medical reason be overtaken by popular belief and public demand.

167 Evidence for a Common Mechanism Causing Hyperprolactinemic Galactorrhea-Amenorrhea Syndromes G. Tolis, J.M. McKenzie and F. Naftolin
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Prolactin profiles were assessed in 52 patients with galactorrhea-amenorrhea syndromes of the Forbes-Albright, Chiarri-Frommel and Ahumada del Castillo variety. All patients had normal pituitary function tests and adequate gonadotropin reserve as tested by serum FSH and LH changes after the subcutaneous injection of 100µgLRF. Prolactin secretion was assessed by measuring serum prolactin every 20 min for 3 h under basal conditions, then every 30 min for 2 h after the administration of prolactin suppressant dopaminergic agents (levadopa 500 mg p.o. or apomorphine 0.75 mg s.c. or bromocryptine 2.5 mg. p.o.), and every 15 min for 2 h after the administration of prolactin stimulants (chlorpromazine 25 mg i.m. and/or thyrotropin-releasing factor 500 µg i.v.). All 3 groups showed similar prolactin secretion profiles. Although random single serum prolactin levels were ‘normal’ (< 30 mg/ml) in 10 of 52 patients, frequent observation (every 20 min) showed a pulsatile pattern of secretion with a mean level in excess of 30 mg/ml in all patients. No discrimination of groups could be obtained on the basis of pattern of basal or manipulated prolactin secretion. In all cases, administration of bromocryptine 2.5 mg twice daily or pituitary microsurgery resulted in disappearance of galactorrhea and resumption of menses. Pregnancy followed in all patients who desired it. These data suggest a common denominator in the genesis of these syndromes, the chemical and biological expressions of which are hyperprolactinemia and galactorrhea-amenorrhea, respectively.

168 Fetal Progesterone and Estrogen Levels at Parturition
Indra Antonipillai and Beverly Pearson Murphy
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While maternal venous levels of progesterone and estrogens have been intensively studied in relation to parturition, little attention has been directed to fetal levels. In this study progesterone (P), estrone (E1), estradiol (E2) and estriol (E3) were measured in arterial and venous cord serum at induced or spontaneous-onset vaginal delivery and at elective cesarcan section (CS). At least 8 samples were included in each group. Umbilical venous levels (UV) were consistently higher than arterial (UA) levels for all four steroids. Progesterone cord levels and A-V differences were higher (p < 0.05) at vaginal delivery than at CS although maternal levels were unchanged. E1 and E2 levels were similar after spontaneous labor and at CS but were higher after induced labor although E3 levels did not alter. These results suggest that maternal hormone levels are an insensitive index of fetal changes and that, in addition to a direct effect on the myometrium, oxytocin may act by increasing the estrogen-progesterone ratio.

E1 6.7 ± 2.7 12.0 ± 2.9 8.1 ± 2.0 19.5 ± 1.7 4.2 ± 1.1 9.9 ± 1.9
E2 1.6 ± 0.5 5.2 ± 0.8 4.3 ± 1.4 7.1 ± 0.8 1.6 ± 0.5 4.0 ± 0.9
E3 74 ± 9 121 ± 11 63 ± 9 113 ± 11 82 ± 18 113 ± 20
P 455 ± 64 766 ± 94 442 ± 60 826 ± 92 270 ± 29 398 ± 32

169 Demonstration of Gonadotropin during the Second Half of the Cycle in Women Using Intrauterine Contraception
Lars L. Cederqvist, Carl G. Beling and Fritz Fuchs
Department of Obstetrics-Gynecology, Cornell University Medical College, and Department of Obstetrics-Gynecology, Downstate Medical Center, New York, N.Y.
A sensitive assay for HCG and HLH in urine was developed by purification of urinary gonadotropins by Sephadex gel filtration, lyophilization of the purified gonadotropin fraction and determination of the gonadotropin content by a hemagglutination inhibition test. The sensitivity of the assay was 30 IU HCG/ml of urine. This sensitivity permitted the demonstration of the urinary LH peak at the time of ovulation. If conception occurred, a steep rise was observed from days 24–25, suggesting that pregnancy could be predicted on the ninth to tenth postovulatory day. Individual urine samples were collected from 101 women using intrauterine contraception at routine visits to the Family Planning Clinic. No measurable gonadotropin was found in subjects in the first 14 days of the cycle but a high incidence of positive values were found on days 15–18 and from day 22 onward. The midcycle values were interpreted as HLH. During the second half of the cycle 32 out of 73 samples showed elevated levels of HCG/HLH. Only 2 of these subjects developed clinical signs of pregnancy. These findings support the hypothesis that an IUD may not prevent fertilization and blastocyst formation but does interfere with implantation and the establishment of pregnancy.

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