169

EFFICACY OF INDOCIN(IN) FOR SYMPTOMATIC(S)PDA: A DOUBLE-BLIND CONTROLLED STUDY. R. Yanagi, A. Wilson, M.A. Fletcher, J. Boehm, R. Inwood, K. Aziz, E. Newfeld, and C.E. Hunt, Northwestern Univ., Chicago, Illinois.

A double-blind controlled study was designed to assess the efficacy and toxicity of IN in neonates with severe RDS and SPDA. All of the following were required for admission to this study: (1) severe RDS requiring assisted ventilation, (2) SPDA and LA:aortic ratio(LA:Ao) $\geq$ 1.3, and (3) persistent LA:Ao $\geq$ 1.3 after 1 day of medical management. 20 patients were admitted to the study and administered orally the unknown contents of a coded vial containing 0.2 mg/kg of either IN or placebo. If unimproved clinically and LA:Ao remained $\geq$1.3, a 2nd and 3rd dose were administered at 24-hour intervals and surgical ligation was performed 1 day later if still unimproved and LA:Ao $\geq$ 1.3. The IN and control(C) groups were similar in all other respects (Table).

	BACKGROUND (Mean $\pm$SEM)				RESULTS		
Study Group	No.	B.W. (kg)	G.A. (wks)	Age (days) 1st "Dose"	Completed Study	Improved	Surgery
IN	9	1.3 $\pm$.1	30.4	10.0 $\pm$2.5	8	6 (75%)	2 (25%)
C	11	1.5 $\pm$.2	30.4	9.2 $\pm$1.3	9	4 (44%)	5 (56%)

There were no renal or hematologic effects of IN. Although more IN than C infants improved and fewer required surgery, the C group spontaneous recovery rate was 44% and the results were thus not statistically different by x^2 analysis. The efficacy of IN is overestimated unless spontaneous recovery rate is also analyzed. IN is apparently not as effective as initially presumed and its precise role in the management of SPDA remains to be clarified.

172

DECREASED DNA-CELLULOSE AFFINITY OF LUNG GLUCOCORTICOID RECEPTORS IN THE FETUS OF HYPERCLYCEMIC RATS. Walter C. Boutwell* and Allen S. Goldman. Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104

Respiratory distress syndrome (RDS) is due to a deficiency of dipalmitoyl lecithin (DPL), the developmental appearance of which is controlled in the fetal lung by glucocorticoid (GC) induction of choline phosphotransferase (CPT). GC produce their effects by binding to cytosolic receptors which in turn bind to nuclei and induce DNA-transcription and consequently enzyme synthesis. Since infants of diabetic mothers (IDM) have an increased incidence of RDS, we investigated this relationship by producing hyperglycemic rats with streptozotocin (STZ), prior to implantation. Mothers were consistently hyperglycemic (> 250mg%). One day prior to term, fetuses were obtained. The concentration of fetal lung cytosol dexamethasone receptor at saturating concentration ($2x10^{-8}$M) was unchanged (500.4 vs. 515.8 fmole/mg prot.). However, in vitro DNA-cellulose affinity and CPT activity were decreased in the fetuses of treated animals (128.6 vs. 236.0 f.mole/mg prot. and 1.28 vs. 4.24 p.mole/min./mg protein respectively; $p < 0.05$ for both). It is concluded that the fetus of the STZ-treated hyperglycemic rat is a useful model for RDS in the IDM, and suggests that steroid receptor DNA-affinity may affect DPL production and the incidence of RDS.

DEVELOPMENTAL BIOLOGY

170

DE-COUPLING OF RNA AND DNA SYNTHESIS IN PLATLET-POOR SERUM STIMULATED G_0 ARRESTED BALB/C 3T3 FIBROBLASTS. Herbert T. Abelson, Harry N. Antoniades, and Charles D. Scher(Spon. by David G. Nathan). Harvard Medical School, Childrens' Hospital Medical Center, Sidney Farber Cancer Institute, Division of Hematology-Oncology, Boston, Ma. 02115.

Addition of serum to 3T3 cells arrested in G_0 induces the cells to enter and progress through G_1; DNA synthesis follows after a 12-14 hour lag period. Whole serum has been fractionated into two sets of components which act synergistically to stimulate the replication of 3T3 cells. One is found in heat(100°C) treated platlet extracts(PE), and the other is found in platlet-poor serum(PPS). We have examined the relation of RNA synthesis to subsequent DNA synthesis using whole serum and these two components. RNA in 3T3 cells was labeled to constant specific activity with $^{32}PO_4$. We found that whole serum or its components (PE and PPS) stimulated an increase in RNA content to the same degree in quiescent cultures of 3T3 cells. Each agent increased messenger RNA(mRNA) content more than ribosomal RNA(rRNA) content and the changes in mRNA occurred before detectable changes in rRNA. Stimulation with either whole serum or PE induced both RNA and DNA synthesis; however, PPS induced only RNA synthesis. Cells stimulated by PPS remain in G_0 since the subsequent addition of PE does not shorten the latent period for DNA synthesis. Therefore, increased RNA synthesis and content does not always lead to DNA synthesis and cell division; PPS mediates this decoupling. Increased RNA synthesis, therefore, cannot itself be considered a criterion for entry of G_0 cells into G_1.

171

THE EFFECT OF FETAL ADRENALECTOMY IN THE OVINE FETUS. Jahangir Ayromlooi (Spon.by P. Lipsitz), SUNY Med. Sch. at Stony Brook, Long Island Jewish-Hillside Med.Ctr.,Dept.Ob-Gyn,New Hyde Park,NY

Adrenalectomy (Adx) was performed at 112 to 116 days of gestation in 32 fetal lambs. Of these, 7 survived and were studied at near term (136-144 days). Compared with age-matched controls (C) body weights were not significantly different. The mean brain weight was less in Adx vs C, (Adx 47.12 $\pm$ 4.94 g. C 51.32$\pm$ 3.15g) but statistically insignificant. Fetal heart rate, blood pressure, carotid artery blood flow, O_2 and glucose consumption of the brain did not show any significant differences between Adx and C. No difference in white blood cell counts, percentage lymphocytes and "B" lymphocyte counts was observed in Adx vs C, but in mitogen tests lymphocytes from C showed responses greater in magnitude than Adx. Five of 7 Adx fetuses showed immature EEG (low amplitude and frequency) in comparison with C. The number of type II alveolar cells were significantly reduced in 4 of 6 lungs of Adx studied vs C. The study indicates that fetal adrenal glands play an important role in the development of vital organs.

173

VULNERABILITY OF THE PREIMPLANTATION MAMMALIAN EMBRYO. Robert L. Brent, Department of Pediatrics, Jefferson Medical College, Thomas Jefferson University, Phila., Pa.

The most sensitive stage of mammalian embryonic development to the lethal effects of X-irradiation is during the preimplantation period. As little as 10 rads has increased the resorption rate in pregnant rats exposed to irradiation on the first day of gestation. In order to determine whether other known teratogenic agents also affect the embryo in the preimplantation period, pregnant rats were exposed to acetylsalicylic acid (200; 400 mg/kg) on the first day of gestation: Acetylsalicylic acid is a known teratogen when administered to the pregnant rat during early organogenesis. The results indicated that the preimplantation embryo was also adversely affected by aspirin exposure. Since ethyl alcohol was used as the carrier, separate experiments were carried out in pregnant rats using three exposures of ethyl alcohol (2.5 g; 5.0 and 10 g/kg). Both aspirin and ethyl alcohol produced an increase in embryonic death when pregnant rats were exposed to these agents on the first day of gestation. It appears that some toxic agents known to be embryotoxic during organogenesis can cause embryonic death during the preimplantation period. (HD 630; HD 7075; HD 11038)

174

CHARACTERIZATION OF A POLYAMINE-CONJUGATED, LOW MOLECULAR WEIGHT POLYPEPTIDE IN HUMAN THIRD TRIMESTER AMNIOTIC FLUID. Wai-Yee Chan, Thomas W. Seale, Jayesh B Shukla, Piers Blackett, Owen M. Rennert. University of Oklahoma Health Sciences Center, Department of Pediatrics and Department of Biochemistry and Molecular Biology, Oklahoma City, Oklahoma.

The qualitative and quantitative characterization of amniotic fluid proteins is important for an assessment of fetal development and for potential prenatal diagnosis. Low molecular weight proteins (molecular weight $\leq$ 12,000 daltons) in human amniotic fluid have not been investigated extensively. Fractionation of third trimester human amniotic fluid by Biogel P10 chromatography yielded at least 6 polypeptides $\geq$ 2000 $\leq$ 13,000 daltons. The predominant peak, with a molecular weight range of 4 to 6,000 daltons, was separated by DEAE chromatography on a linear NaCl gradient, which yielded two peptide species at 0.55M NaCl and 0.87 NaCl. The 0.55M NaCl peptide (AFP3-4A) proved to be homogeneous by paper chromatography and Biogel P6 column chromatography. The molecular weight was found to be approximately 4200 daltons. The amino acid composition was determined by Durrum high pressure chromatography following acid hydrolysis. 37 amino acid residues were found including trace ornithine concentration and absence of cysteine and methionine. The most abundant amino acids were glycine, glutamic, aspartic acids, alanine and serine. The presence of hexosamine, elution time indistinguishable from glucosamine, was also found. One mole of putrescine was covalently bound per mole peptide. This unusual polypeptide has similar structural characteristics to the plasma putrescine-conjugated polypeptide, putrescinin recently described by us.