283 PERINATAL PROBLEMS (EXCLUDING NEONATAL WITHDRAWAL) ASSOCIATED WITH MATERNAL DRUG ADDICTION: A REVIEW OF 830 CASES.

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This study shows that besides neonatal withdrawal, there are other important complications during pregnancy and postnatal period that we should be aware of when dealing with the pregnant drug addict. This study is based on a review of 830 cases covering the period from 1972-76.

Among the maternal problems, a high incidence of the following conditions were noted: maternal age <20 yrs (17%), meconium stained amniotic fluid (13%), anemia (13%), PROM (12%) and infection (10%). As for infection, venereal disease (57%) urinary tract infection (15%) and hepatitis (6%) were the most common. There was a uniform 3-5% incidence of abruptio placenta, hypertension and toxemia. The Apgar score was <6 at 1 minute in 20% of the infants. Birth weight <2.5 kg occurred in 31%. Of the total infants 19% were premature and 16% were SGA.

The postnatal problems that occurred (excluding withdrawal) were: jaundice (14%), infection (11%), aspiration (including meconium) pneumonia (9%), transient tachypnea (7%) and HMD (5%). Congenital malformations were noted in 4% of the infants with the major anomalies involving principally the genitourinary system. A total of 22 (2.6%) infants died. Thirteen (13) were premature with severe HMD and 9 were fullterm (5 with meconium aspiration and 4 with major congenital anomalies).

SUMMARY: (1) The lifestyle of the pregnant addict predisposes her and her infant to a high incidence of infection, particularly venereal disease, (2) the high incidence of meconium stained fluid and low Apgar score in the infant indicate that fetal withdrawal leading to asphyxia is a serious and not an uncommon complication during the prenatal period, (3) postnatally, despite the high incidence of low birth weight and prematurity, the aspiration syndromes, particularly meconium aspiration, constitute the major pulmonary problem and a leading cause of death in the infant.

284 TISSUE DISTRIBUTION OF MORPHINE IN NEWBORNS OF ADDICTED HUMANS AND SUB-HUMAN PRIMATES.

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A knowledge of the distribution of morphine in the fetal tissues may lead to an understanding of some of the clinical characteristics of the infant of the drug dependent mother (IDDM). Passive narcotic addiction was induced in the fetuses of 5 pregnant Rhesus monkeys by IM injection of 30-60 mgs morphine TID to the mother at the first sign of pregnancy. The fetuses, once delivered, were sacrificed and tissues from the different organs were analyzed for morphine content. Tissues were similarly assayed on 3 human infants (3-5 days old) who died and were born to drug dependent mothers.

RESULTS: The mean morphine content (µgs morphine/gm tissue) in the monkey and human tissues were:

ORGAN	MONKEY	HUMAN
Cerebellum	31.7	5.7
Brainstem	-0-	17.0
Cerebrum	2.2	-0-
Intestine	69.8	-0-
Heart	28.8	1.3
Kidney	4.1	-0-
Liver	27.1	4.7
Lung	8.1	5.7
Muscle	-0-	3.4
Spleen	28.4	9.6
Stomach	51.3	-
Thymus	19.6	9.3

INTERPRETATION: The higher level of morphine measured in the tissues of the fetal monkey is probably due to the higher dose of morphine consistently given to its mother. A phylogenetic dominance during fetal life of the cerebellum and brainstem over the cerebrum is suggested by the higher concentration of morphine in these organs. The significant amount of morphine in the lungs and liver (10%) may favor a drug induced enzyme maturation in these organs and possibly explain the lower incidence of RDS and jaundice in the IDDM. The high morphine concentration in the contents of the stomach and intestines of the fetal monkey provides a possible endogenous source of morphine to the fetus and a likely safeguard against fetal withdrawal. The high level of morphine in the thymus, spleen and heart remain unexplained.

285 GROWTH FAILURE: STATISTICS APPLIED TO MEDICAL THERAPY,

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To minimize subjective bias and to shorten control and trial-treatment periods, especially when using hazardous or scarce medications, we applied statistical methods to evaluate the influence of treatment upon the growth rates of children with growth disturbances. Utilization was encouraged by programming techniques for a desk-top calculator and demonstrating uses with six questions. The program assumes linearity of data and requires groups of paired variables, i.e. age and height. Section 1 describes growth statistically: 1. By my measurements, what is the child's growth rate? (linear regression and correlation) 2. What is my average error when measuring this child? (standard error of measurement) 3. How can I know when I have sufficient measurements to permit a therapeutic change? (F-test for regression) 4. What do I use to compare this child's growth to "normal" growth? (t test for confidence limits of slope). Section 2 compares growth periods statistically: 1. Are growth periods 1 and 2 different? (linear covariance for comparison of slopes).2. If different, how do they differ? (linear covariance discriminates change in rate from parallelism due to difference in measurement techniques or non-consecutive periods). The program can also be used to facilitate evaluation, retrospective or prospective, of a wide variety of influences on linear functions ranging from pharmacokinetics to applications in behavioral science, e.g. comparison of teaching techniques on rates of learning.

286 AGE-DEPENDENT CHANGES IN BETA-ADRENERGIC RECEPTOR ACTIVITY OF RABBIT MYOCARDIUM.

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Myocardial response to beta-adrenergic stimulation, isoproterenol(ISO), was evaluated in 1 day, 1 week, 1 month and 4 months old rabbits by measuring maximal developed tension(MDT), ED_{50} and cyclic AMP(cAMP) production. Isolated electrically stimulated (2/sec) atrial strips were studied. The ratio of MDT to ISO and $CaCl_2$(Ca) increased progressively with age: 45.3 ± 2.7%, 61.1 ± 2.6%, 70.1 ± 2.3%, and 89.1 ± 1.5% ($p < 0.05$). This ISO/Ca ratio normalizes the data for the increase in muscle mass with age. ED_{50} values for Ca were the same for the 4 age groups. ED_{50} for ISO progressively decreased from 1 day to 1 month of age: 74.3 ± 13.1, 31.9 ± 9.2, 5.5 ± 0.8, x 10^{-9}M ($p < 0.05$), but there was no difference between 1 month and 4 months old (5.6 ± 0.8, x 10^{-9}M) groups. These findings indicate that newborn myocardium has a decreased sensitivity to ISO and a relatively less MDT to ISO as well. The mechanism of this decreased responsiveness to ISO was evaluated by measuring cAMP production in response to ISO. Myocardial slices were incubated for 5 min in Krebs-Ringer's buffer with/without 10^{-6}M ISO. In contrast to the decreased tension response shown above there was a greater increase in cAMP production in newborn than adult myocardium: Δ10.0 ± 0.08, Δ5.3 ± 0.09, Δ1.2 ± 0.2, and Δ1.7 ± 0.3 pmol/mg tissue ($p < 0.05$). These findings suggest that the difference in responsiveness to ISO of newborn and adult myocardium is in the step(s) distal to cAMP production and proximal to Ca-contractile element interaction.

287 IN-UTERO DEATH AS A POSSIBLE CONSEQUENCE OF PRENATAL ADMINISTRATION OF INDOMETHACIN.

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Indomethacin, a non-specific prostaglandin synthesis inhibitor, has been advocated for use in a variety of areas including obstetrics. It rapidly crosses the placenta and significant concentrations occur in fetal blood and amniotic fluid. The present study was designed to determine the effects of indomethacin on near-term fetuses of mongrel dogs. Fetuses removed by Caesarian section (following maternal administration of 1 mg/kg/day indomethacin for 7 days prior to anticipated delivery) were fully developed but nonviable. Some placental separation was found on Caesarian section, and this was the major gross abnormality observed. In-utero closure of the ductus arteriosus was considered a possible cause of death but autopsies of the animals failed to confirm this. The ducti of the fetuses were found to be either of the same caliber as the pulmonary artery or only partially constricted (to the extent that the lumen was approximately one-half that of the pulmonary artery). The lungs had the appearance of normal unborn lungs. Since signs of obvious maternal complications were absent, it is probable that fetal demise was the result of the administration of the indomethacin. Autopsy findings demonstrated that in-utero closure of the ductus arteriosus was likely not the responsible factor.

288 DECREASED HYPOXIC, HYPEROXIC AND BRADYCARDIC EPISODES AS RESPONSES OF NEONATES TO THEOPHYLLINE.

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Transcutaneous PO_2 (t_cPO_2) is a new approach to the evaluation of drug effects. We investigated the effect of theophylline on 4 prematures (1130-1720 g) with apnea. T_cPO_2, heart rate (beat-to-beat) and thoracic impedance were continuously monitored during each of three 4-hour study periods; 12 hr before T, 12 hr after initiation of T, (administered as aminophylline, 8 mg/kg per rectum q 12 hr x 2, 4 mg/kg q 12 hr x 1-4 d) and 24-58 hr after discontinuing. Plasma levels were measured by a radioimmunoassay developed in our lab. Polygraphic recordings were analyzed without knowledge of treatment.

Treatment	Plasma T µg/ml	# apneic Spells	t_cPO_2 duration (sec) < 40 Torr	>90 Torr	# Episodes HR < 100
None	--	115	3138	4356	47
T	12.58 ± 2.3	26	190	1495	10
PostT	5.6 ± 3.3	38	1003	2393	13

In each case during T, cardiorespiratory patterns were altered, with more regular respirations, apneic spells were reduced, PO_2 was stabilized resulting in less hypoxia and hyperoxia and the number of bradycardic episodes decreased. These beneficial effects reverted upon cessation of short-term therapy.