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THE METABOLISM OF LEAD (Pb) IN THYROPARATHYROID-ECTOMIZED (TPTX) RATS AFTER INFUSIONS WITH CaNa₂EDTA (EDTA) AND PARATHYROID HORMONE (PTH). John F. Rosen,

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Previous data in bone organ culture have demonstrated a mobile compartment of Pb regulated like bone mineral. To test for its existence *in vivo*, after 7mg/kg of Pb plus 25μCi ²⁰³Pb were given IV, TPTX rats were placed in metabolism cages; and 4 days later, EDTA or PTH was infused via a catheterized tail vein for 6 hours. Measurements were made of stable Pb and ²⁰³Pb from aliquots of total organs, urinary Pb/creatinine (Pb-U), and blood Pb (Pb-B), μg/dl. 3 days later the rats were sacrificed and the cpm of ²⁰³Pb from bone (B), liver (L), and kidney (K) were expressed as the % change vs saline-infused controls. The results (* = p < .01; ** = < .001) were: PTH infusion period: Pb-U = 2.29 ± .04*; Pb-B = 34 ± 2*; PTH 72-H after infusion: Pb-U = .56 ± .10; Pb-B = 9.0 ± 2; EDTA infusion period: Pb-U = 20.28 ± 5.16**; Pb-B = 33 ± 2**; EDTA 72-H after infusion: Pb-U = 1.35 ± .04*; Pb-B = 8 ± 2. In EDTA-treated rats, ²⁰³Pb decreased from B, L, K by 22 ± 1*, 46 ± 4**, and 40 ± 6**, respectively. In PTH-treated rats, ²⁰³Pb decreased from B, L, K by 11 ± 2*, 29 ± 4** and 30 ± 2**. Similar increases in the urinary excretion of calcium, phosphate and hydroxyproline were produced by both agents.

These *in vivo* data are consistent with previous *in vitro* observations. Moreover, PTH's dramatic effects on the redistribution of Pb in soft and hard tissues may well modify the toxic activities of Pb and thereby be of considerable clinical importance.

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EFFECTS OF CHRONIC PROPRANOLOL ADMINISTRATION ON THE FETAL AND NEWBORN RAT. Tove S. Rosen, Linda S. Potter, George Reiss, Michael R. Rosen, Depts. of Ped. & Pharm., Col. Univ., Coll. of P & S, N.Y. (spons. by L. Stanley James)

Normal cardiac β-adrenergic function is important for maintenance of an intact stress response in the fetus and neonate. Propranolol (P), a β-adrenergic blocker is used to treat hypertension, arrhythmias and thyrotoxicosis in pregnancy and appears to cross the placenta. To determine the effects of daily oral P administration on perinatal mortality and growth and cardiac β-receptor function in the fetus and neonate, we administered P in a graded dosage schedule (5-20 mg/kg/day) to 20 Wistar rats on days 7-22 of pregnancy; 19 rats served as controls. 6 (3 controls) were delivered by caesarean section on day 22 for fetal studies. Neonates were studied at 0-12, 24-36, 48-60 hours postpartum. There were no differences (p>.05) between P and control rats in maternal weight gain, litter size, number of resorption sites and stillbirths, and pup size and heart weight. Cardiac β-receptor function was studied by recording spontaneous rates of impulse initiation of isolated right atrial strips during control superfusion with Tyrode's solution and following superfusion with epinephrine (E), 1 × 10⁻⁵M. E induced a significant rate increase in atria from the controls (p<.01). No rate change (P>.05) was seen in atria from fetuses of P-treated mothers. As age increased to 60 hours postpartum the response to E of P-treated neonates increased. By 48-60 hours this did not differ significantly from control. Hence chronic P administration significantly depresses β-responsiveness of fetal & newborn rat hearts which could be potentially dangerous to the fetus in his adaptation to the stresses of labor.

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HYPOTENSIVE EFFECT OF DIAZEPAM IN SPONTANEOUSLY HYPERTENSIVE RATS (SHR). Richard M. Schieken, Michael J. Brody, (Spon by R.M. Lauer) Univ. of Iowa, Col. of Med., Depts. of Peds. and Pharm., Iowa City, Iowa 52242

To test if hypertension in SHR is related to exaggerated central responsiveness to environment, Diazepam (D) was chronically administered from the newborn period to adulthood. Four groups (10 each) were studied receiving either daily D 0.02 mg/gm S.C. or D vehicle (V): (1) SHR-D; (2) SHR-V; (3) normotensive control (NC-D); (4) NC-V. Tailcuff blood pressure was consistently 20-30 mm Hg lower in SHR-D than SHR-V (p<.01). Blood pressure of NC-D and NC-V were similar. Pulse rate was similar. Vasomotor reactivity was studied at 12 weeks by hindquarter vascular resistance. Though SHR-V developed high vascular resistance (VR), VR in SHR-D was reduced (p<.05), the VR of NC-D and NC-V were similar. The change in vascular resistance to norepinephrine (NE), epinephrine (E), barium chloride (BaCl₂), angiotensin (Ang) and acetylcholine (ACH) are summarized below: (*p<.05; †not significantly different)

	NE	E	BaCl ₂	Ang	ACH
SHR-D	17.3±4.7*	19.1±5.3*	7.66±3.6*	8.16±3.3*	7.8±1.2
SHR-V	25.7±4.5*	28.0±2.4*	17.0±5.7†	17.2±2.6†	16.4±1.7
NC-D	11.9±3.8†	12.7±2.4†	16.4±4.7†	17.8±2.7†	18.2±1.8†
NC-V	14.1±3.9†	14.3±3.4†	17.2±5.2†	16.2±2.4†	17.7±1.3†

Response to lumbar sympathetic stimulation was blunted in SHR-D. Conclusions: D, by peripheral and or central mechanisms depresses vascular smooth muscle reactivity to a wide variety of stimuli, however these effects are related to a hypotensive action only in SHR.

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STUDIES OF THE ANTIMITOTIC EFFECTS OF CARDIAC GLYCOSIDES: MOLECULAR FEATURES AND POTENCY. Bruce R. Gordon, George B. Segel and Marshall A. Lichtman, Depts. of Ped. & Med., U. of Roch. Sch. of Med., Rochester, N.Y.

Cardiac glycosides are known to inhibit spontaneous and induced human cell division. We have studied a large number of genin and glycoside congeners to determine (a) whether the saccharide or genin portion of the molecule contributes to its antimitotic effect, (b) whether the antimitotic effect is correlated with inhibition of Na⁺ K⁺ ATPase activity, and (c) whether antimitotic effects can be dissociated from cardiac arrhythmogenicity. The concentration of glycoside required to inhibit PHA stimulated thymidine incorporation into DNA at 72 hours in human lymphocytes was studied. The 50% inhibitory dose could be varied by greater than 10-fold by a change in either the genin or the saccharide. Therefore, both genin and saccharide were related to the antimitotic effect of the glycosides. The effect of varying genin or saccharide and the dose-inhibition curves indicated that the antimitotic effect was qualitatively similar to the known effects of these drugs on ATPase activity. Cardiac glycosides were much more potent and rapid-acting inhibitors of lymphoproliferation *in vitro* than glucocorticoids. The antimitotic effects of most of the agents studied appeared to be at concentrations which have a very high risk for arrhythmogenicity of the myocardium. However, these studies may provide incentive to explore structural variants of cardiac glycosides as pharmacologic agents to inhibit cell division.

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FETAL BRAIN DAMAGE AND STILLBIRTH FOLLOWING MATERNAL INGESTION OF INDOMETHACIN AND SALICYLATE.

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Since closure of the fetal ductus arteriosus can be accomplished near term by maternal indomethacin and salicylate administration, an animal model was devised to study the possibility of brain damage through alteration of fetal hemodynamics. Pregnant S-D rats on d 18, 19 and/or 20 received sc either 100 mg/kg sodium salicylate (13 rats), 5 mg/kg indomethacin (6 rats) or vehicle (8 controls) in a single blind study. Dams were sacrificed prior to onset of labor at term (d 21) and uteri were examined for stillbirths and resorptions. Surviving pups were fixed in Bouin's solu. and diencephalon sections were quantitatively graded for neuronal necrosis as per method of Ornoy and GPA (AJOG 124:196,1976). Indo produced severe changes and sal mod-severe effects when compared to vehicle treatment. Control dams had no stillbirths while indo and sal groups had stillbirths in 2 and 3 litters respectively. The neuronal damage and stillbirths may be mediated via the constrictor effect of prostaglandin synthetase inhibitors (indo and sal) on the fetal ductus, a direct neuronal toxic effect or both. The hypoxia and respiratory acidosis in pups and infants surviving maternal indo treatment is further evidence that this class of drugs can influence neonatal hemodynamics (Prostaglandins 8:363,1974. AJOG 126:467, 1976). Maternal ingestion of such inhibitors whether by self medication or prescription (inhibition of parturition) may contribute to adverse perinatal events.

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A PARADOXICAL RESPONSE TO METHYLPHENIDATE IN AN EXPERIMENTAL MODEL OF MINIMAL BRAIN DYSFUNCTION (MBD) IN DEVELOPING RAT PUPS. Bennett A. Shaywitz, Jeffrey H. Klopfer, Judith W. Gordon, Dept. of Ped., Yale Univ. Sch. of Med., New Haven.

Minimal Brain Dysfunction (MBD) is one of the most prevalent problems in present day pediatrics affecting an estimated 5-10% of the school age population. Recent evidence from several lines of investigation support the notion that brain catecholamines are involved in the basic pathophysiologic mechanisms of MBD. In order to explore these mechanisms in more detail, we have produced an experimental model of MBD in the developing rat pup that has many of the similarities of the clinical disorder found in children. The model is effected by the intracisternal administration of 6-hydroxydopamine (6-OHDA) in the 5 day old rat pup, resulting in a rapid and permanent reduction of brain dopamine to values less than 50% of controls. Treated rat pups develop hyperactivity which abates with maturity and persistent learning deficits. We now report the effects of methylphenidate (0.25-2.0mg/kg) on activity levels at 12, 19 and 26 days and T-maze learning at 20 days of age. Methylphenidate significantly increased activity levels and had no effect on T-maze learning in normals. In contrast methylphenidate reduced activity and significantly improved T-maze performance in 6-OHDA treated animals. Our results suggest that the "paradoxical" response to methylphenidate found in 6-OHDA treated rat pups may result from central denervation supersensitivity.