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GESTATIONAL AGE DEPENDENCE OF REGIONAL PROLIFERATION IN FETAL KIDNEYS AN IMMUNOCYTOCHEMICAL STUDY

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Background: Having established a glomerular number deficit in fetal growth retardation(1), human fetal kidneys were studied with the aim of determining periods of specific vulnerability related to proliferative activity.

Materials and Methods: 24 Fetus, evenly distributed between 13 and 22 weeks gestational age were used. Tissue was routinely fixed and embedded. Monoclonal antibodies (DAKO, PC10, MIB-1) were used (2,3) to separately assess proliferation of renal blastema, stroma and glomeruli and epithelial components such as tubuli, Henle's loops and collecting ducts.

Results, Discussion: Proliferative activity remains high in the epithelial components of the nephrogenic zone, with glomerular and blastematous tissue showing reduced activity after week 18. A period of significantly increased activity for collecting ducts, thick and thin segments of Henle's loops and stroma was found between weeks 16 and 18 for both cortex and medulla.

Conclusion: Proliferation related vulnerability of glomerulogenesis is not limited to a specific period of intrauterine development in contrast to the development of the remainder of the nephrons, which may be especially vulnerable between 16 and 18 weeks of gestation.

Ref.: 1: Br J Obst Gynaecol 1992; 99:296-301, 2. J Pathol 1990; 162: 285-294, 3. J Pathol 1992; 168:357-363

INFECTIOUS DISEASES

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NITRIC OXIDE (NO) PRODUCTION BY PULMONARY ALVEOLAR MACROPHAGES (AM) FROM NEONATAL, INFANT AND ADULT RATS.

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Objectives: This study addresses whether an age-related reduction in inducible NO synthase (iNOS) activity by AM causes the high incidence of opportunistic pneumonias in infants who have human immunodeficiency virus (HIV) infection. Opportunistic pathogens (e.g., *Mycobacterium* spp.) are inhibited or killed by NO.

Design and setting: A rodent study preformed in an university research laboratory.

Subjects: Four litters of newborn or infant rats, and 4 adult rats, were used.

Interventions: Cultured AM lavaged from newborn (3-day-old), infant (10-day), or adult rats were stimulated with interferon-γ and lipopolysaccharide.

Measurements: Supernatants from AM had NO production determined as its end products, nitrite [NO_2^-, Griess assay] and nitrate [NO_3^-, nitrate reductase enzyme method]. iNOS activity by AM was equated to superoxide anion (O_2^-) production [ferricytochrome c assay] and lysozyme content [lysoplate method].

Results: Micromolar content of NO_2^- & NO_3^- were: 114±4 & 59±15* (3-day), 40±9 & 37±6 (10-day), and 36±5 & 42±6 (adult). O_2^- production (nmol/10^6 AM/10 min) was: 18±1 (3-day), 15±1 (10-day), and 16±2 (adult). Lysozyme content (ng lysozyme/μg cell protein) was: 6±1* (3-day), 13±4 (10-day), and 27±6 (adult). Data presented as mean±SEM; * = $p<0.05$ v. adult.

Conclusions: Inducible NO production by AM is elevated in newborns compared to adults suggesting that infantile susceptibility to opportunistic pneumonias associated with HIV infection is not due to an age-related reduction in iNOS expression.

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MACROPHAGE CANDIDACIDAL ACTIVITY IN HUMAN NEONATES: DECREASED SENSITIVITY TO MODULATION BY IFN-γ

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In an attempt to understand the mechanisms of host defense in the term neonate against candida, we studied interaction between Calbicans and monocyte-derived macrophages (MDM) cultured for 5 days from the cord blood. In the presence of 2.5% normal adult serum, the extent of phagocytosis of candida was equivalent by newborn and adult MDM. In the absence of serum, phagocytosis of candida was reduced by about half but was still equivalent with cord or adult MDM. In contrast to candida, MDM did not phagocytose non-opsonized group B Streptococcus type III. Mannosylated BSA (ManBSA, molar ratio of mannose to BSA = 23:1) inhibited non-opsonic ingestion of candida by cord and adult MDM in a concentration-dependent manner (with cord MDM, 57 and 84 inhibition and with adult MDM 74 and 87 inhibition by 64 and 320 µg mannose/ml, respectively, after 60 min incubation; means, n=6), suggesting a role for the mannose receptor. Cord MDM killed both opsonized and unopsonized Calbicans as effectively as did adult MDM (n=7). However, exposure of adult and cord MDM to IFN-γ (10-500 U/ml) gave quantitatively different results in candida killing and O_2 release: maximal increase in these functions with adult MDM were achieved with 100 U/ml IFN-γ, whereas no enhancement with cord MDM could be detected after treatment with 100 U/ml, and at 500 U/ml there was still a significantly lower killing and O_2 release by cord MDM compared to adult cells. These data suggest that: 1. clearance of candida from the blood stream may occur in the absence of full opsonization, a condition that might exist in the newborn; 2. resistance of cord MDM to the effect of IFN-γ may represent a developmental immaturity of human mononuclear phagocytes.

MICROCIRCULATION

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THE EFFECT OF IBUPROFEN (IB) ON RETINAL (RBF) AND CHOROIDAL (ChBF) BLOOD FLOW DURING NORMOXIA AND HYPEROXIA IN NEWBORN PIGLETS.

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Previously we demonstrated that indomethacin (IND) reduced basal RBF, but had no effect on ChBF and did not modify the hyperoxic response. We speculated that inhibition of cyclooxygenase was the mode of action, but could not exclude other pharmacological properties of IND. To establish if this effect during normoxia was due to cyclooxygenase inhibition, the effect of IB, a specific cyclooxygenase blocker, was investigated in newborn piglets, age ≤7 days old. We also wanted to verify possible role of the prostanoids as mediators of hyperoxic vasoconstriction. Ocular blood flow was examined before (RA_1) and after (RA_2) either saline (controls; S, n=7), or ibuprofen infusion (30mg/kg) (IB, n=9), and after 90 min of hyperoxia (O_2). Radiolabelled microspheres were used to measure blood flow. Results: (ml/min/100g tissue±SEM):

	RBF_S	RBF_{IB}	$ChBF_S$	$ChBF_{IB}$	
RA_1	60±8	61±4	3048±333	3126±388	*p<0.05 (RA2 vs RA1),
RA_2	59±3	50±4*	3055±395	2589±455	#p<0.05 (O2 vs. RA2)
O_2	43±7#	36±4#	2035±363#	1648±222#	

RBF was significantly reduced by IB whereas ChBF was not. Further, hyperoxia significantly decreased RBF and ChBF in both groups. Thus, our results suggest that prostanoids play a role in maintaining basal retinal vascular tone. However, the response to hyperoxia is mediated through mechanisms other than the by-products of arachidonic acid metabolism.

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DETECTION SENSIBILITY OF LIGHT-SENSE AND FLICKER PERIMETRY IN DIABETIC RETINOPATHY

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In order to study the sensibility of 2 functional tests, Light-sense(LSP)Humphrey Perimeter: prog 24-2) and Flicker perimetry(FP)(Perimex: Central Program) 40 diabetics, 20 without and 20 with fluoroangiographic signs of retinopathy, have been evaluated. Their mean±sd age was 12.1 ± 4.7 (range 10.1-17.4) years, duration of disease 6.7 ± 2.9 (2.0-9.1) years, glycated haemoglobin (HbA1c) 12.1%±3.4 (9.4-14.1) no patient showed early signs of nephropathy and/or neuropathy. The 2 groups of patients (with and without retinopathy) were sex, age, duration of the disease and HbA1c-matched. Visual field mean sensitivity (MS) in 3 sectors for LSP and MS for FP have been evaluated. Retinopathic patients showed lower sensibility both at LSP and FP in 7 eyes LSP and in 6 eyes FP showed no loss of retinal sensitivity in comparison with diabetic without retinopathy (tab 1). The concordance of fluoroangiographic signs of retinopathy with LSP and FP was 82.5% and 85% respectively. Association between LSP and FP allowed a concordance of 97.5% and seems to be useful to detect retinal damage, particularly when retinal angiography cannot be performed frequently.

	LSP	FP	LSP+FP
False +	4 (10.0%)	4 (10%)	0
False -	7 (17.5%)	6 (15%)	1 (2.5%)

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THE RESPONSE OF TOTAL AND REGIONAL CEREBRAL BLOOD FLOW TO DEXAMETHASONE (DEX) INFUSION IN NEWBORN PIGLETS DURING NORMOXIA.

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We questioned the effect of DEX (a phospholipase A inhibitor) on total and regional cerebral blood flow during normoxia in spontaneously breathing newborn piglets, age ≤7 days old. The animals were randomly assigned to either a control group receiving saline infusion, serving as controls (n=7), or a dexamethasone group (DEX) (n=9) receiving DEX 2mg/kg IV. We have shown that this dose reduces the prostanoids in cerebrospinalfluid (CSF). The organ blood flow was measured with the radiolabelled microsphrere technique. **The results were** (flow expressed as ml/min/100g tissue ± SEM): A significant increase ($p<0.05$) after DEX infusion in total cerebral blood flow (CBF) (105±12 to 149±22), brainstem (158±22 to 232±40), dienecephalon (129±18 to 185±33), periventricular area (76±9 to 101±16) and hypocampus (74±7 to 100±16). In the cortex, caudate nucleus and cerebellum, DEX did not alter blood flow. In the control group there was no differences in blood flow before and after saline infusion, neither in total cerebral nor regional cerebral blood flow. **In conclusion**, the cerebrum shows regional differences in its response to DEX. Whereas in some parts regional blood flow significantly increased, others did not demonstrate this phenomenon. Thus, the pharmacological properties of DEX do not modulate the cerebral vascular tone equally in all cerebral regions.