HEMATOLOGY AND ONCOLOGY

877 SICKLE CELL ANEMIA IN SAUDI ARABIA: SPECULATIONS ABOUT REGIONAL VARIABILITY IN FREQUENCY AND SEVERITY Baker Al-Awamy, Fouad Zamachari, and Howard A. Pearson, King Faisal Univ. Sch. of Med., Dammam; Woman's & Children's Hosp., Jeddah, and Yale Univ. Sch. of Med., New Haven

The Hb S gene is widely distributed in Saudi Arabia with a prevalence of 5% in parts of the Western (Red Sea) area and 24% in parts of the Eastern (Gulf) region. We compared hematological data of Hb SS patients from Jeddah (west) and Dammam (east).

Location	N	Age(yr)	Hb(Gm/dl)	HbF(%)	MCV(fl)	PK RBC(%)
Dammam	26	10.3	10.9	17.8	75	3.7
		± 5.3	± 2.0	± 5.9	± 10	± 5.7
Jeddah	30	6.3	8.4	10.7	85.7	12.4
		± 3.1	± 1.3	± 5.7	± 9.6	
New Haven	30	10.4	8.3	5.2	89.3	14.5
		± 5.7	± 0.7	± 2.2	± 5.0	± 4.1

Compared to Jeddah and American patients, Dammam patients were less anemic, more microcytic, had higher HbF levels. Most retained splenic function. We speculate that the Hb S gene may have entered the southwestern Arabian peninsula from Africa in antiquity. As it progressed northeasterly it interacted with other endemic, genetic traits in isolated populations (α thal, h HPFH, etc.). These interactions ameliorated HbSS disease reducing hemozygous lethality. Reproduction by homozygotes, a high rate of consanguinity and the selective advantage of endemic falciparum malaria could have combined to produce the high prevalence of the HbS gene found in the eastern regions today.

These preliminary studies indicate a wide and unique variability of sickle cell hemoglobinopathies of the Arabian Peninsula.

878 INCREASED ACTIVITY OF THE RESPIRATORY BURST IN CORD BLOOD NEUTROPHILS: KINETICS OF NADPH OXIDASE IN SUBCELLULAR FRACTIONS. Daniel R. Ambruso, Linda C. Stork, Bruce G. Gibson, Dept. of Peds., Univ. of Colo. Sch. of Med. and the Bonfils Mem. Blood Ctr., Denver. (Spon. J. Githens)

Generation of toxic oxygen metabolites through the activity of the respiratory burst is crucial to the antimicrobial activity of neutrophils (PMNs). We have previously shown that cord blood PMNs generate increased amounts of superoxide anion (O_2^-) compared to cells from adults. To determine the basis for this increased respiratory burst activity, we measured O_2^- generation in subcellular fractions of PMNs. Blood was obtained from 6 placentas of term, vaginally delivered infants and 6 adults; and PMNs were separated by standard techniques with LPS-free reagents and disrupted by nitrogen cavitation. Plasma membrane-rich fraction (MRF) was separated by differential centrifugation. O_2^- was measured as superoxide dismutase inhibitable cytochrome c reduction at various concentrations of NADPH. Kinetic parameters were calculated by Lineweaver-Burk analysis. The apparent Km for NADPH of cord blood PMNs was increased (numbers are mean ± SEM, $p<0.05$) compared to adult PMNs, but not to a level implying abnormal cell function. Vmax was strikingly increased ($p<0.05$) in cord blood samples. The data suggests a small difference in affinity for NADPH in cord blood PMNs. The increased Vmax may be related to "priming" of the oxidase, possibly as a result of partuition; and this could explain the increased respiratory burst activity of intact cord blood PMNs.

	K_m^{app} (μM NADPH)	Vmax (nmol/min/mg)
Adult	30.0±0.6	180±40
Cord	66.0±1.0	306±27

879 NEUROBLASTOMA IN INFANTS: WHEN IS THERAPY NECESSARY? Michael D. Amylon, Michael P. Link, Susan P. Perrine Stephen J. Shochat, Sarah S. Donaldson, and Bertil E. Glader. Departments of Pediatrics, Surgery and Radiology, Stanford University School of Medicine, Palo Alto, CA.

From 1974 through 1983, 19 new neuroblastoma patients less than one year of age were seen at our institution. We have followed 17 of these patients for 18-130 months. Primary tumor site in this group was adrenal (8), mediastinum (6), pelvis (2) or retroperitoneum (1). Staging by Evans' criteria was I (1), II (4), III (5), IV (6) or IV-S (1). Three stage IV patients would have been IV-S except for distant node involvement. Only 1 patient had bony metastases at diagnosis. Of these 17 patients, 11 had complete excision of primary tumor, 4 had subtotal resection, 1 had biopsy only and 1 had biopsy of metastatic disease. Two patients had progession of disease following the primary surgical procedure, 1 to skin and 1 to bone. Both patients with bony metastases were treated with aggressive multiagent chemotherapy; both died with progressive disease. The other 15 patients are all alive and disease-free with follow-up of 18+ to 130+ months. Thirteen of these 15 patients, including many with widespread metastatic disease and large primary tumors, received no therapy other than the initial surgical resection or biopsy. Two patients received 2500 rad to the primary tumor site and 1 received cyclophosphamide as a single agent. These observations suggest that many infants with neuroblastoma without skeletal metastases will undergo spontaneous regression of tumor, and should be followed expectantly without further therapy.

880 SECRETORY DETERMINANTS OF IMPAIRED ADHERENCE & MOTILITY OF NEONATAL PMNS. Donald C. Anderson, Katherine B. Freeman, Bonnie J. Hughes and Greg J. Buffone, Baylor College of Med. Dept. of Ped., Houston, TX.

To evaluate possible secretory determinants of pathologic neonatal PMN (NP) adherence and stimulated migration, correlative studies of 2° granule lactoferrin (LF) release (RIA), chemotactic factor receptor "up regulation" (fML^3HP binding, 4°C), and the induction of OKM1, & p150,95 glycoprotein (GP) surface expression (Flow Cytometry) mediated by secretory or chemotactic stimuli were performed. LF content of 31 healthy term NP suspensions (x 15.2 g/10^7 PMNs) was diminished ($p<.001$) compared to that of 38 healthy adult (AP) suspensions (x 31 g/10^7 PMNs). NP demonstrated diminished ($p<.01$) LF release in suspension in response to PMA (500 ng/ml) or A23187 (>10^{-7}M) and during adherence to glass substrates in the presence of PMA or fMLP ($p<.01$). "Up regulation" of specific fML^3HP binding (stimulated - baseline values) of NP by PMA (>500 ng/ml) or A23187 (>$2.5X10^{-8}$M) was also diminished (x CPMx10^3/10^7 PMN: PMA; 5.8 (NP), 10.4 (AP), A23187; 9.1 (NP), 21.2 (AP) ($p<.001$). PMA mediated a minimal enhancement of surface expression of OKM1 α, β, & p150,95α (x̄ fold increase; 1.4, 1.6, 1.5) compared to AP (x̄ fold increase; 5.6, 5.9, 5.3). Diminished ($p<.001$) induction of these GPs on NP by fMLP or C5a was directly related to impaired enhancement of adherence by these chemotactic factors ($r=.89; p<.001$). These studies suggest that impaired hyperadherence and stimulated migration by NP are functionally linked to abnormalities of 2° granules & a resultant diminished availability of LF, fMLP receptors & "adhesive" GPs which are required at the cell surface for these events.

881 ERYTHROCYTE PYRIMIDINE 5' NUCLEOTIDASE ISOENZYMES IN CONGENITAL DEFICIENCY AND IN LEAD EXPOSURE. Carol R. Angle, Sidney J. Stohs, Laura R. Cook, Mildred S. Mitchell, University of Nebraska Medical Center, Department of Pediatrics, Omaha, Nebraska.

Red blood cell (rbc) pyrimidine 5' nucleotidase deficiency (P5N) is a cytosolic enzyme system that dephosphorylates CMP, UMP, dCMP, dUMP and dTMP. The kinetics and metallosensitivities of enzyme activity were determined in normal subjects, congenital pyrimidine 5' nucleotidase deficiency (PND) and subjects with increased blood lead. The apparent Michaelis constants and Kmax suggest 3 isoenzymes of decreasing substrate affinity for 1) dUMP and dCMP, 2) dTMP, 3) UMP and CMP. In PND, activity with UMP and CMP is < 15% normal with an increased K_m for both substrates. In PND rbc, enzyme activity is normal to increased with dUMP, dCMP, dTMP. These observations are consistent with the accumulation of CDP-choline and CDP-ethanolamine in PND rbc and our inability to identify, by MS or NMR, the presence of deoxypyrimidine esters in PND rbc. The maximal affinity of the enzyme for the deoxypyrimidines suggests a role in the clearance of DNA as well as RNA during red cell maturation. In vitro sensitivity to Pb^{2+} and Cu^{2+} (> 50% inhibition at 10^{-4}) is more evident in normal rbc than PND. In rbc from lead exposed subjects, rbc P5N activity with UMP as substrate is directly correlated with the level of blood lead.

† **882** INTERFERON GAMMA MODULATES PROTEIN KINASE C IN MURINE PERITONEAL MACROPHAGES. DL Becton‡ TA Hamilton‡ SD Somers‡ JM Falletta, DO Adams‡ Departments of Pediatrics and Pathology, Duke University Medical Center.

Macrophage (Mφ) activation for tumoricidal activity can be induced by sequential application of two discrete molecular signals: interferon γ (IFNγ) and endotoxin. The mechanism of signal transduction leading to activation is unclear. Protein kinase C (PK_C) has been implicated in cell regulatory functions and as a binding site for phorbol esters. PK_C activity was measured in detergent extracts of murine peritoneal Mφ before and after treatment with IFNγ. Treatment resulted in a specific 3-4 fold increase in maximal PK_C activity. The optimal response occurred at a dose of 1-3 U IFNγ/ml at 3-6 hrs. Inhibition of protein synthesis by cyclohexamide did not prevent this effect. Phorbol binding sites were not affected by IFNγ treatment, and the subcellular localization of PK_C was unchanged. Characterization of partially purified enzyme from control and treated Mφ demonstrated 1) no direct in vitro activation of PK_C by IFNγ, 2) no difference in cofactor ($Ca^{\#}$ and phospholipid)requirements, 3) no difference in Km for substrate ATP, 4) increased Vmax in enzyme from treated cells, and 5) enhanced (2-3 fold) response to in vitro phorbols in enzyme from treated cells. These data suggest that the increased PK_C activity does not require de novo synthesis of PK_C but results from modification of existing PK_C leading to enhanced catalytic efficiency. Additionally, we have shown that treatment of Mφ with the pharmacologic agents calcium ionophore (A23187) and phorbol myristate acetate mimics the effect of IFNγ on activation. Thus PK_C appears to be an important regulator of Mφ activation by IFNγ.