53 EFFECT OF HUMAN MILK (HM) AND FORMULA FEEDS (FF) ON TOTAL FREE RADICAL TRAPPING CAPACITY (TRAP) OF PRETERM BABIES.

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Antioxidants (Vitamin E and C [VE, VC]), uric acid (UA), bilirubin (Bili), sulfhydryl groups (SH) work synergistically and thus HM may have advantages over FF in protecting babies from oxygen toxicity. We measured (day 0,3,7,14,21) plasma protein fluorescence ratio (PF) as an index of free radical damage, the various antioxidants, and, using a new assay, the plasma TRAP in preterm babies (31-35 wks ga) fed on HM (n=8) and FF (n=12).There were no differences in these measurements except for a higher bili ($p<0.01$ on day 21) in the HM group. The TRAP correlated with UA ($r=0.66$, $p<0.001$) and VC ($r=0.41$, $p<0.001$). There was a postnatal decline in the TRAP (HM d0 929.6±245.0, d21 667.8±148.3, $p<0.05$, FF d0 1077.6±157.5, d21 577.6±128.0 µmol/L, $p<0.001$), associated with a rapid fall in VC and a gradual fall in UA. PF showed a slight rise postnatally which was not statistically significant, and did not differ in the HM and FF babies. (HM d0 6.7±3.5, d21 9.3±3.1, FF d0 7.7±4.3, d21 9.0±2.5).
Postnatally the free radical trapping capacity of enterally fed well preterm babies falls. HM feeding does not appear to improve the plasma antioxidant capacity in well babies. These findings need to be compared with those in ill babies, fed parenterally who are at risk for oxygen toxicity.

54 ROLE OF A NOVEL GTP-SENSITIVE APICAL CHLORIDE CHANNEL IN CHOLERATOXIN- AND CYCLIC AMP-PROVOKED INTESTINAL Cl^- SECRETION AND ITS RELEVANCE IN CYSTIC FIBROSIS

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Chloride conductance measurements in apical membrane vesicles isolated from the HT-29 c.19A human colon carcinoma cell line and from rat enterocytes, and electrophysiological analysis of single Cl^- channels in apical membrane patches excised from HT-29.cl.19A monolayers, revealed the existence of two major types of Cl^- channels: (1) an outwardly rectifying 32 pS anion channel (A channel) activated by cyclic AMP and ATP in the presence of protein kinase A, and (2) an inwardly rectifying 20 pS channel (G channel) activated by GTPγS (10^{-9} M) and inhibited by GDPβS (10^{-4} M), indicative for the involvement of a GTP-binding protein in channel regulation. The GTP-activation of the G channel was inhibited by the phospholipase A_2 ($PL\text{-}A_2$) inhibitor mepacrine (10^{-5} M) and mimicked by arachidonic acid (AA, 5.10^{-5} M), suggesting a role for $PL\text{-}A_2$ and AA metabolites as coupling factors between the G-protein and the Cl^- channel. Short circuit current (SCC) measurements on HT-29 monolayers and ileal mucosa from control and cystic fibrosis (CF) patients mounted in Ussing chambers showed that choleratoxin (CT)-and cyclic AMP-provoked active Cl^-secretion was inhibited for 40-60% by mepacrine ($2\text{-}5.10^{-5}$ M) and the lipoxygenase inhibitor NDGA (2.10^{-5} M) but was completely absent in CF patients carrying the major CF mutation (ΔF508). These data together suggest that (i) CT- and cyclic AMP-induced Cl^- secretion is mediated in part by activation of $PL\text{-}A_2$ resulting in AA release, formation of lipoxygenase products and activation of G channels; (ii) the residual Cl^- secretion results from a cyclic AMP- and protein kinase A-induced phosphorylation and opening of apical A channels; (iii) since both types of Cl^- channel apparently fail to respond to cAMP signals in CF, the CF gene-encoded protein ('CFTR') most likely functions as a common regulator of both channels rather than as a Cl^- channel itself.

55 ESSENTIAL FATTY ACIDS IN LOW BIRTHWEIGHT INFANTS: EFFECT OF PARENTERAL NUTRITION, FORMULA OR BREAST MILK

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Long chain polyunsaturated fatty acids 20:4 n-6, 22:4 n-6 and 22:6 n-3 (LCP) are crucial components of all cell membranes, particularly in CNS. Lower n-3 LCP in red cell lipids of infants, and CNS lipids of piglets, fed formula rather than breast milk have been reported. Whether this is due to inadequate 18:3 n-3 in formula fats, or reflects a need for dietary n-3 LCP in the newborn, is controversial. Therefore, the effect of feeding (LBW) infants exclusively formula containing 2% fat as 18:3 n-3 or mother's expressed breast milk for 28d (mean postnatal age 42d) was studied. LBW infants commonly require parenteral nutrition until full enteral feeds can be established. Thus, the effect of time (0-33 days) to establish full feeds (120 mL/kg/day) on LCP status was also determined (n=52 LBW infants). Red cell phosphatidyl-choline, - ethanolamine and plasma phospholipids were purified and fatty acids analyzed by GLC. N-6 and n-3 LCP declined with increasing duration of parental nutrition, irrespective of lipid infusion. Once enteral feeds were established, the levels of 20:4, 22:4 and 22:5 n-6, 20:5, 22:5 and 22:6 n-3 and their ratios in all lipids remained equivalent, and were similar among the 3 feeding groups over the next 28 days. It is suggested preterm infant formula should contain at least 1% Kcal as 18:3 n-3, and that this intake provides for similar levels of 22:6 n-3 to infants fed breast milk for over the first 1-2 mths of life. Early parenteral nutrition, however, results in depletion of LCP.

56 SURVIVAL, GROWTH AND QUALITY OF LIFE AFTER LIVER TRANSPLANT IN CHILDREN.

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To investigate outcome and evaluate areas of potential ongoing concern after orthotopic liver transplantation (OLT) in children, overall actuarial survival rates in relation to age and degree of undernutrition at the time of OLT have been evaluated and followup studies of growth parameters and quality of life undertaken in a group of 48 children (age 0.5-14.2 yr) undergoing OLT for end-stage liver disease. Overall 3 yr actuarial survival was 68%. Survival rates did not differ between age groups (actuarial 1 year survival for ages 5-15 yr, 1-5 yr and <1 yr were 68%, 72% and 62% respectively) but did differ according to nutritional status at OLT (actuarial 1 year survival for children with Z scores for weight <-1 was 58%, >-1 was 94% p=0.01). Significant catchup weight gain and growth were observed by 6, 12 and 18 months post transplant (n=17). Of 28 survivors studied 12 months after OLT, quality of life was assessed by adaptive behaviour and social skills indices. In all but 3 cases, quality of life was judged to be excellent and all school aged children bar one were attending normal school. Two cases had intracerebral perioperative complications with mild to moderate intellectual handicap.

Satisfactory long term survival can be achieved after OLT in children regardless of age but the importance of preoperative nutrition is emphasized. Survivors have an excellent chance of good quality of life and catchup growth by 1 year post-transplant.

57 EVALUATION OF TYROSINEMIC CHILDREN FOR LIVER TRANSPLANTATION.

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We evaluated 19 patients (8/12-16 8/12 years) with Tyrosinemia for possible liver transplantation. Ten children had repeated neurological crises (severe paresthesias, automutilation, paralysis), and 12 had evidence of renal disease as assessed by a GFR < 60 (4), Fanconi-like syndrome (5), nephromegaly with or without nephrocalcinosis (10). The following liver tests were abnormal; AST/ALT (12), Alk. Phos. (8), bilirubin (5), γ GT (13), PT (11), PTT (7), albumin (6). Portal hypertension was present in 8 patients. Nodules were present on liver imaging in 10 children, with α fetoprotein (AFP) levels ranging from normal to 33000 ng/ml. Of the 8 whole livers available for histological examination, 2 contained foci of hepatocarcinoma. No relationship between AFP, hepatocarcinoma, or the presence of nodules could be found. Five children had a liver transplant, and 2 a combined liver-kidney transplant (one of the two died from primary non-function of the liver graft). The 6 remaining transplanted patients are alive and thriving with normal liver tests, and none have had recurrence of neurological crises. Two patients died while on the waiting list and 3 during severe neurological crises. Liver transplantation cures the hepatic metabolic disease, protects from the development of hepatocarcinoma, and prevents further neurological crises. Combined liver-kidney transplantation should be considered in children with low GFR's in light of the long-term effects of CSA.

58 IMPROVEMENT IN TRUE GFR AFTER CYCLOSPORINE (CSA) FRACTIONATION POST LIVER TRANSPLANTATION.

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Long-term liver transplant (LT) survivors have been reported to have an alarming decrease in GFR with time (Transplantation 1989;47:314). It is unknown whether this phenomenon is reversible, particularly at distance after transplant. We therefore began evaluating the CSA kinetics in our transplant population in order to assess whether a dose modification could decrease CSA nephrotoxicity. CSA levels were determined using a monoclonal antibody on whole blood (Sandimmune) at T_0 and hourly for 8 hours after the patients' usual oral dose. Eight children aged 2½ to 18 years were thus evaluated 7 to 36 months post LT. CSA trough levels ranged from 50-148 ng/ml; time to peak (1-6 hrs), peak levels (80-1179 ng/ml) and half-life (1½-4 hrs) varied widely. GFR (DTPA method) ranged from 32-93 ml/mn/1.73 m^2. Five were placed on Q8H CSA as suggested by their kinetic study (Q6H being unacceptable to parents), allowing for a reduction of total CSA daily dosage from 15-50% to obtain the same trough level. Three patients have had repeat GFR studies 4-7 months after CSA fractionation. One GFR was unchanged (65 → 63), but the 2 others improved (31 → 54, 32 → 64). Repeat GFR studies are not yet available in the other 4 patients. CSA absorption and metabolism is erratic in children post-LT, and dose fractionation may decrease its nephrotoxicity.