

is 2  $\mu$ M). All of these mitochondrial reactions are membrane linked. Electron microscopy confirms the biochemical data of swelling.

Lysosomes of rat liver and L-929 cells demonstrate increased permeability within one hour of exposure to bilirubin using acid phosphatase activity as a monitor of membrane fragility. This effect is seen at relatively high bilirubin levels (500  $\mu$ M) but preliminary evidence suggests concentration of bilirubin by lysosomes.

Influence of early malnutrition on drug metabolism and effect.

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Male Sprague-Dawley rats were raised in litters of 10 (controls, C) and 18 (malnourished, M) until 21 days of age (weaning). Total body and liver weights were decreased by 30% in the M group. As a consequence liver weight remained at the same percentage of body weight ( $4.89 \pm 0.1$ ) as in the controls ( $4.75 \pm 0.2$ ). The microsomal components of the electron transport chain for oxidative pathways were similar in both groups. Metabolism for several different oxidative substrates (aminopyrine, aniline, and benzpyrene) was increased significantly in liver homogenates in the M group. Since drug metabolism is the most important determinant of drug effect, hexobarbital was used in correlative *in vivo* studies. The duration of sleep (the major action of hexobarbital) was surprisingly longer in the M animals ( $160 \pm 9$  minutes) than in the controls ( $112 \pm 6$  minutes) at a dose of 100 mg/kg. Since hexobarbital metabolism was not decreased in the M group these findings strongly suggest that brain sensitivity is altered. This may have important consequences for drug usage in malnourished children.

Pharmacologic modification of bilirubin toxicity in tissue culture.

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While several areas of bilirubin toxicity have been identified, the mechanism of bilirubin entry into cells and the mode of cell death are not understood. Several substances which have been associated with membrane functions were examined to determine if they would influence bilirubin toxicity. Strain 929 L-cells were washed four times in protein free media and incubated one hour with the test drug before adding bilirubin. Ten  $\mu$ M bilirubin killed >90% cells in four hours as determined by cell penetration of erythrocin B. Hydrocortisone totally protected the cells from bilirubin toxicity; prednisolone was slightly less effective. The rate of cell death was retarded by insulin, but only in very high concentrations (0.2 units/ml). Theophylline and caffeine, which inhibit the breakdown of cyclic AMP by the enzyme phosphodiesterase, offered partial protection. Paradoxically, epinephrine and glucagon, which stimulate adenyl cyclase, and cyclic AMP and dibutyl cyclic AMP either failed to protect or even accelerated cellular death with bilirubin. These effects could be blocked with theophylline and caffeine, suggesting that AMP or phosphodiesterase itself may be involved in bilirubin toxicity.

These studies reveal additional parameters of bilirubin toxicity and suggest the possibility of altering susceptibility for kernicterus with pharmacologic agents.

A six year prospective controlled study of neonatal hypoglycemia.

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Between 1961-1964, thirty-nine newborns with transient neonatal hypoglycemia (Group I) were matched with 41 controls (Group II) on the basis of 9 weighted clinical criteria. On-going medical and social service care was provided and yearly EEG's, neurological and psychological examinations were done. Computer analysis indicated the infants to be well matched according to medical criteria as well as socio-economic background. The incidence of R.D.S., sepsis, hyperbilirubinemia, polycythemia and C.N.S. problems was similar in both groups. Nevertheless, the clinical course of Group I was more severe due to the manifestations of hypoglycemia. Recurrent hypoglycemia was seen in 4 children; there were no deaths in either group. The follow-up data on physical development indicate that Group I showed a significant lag in height and weight until 3 years of age, after which both groups were in the 25th percentile. Head size, significantly smaller at birth in Group I, remained below the 3rd percentile at age 6. An analysis of 214 EEG's failed to reveal any significant differences in abnormalities between the groups. Stanford-Binet scores at age 5 showed a mean IQ of  $87 \pm 4$  in Group I (22) vs  $94 \pm 4$  in Group II (20) children. At age 6, the mean IQ was  $88 \pm 4$  in Group I (14) and  $96 \pm 3$  in Group II (18) children. These differences are not significant. W.I.S.C. scores at age 5 and 6 were similar in both groups. To date, the prompt and vigorous treatment of symptomatic neonatal hypoglycemia would appear to obviate marked differences in development.

## GENETICS

Normal, Duarte Variant, and galactosemic alleles code for immunologically identical gal-1-P uridyl transferase enzyme protein. THOMAS A. TEDESCO and WILLIAM J. MELLMAN. *Univ. of Pennsylvania Sch. of Med., Philadelphia, Pa.*

Human galactose-1-phosphate uridyl transferase was purified from post-mortem liver to a preparation having a single band in polyacrylamide gel electrophoresis. This preparation was used successfully to produce a rabbit antibody that precipitates transferase activity from solution and that forms a precipitin band in double immunodiffusion. Hemoglobin-free erythrocyte preparations from homozygous normal ( $Gt^+/Gt^+$ ), Duarte Variant ( $Gt^D/Gt^D$ ), and galactosemic ( $Gt^G/Gt^G$ ) individuals show immunoprecipitin bands in double immunodiffusion against this antibody that are identical with that of the purified transferase preparation. The results indicate that the three alleles code for immunologically similar enzyme proteins suggesting that the functionally less active Duarte Variant and inactive galactosemic enzyme proteins have resulted from "point" mutations.

Fabry's disease: Evidence for structural mutation of  $\alpha$ -galactosidase. GIOVANNI ROMEO and BARBARA R. MIGEON, *Johns Hopkins Hosp., Baltimore, Md.*

Fibroblasts from a patient with Fabry's disease have an  $\alpha$ -galactosidase activity corresponding to 10-20% of control values, and the same difference has been found between the 2 clonal populations derived from the patient's mother and sister (Science 170: 180, 1970). The  $\alpha$ -galactosidase present in fibroblasts of 2 unrelated patients and in "negative" clones of 2 heterozygotes shows a slower rate of heat inactivation than the enzyme of