three and five weeks. Transferase activity was 0.45% of the control mean of 38.9 units (μmol of UDP galactose formed/hr) per gramme of protein (range 33.7 U-54.1 U/g protein), the fetus being judged to be affected. The parents decided to continue with the pregnancy, and the mother was delivered at term when the diagnosis of galactosaemia was confirmed by blood transferase assay.

Case 2.—This 25-year-old woman had previously been delivered of a girl with galactosaemia, who at 2 years 9 months had a blood transferase activity of 3.9 units per gramme of haemoglobin. Both the girl's parents had activities in the heterozygote range (mother 21.2 U/g Hb; father 17.7 U/g Hb; normal adult mean 34.0 U/g Hb; range 29.5 U-38.5 U/g Hb). In the pregnancy we studied amniocentesis was performed at 15 weeks' gestation. After three weeks of culture amniotic cells were found to have normal transferase activity (43.3 U/g protein), the fetus being judged to be unaffected. We confirmed this at birth by showing normal cord blood transferase activity (41.6 U/g Hb).

Conclusion

These results suggest that assay of transferase activity on amniotic cells collected at amniocentesis and cultured for about three weeks allows accurate prenatal diagnosis of galactosaemia. Methods for assay which depend on reduction of the enzymes

NAD or NADP, however, are unsuitable for amniotic cell transferase assays.

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MEDICAL MEMORANDA

Gross Impairment of Hepatic Drug Metabolism in a Patient with Chronic Liver Disease

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The biotransformation of drugs occurs mainly in the liver. Patients with liver disease may therefore be unable to metabolize drugs normally and effects may be exaggerated and prolonged with an increased risk of toxicity. Selden and Sasahara, (1967). The results of drug metabolism studies in patients with liver disease have been conflicting, however, and some workers have reported a normal or even an increased rate of drug metabolism (Nelson, 1964; Held and Oldershausen, 1971). We found such gross impairment of lignocaine and antipyrine (phenazone) metabolism in a young woman with active chronic hepatitis that chronic administration of many drugs in conventional doses would undoubtedly have led to rapid cumulation with severe and probably fatal toxicity.

Case Report

A 28-year-old housewife was first admitted to hospital in 1968 with painless jaundice which resolved spontaneously after nine months. She remained well until 1970 when there was a recurrence of jaundice associated with dark urine, pale stools, and pruritus. Despite treatment with prednisolone in doses of up to 60 mg daily her condition did not improve, and in April 1973 she was readmitted to hospital because of anorexia, vomiting, upper abdominal pain, and increasing ankle oedema. One examination she was fully orientated and there was no evidence of hepatic precoma. She was deeply jaundiced, with multiple spider naevi, moderate hepatosplenomegaly, and ascites.

Laboratory investigations were as follows: prothrombin ratio 3.6:1, serum bilirubin 11.3 mg/100 ml, alkaline phosphatase 170 K. A. units, aspartate and alanine aminotransferases 129 IU/l. and 29 IU/l. respectively, total plasma proteins 8.7 g/100 ml (albumin 26.2% and gammaglobulin 57.4%), and plasma urea 21 mg/100 ml. Tests for antinuclear factor were positive, but antibodies to mitochondrial, smooth muscle, and hepatitis B antigen were not detected. There was no radiographical evidence of oesophageal varices. The patient was a Jehovah's Witness and a liver biopsy was considered an unjustifiable risk without permission to give a blood transfusion. A diagnosis of active chronic hepatitis was made. Drug therapy before admission had consisted of oral and intramuscular phytomenadione, prednisolone, Slow-K, and frusemide: spironolactone and folic acid were added after admission.

DRUG METABOLISM STUDIES

Twenty days after admission the patient ingested 400 mg lignocaine hydrochloride with 40 ml of water after an overnight fast. Venous blood was sampled at intervals for eight hours and urine was collected for three days. Five days later 18 mg/kg of antipyrine was given by mouth and the plasma half life was measured as described by O'Malley *et al.* (1971).

Control studies of lignocaine metabolism were carried out in seven healthy ambulant adult male volunteers aged 19-37 years. Plasma and urine samples were stored at -20°C . Lignocaine, its metabolites ethylglycylxylidide (EGX), glycylxylidide (GX), and 4-hydroxyxylidine, and antipyrine were estimated by gas-liquid chromatographic methods (Adjepon-Yamoah, 1973; Prescott *et al.*, 1973).

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Percentage of Dose recovered in Urine in 48 Hours as Lignocaine, EGX, GX and 4-Hydroxyxylylidine in Patient with Chronic Liver Disease and seven Healthy Volunteers after 400 mg Lignocaine by Mouth. Results in Volunteers expressed as Means $\pm$ S.E. of Mean

	Lignocaine	EGX	GX	4-hydroxyxylylidine	Total	Urine pH
Patient	8.0	9.7	0.3	8.8	26.8	7.1
Healthy volunteers	0.8 $\pm$ 0.2	4.2 $\pm$ 0.6	6.2 $\pm$ 1.2	33.8 $\pm$ 2.7	45.0 $\pm$ 3.3	6.2 $\pm$ 0.14

The metabolism of lignocaine was found to be grossly impaired in the patient. The plasma lignocaine half life was 19.1 hours whereas the mean half life ($\pm$ S.E.) determined under identical conditions in four healthy volunteers was only 1.4 ± 0.01 hours (fig. 1). In addition the peak plasma concentration of lignocaine was higher in the patient ($1.3 \mu\text{g/ml}$) than the mean value observed in the healthy volunteers ($0.81 \pm 0.11 \mu\text{g/ml}$). Six hours after administration the plasma concentration of lignocaine in the patient was about 20 times higher than in the healthy volunteers.

The metabolism of lignocaine to EGX and GX was depressed in the patient. The peak plasma concentrations of EGX and GX were $0.31 \mu\text{g/ml}$ and less than $0.03 \mu\text{g/ml}$ respectively, while the corresponding mean values ($\pm$ S.E.) in the healthy volunteers were $0.66 \pm 0.11 \mu\text{g/ml}$ and $0.27 \pm 0.05 \mu\text{g/ml}$. The 48-hour

urinary recovery of lignocaine and its metabolites is shown in the table. In comparison with the healthy volunteers the patient excreted more lignocaine and EGX but much less GX and 4-hydroxyxylylidine.

Antipyrine disappeared from the plasma extremely slowly and the calculated apparent plasma half life was 137 hours (fig. 2). This is about 13 times longer than the mean antipyrine half life ($\pm$ S.D.) of 10.3 ± 2.1 hours in healthy young women reported by O'Malley *et al.*, (1971).

Comment

The metabolism of lignocaine and antipyrine was strikingly impaired in this patient, and both drugs were eliminated at only 7-8% of the normal rates. Prolongation of the plasma half life of lignocaine and antipyrine has been described in patients with chronic liver disease (Thomson *et al.*, 1971; Branch *et al.*, 1973), but the half life values of 19.1 hours for lignocaine and 137 hours for antipyrine in our patient were far longer than any reported previously. The higher urinary recovery of lignocaine and EGX and the lower recovery of GX and 4-hydroxyxylylidine in the patient suggest selective impairment of the different metabolic pathways of lignocaine.

Patients with such severe depression of drug metabolism are extremely vulnerable, and some means by which they can be recognized is essential if therapeutic disaster is to be avoided. Though decreased metabolism of amylobarbitone and antipyrine in some patients with liver disease has been correlated with hypoalbuminaemia, abnormal bromsulphalein retention, and prolongation of the prothrombin time, there is no certain way of predicting drug metabolizing capacity in the individual patient. Studies of drug metabolism should be carried out on a routine basis in patients with severe liver disease.

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FIG. 1—Plasma concentrations of lignocaine in four healthy volunteers and patient with chronic liver disease after 400 mg by mouth.

FIG. 2—Plasma concentrations of antipyrine in patient after 18 mg/kg by mouth.