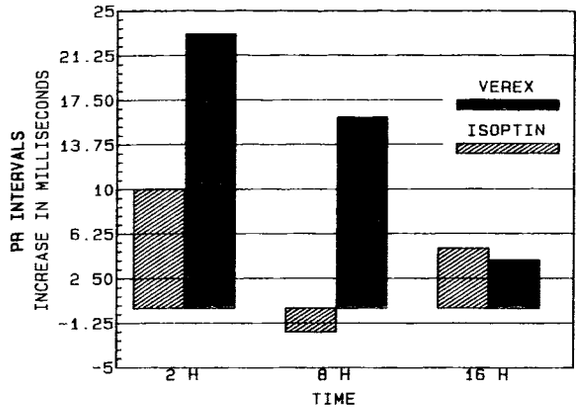

Fig 2—Changes in PR interval.

experimental formulation and from a liquid dosage form. The solid dose formulation ('Verex' 250 mg) was given once daily while the liquid form ('Isoptin' 83·33 mg) was given every 8 h over 24 h.

The main physiological effect of verapamil is prolongation of the P-R interval, and, as a safety precaution, computer-aided electrocardiograms were done at 2, 8, and 16 h. The blood verapamil and norverapamil levels (fig 1) and the changes in P-R interval (fig 2) suggest that the new dosage form provides for a slow continuous release of active drug from the tablet matrix over 20–24 h, permitting once-daily dosage.

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BIRTH DEFECTS AND VIDEO DISPLAY TERMINALS

SIR,—While working on video display terminals (VDTs) some secretaries now wear leaded aprons for protection against assumed radiation risk. Chick embryos exposed to very-low-frequency magnetic fields have been reported to show serious embryological disturbances.[1] The lay press has cited several clusters of defective pregnancy outcomes, including birth defects, among VDT users,[2,3] and the medical news page of the London *Times* of Nov 16, 1984, carried an account, entitled "The screen of fear", of a study which found abnormal pregnancy outcomes in 36% of VDT workers and 16% of non-VDT staff. The fears have spread to other countries, so we analysed the interview forms of 1475 mothers of malformed children and their paired referents.

The inquiry was an extension of the standard operating procedure[4] of the Finnish national register of congenital malformations. Detailed information has been collected about possible occupational and leisure-time exposures of the mothers.[5] Included were 365 consecutive defects of the central nervous system, 581 orofacial clefts, 360 structural defects of the skeleton, and 169 selected cardiovascular malformations.

The scrutiny revealed 386 discordant pairs with respect to potential VDT exposure by occupational title such as clerical worker, secretary, and typist, or automated data processing employee. 183 of the potentially VDT exposed were case mothers and 203 were referent mothers. The interview forms of the mothers with potential exposure were then perused for VDT information by someone unaware of the case/referent status. VDT work during early pregnancy was explicitly described in questionnaire forms of 108 pairs out of which 50 were case mothers and 58 referrent mothers. (The age structure, parity, previous miscarriages or stillbirths, drug consumption, and alcohol intake during pregnancy were comparable for the VDT exposed and non-exposed mothers.) The comparison of the mothers exposed to VDT for at least 4 h a day during early pregnancy with those not exposed at all showed an overall odds ratio point estimate of 1·0 with 95% confidence limits of 0·6 and 1·6.[6] Thus, our results do not give support to rumours that exposure to VDTs causes birth defects.

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PRENATAL DETECTION OF ZELLWEGER SYNDROME

SIR,—The peroxisomal enzyme dihydroxyacetone phosphate acyltransferase (DHAPAT), which catalyses the first step in the biosynthesis of ether phospholipids, is deficient in tissues and cultured skin fibroblasts of patients with the cerebrohepatorenal (Zellweger) syndrome.[1] This autosomal recessive disease[2] is usually lethal in the first year of life and is characterised by the absence of morphologically distinct peroxisomes in liver and kidney[3] and by an accumulation of very-long-chain fatty acids,[4] pipecolic acid[5] and trihydroxycoprostanoic acid[6] in blood and urine and by the virtual absence of plasmalogens in tissues.[7,8] The finding that DHAPAT expressed in amniotic fluid cells of controls suggested a prenatal test for Zellweger syndrome. We now report (table) that this enzyme is indeed deficient in amniotic fluid cells from two fetuses with Zellweger syndrome (courtesy of Dr H. W. Moser). Biosynthesis of ether phospholipids was strongly impaired in those cells also, as shown by much reduced incorporation of a radioactive precursor of ether phospholipids (^{14}C-hexadecanol) into plasmalogens. In six other pregnancies at risk for Zellweger syndrome both types of analysis suggested that the fetuses were not affected; five of these pregnancies have resulted in the birth of a healthy child (the other pregnancy is still in progress).

DHAPAT ACTIVITY AND DE NOVO BIOSYNTHESIS OF PLASMALOGENS IN CULTURED FIBROBLASTS OF ZELLWEGER PATIENTS AND CONTROLS AND IN CULTURED AMNIOTIC FLUID CELLS OF CONTROLS, ZELLWEGER FETUSES, AND AT-RISK PREGNANCIES

Cells	DHAPAT*	^{14}C-hexadecanol incorporation†	
		pPE	pPC
Fibroblasts:			
Controls	9·80±2·10 (n=27)	52·1±7·5	7·9±2·3 (n=6)
Zellweger	0·66±0·50 (n=9)	10·9±1·7	1·5±0·6 (n=6)
Amniocytes:			
Controls	8·52±2·52 (n=6)	43·4±6·4	15·4±6·0 (n=6)
Zellweger fetus A	0·14	11·4	1·6
Zellweger fetus B	0·04	5·6	0·8
At-risk fetuses:			
1	5·20	46·8	21·8
2	7·80	45·7	21·8
3	8·60	61·1	9·5
4	10·86	36·0	9·1
5	8·50	21·4	33·0
6	4·84	43·4	21·1

*Units are nmol per 2 h per mg protein (mean±SD) †As % of phospholipid radioactivity (mean±SD) (pPE = plasmalogen phosphatidylethamolamine, pPC = plasmalogen phosphatidylcholine)

Moser et al[9] and Björkhem et al[10] have demonstrated the feasibility of prenatal detection of Zellweger syndrome by measurement of very-long-chain fatty acids in cultured cells or amniotic fluid. An important advantage of the present procedure is the much smaller number of cells required for analysis; usually amniotic fluid cells have to be cultured for only 1–2 weeks.

DHAPAT acetone phosphate acyltransferase is also expressed in chorionic villi, so detection of Zellweger syndrome in the first trimester of pregnancy may be feasible.

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FIRST-TRIMESTER (CHORION BIOPSY) DIAGNOSIS OF CITRULLINAEMIA AND METHYLMALONICACIDURIA

SIR,—Dr Vimal and colleagues (Sept 1, p 521) reported a false-negative result when monitoring a pregnancy at risk for argininosuccinicaciduria by studying the incorporation of radiolabelled citrulline into intact chorionic villi. This direct assay suggested an unaffected fetus but the same test on cultured chorionic villus cells correctly predicted that the fetus was affected. In pregnancies at risk for citrullinaemia and methylmalonicaciduria we have found prenatal diagnosis at 9 and 10 weeks to be reliable by studies on intact chorionic villi, without the 3 or 4 week delay necessitated by chorionic cell cultivation.

In the 9th week of the pregnancy of a woman with a previous child with citrullinaemia, chorionic villi were obtained in Düsseldorf by ultrasound-directed aspiration, and sent in culture medium to Rotterdam. Controls were obtained at elective pregnancy terminations and stored in cultured medium at room temperature during the period required for transport of the at-risk sample (20 h). After preincubation of the villi during 20 h in arginine-free modified Eagle's medium with 10% dialysed fetal calf serum, the incorporation of ^{14}C-citrulline and ^{3}H-leucine during 24 h was determined.[1] In three chorionic tissue fragments (about 5 mg each) from the pregnancy at risk the incorporation of ^{14}C-citrulline (relative to ^{3}H-leucine) into tricholoracetic acid precipitable protein was deficient (dpm $^{14}C/^{3}H \times 100 = 0 \cdot 3$, $0 \cdot 9$, and 16; three controls showed 128, 187, and 196) which indicated that the fetus was affected. The pregnancy was terminated in the 10th week and the diagnosis was confirmed by the analysis of fibroblasts in culture (ratio $0 \cdot 1$; control 244; fibroblasts of previous affected child $0 \cdot 5$).

A second example of a successful first-trimester diagnosis by direct analysis of intact chorionic villi was in a pregnancy at risk for methylmalonicaciduria. Two 5 mg fragments of villi were incubated during 17 h in Puck's saline with 10% dialysed fetal calf serum and ^{14}C-propionate and ^{3}H-leucine.[2] The incorporation of ^{14}C-propionate into protein was normal (ratio dpm $^{14}C/^{3}H \times 10^{3} = 83$ and 84; controls 48–145, n = 5).

The prediction that the fetus would be unaffected was confirmed by assays of methylmalonyl coenzyme A mutase in a sample of 40 mg, which was sent on dry ice to Manchester and which showed normal activity (176 pmol/min/mg protein; controls 61–388, n = 5). Further confirmation was obtained by the normal concentration of methylmalonic acid in the amniotic fluid at 16 weeks ($0 \cdot 28$ μmol/l, Dr C. Jakobs, University Hospital, Amsterdam), a normal ^{14}C-propionate uptake, and a normal mutase activity of the amniotic fluid cells; fibroblasts of the previous affected child showed less than 5% of normal activity in these tests.

Vimal et al suggested interference of maternal enzyme in early pregnancy as a explanation for their false-negative finding in intact villi. Such interference has not been observed so far in the first-trimester fetal diagnoses of Hunter's disease[3] and Krabbe's disease[4] where enzyme deficiencies were demonstrated in the chorionic villous homogenates. Our results reported here suggest that incorporation of radiolabelled precursors into intact chorionic villi is a reliable means of rapid first-trimester monitoring for a variety of aminoacidopathies and organicacidurias.

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THIRST AND OSMOREGULATION IN THE ELDERLY

SIR,—The interesting article by Phillips et al[1] discussed in your Nov 3 editorial raises the question of why the fit elderly without intercurrent illness do not become dehydrated more often. The answer to this lies presumably in the strong behavioural patterns developed in the elderly so that they drink at regular times each day. However, if the order of the day's events is altered, opportunities for drinking may be subconsciously lost, and without any other cause such a patient can become dehydrated. I have seen a 75-year-old woman who got home in the evening after a 3 h journey by air. She had been fit when she left. Although she had access to fluids and a lavatory throughout the journey, she did not drink. The following day she was admitted dehydrated with an acute confusional state. She responded to rehydration only, and routine tests for other causes of acute confusional state were entirely negative.

The reduction in fluid intake may even be deliberate. Elderly patients on diuretics frequently drink less to avoid urinary frequency, but they continue to take their diuretics and become dehydrated. Behavioural patterns may thus exacerbate the physiological tendency of the elderly described by Phillips et al and lead to dehydration without clinically apparent intercurrent illness.

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