revealed that both low and high doses of chlorpromazine caused a marked and prolonged retention of mescaline, and that this effect was unrelated to the chlorpromazine-induced hypothermic response. Chlorpromazine perhaps interferes with the processes that remove mescaline from the tissues. Thus, chlorpromazine would have an effect on the elimination of mescaline by blockade of efflux processes, by increased binding to subcellular particles, or by diminished neural activity. Phenothiazines are known to influence the membrane transport mechanism.[14] Previous studies on subcellular distribution revealed that from two-thirds to three-fourths of mescaline in the liver and brain remained in the soluble supernatant fraction after i.p. administration of mescaline to mice.[15]

In a clinical situation, the manifestations of mescaline toxicity or psychosis are already present before an antipsychotic agent is administered. In our studies, chlorpromazine (5·0 mg/kg) was injected 45 min after mescaline to observe the effects on the previously administered hallucinogen. Under the experimental condition, chlorpromazine markedly blocked the disappearance of mescaline from the fetal and maternal brain and liver. These findings may have a potential significance in view of the interaction between an antipsychotic agent and a hallucinogen. Recently, disturbing effects of chlorpromazine on adverse LSD and amphetamine reactions have been reported in humans.[16]

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3,4-Benzpyrene and aniline are hydroxylated by human fetal liver but not by placenta at 6–7 weeks of fetal age

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IN RECENT years the ability of the human fetal liver to metabolize drugs and other foreign compounds has been demonstrated by many authors.[1–12] Juchau[11] has shown that the nitro group can reduce *p*-nitrobenzoic acid as early as the seventh week of fetal age. Pelkonen[13] has shown that several oxida-

tive and reductive drug-metabolizing pathways were present in the smallest fetuses studied, which weighing approx. 6–10 g, corresponded to about 8-weeks of fetal age. As embryogenesis, which occurs from 3- to 8-weeks of fetal life, is the most sensitive period as morphological and functional differentiation takes place, considerable interest has been centred on establishing the ability of the human embryo to metabolize foreign compounds at such an early stage. It has been suggested that drug hydroxylations involving the formation of reactive epoxides may play an important role in harmful reactions produced by foreign compounds, e.g. in the production of malformations.[14,15] We therefore decided to study the hydroxylating capacity of human fetal liver and placenta at the earliest stage of pregnancy possible.

The material studied consisted of the conception products of 40 pregnancies terminated by dilatation and curettage. As the fetus macerated during this procedure it was impossible to obtain fetal weight. Estimation of fetal age was therefore based on the last menstruation of the mother. The liver weight also gave some indication of fetal age.

In most cases, when it was impossible to recognize the fetus or its parts from the material recovered, studies were performed on placentas alone. In ten cases we were able to find the whole fetal liver. After preparation the liver was weighed and homogenized in 0·5 ml of 0·1 M potassium phosphate buffer, pH 7·4, in the incubation tube and the incubation was initiated by the preincubated cofactor mixture. All incubations were made in a final volume of 2 ml. Incubation time was 20 min. The composition of the incubation mixture is described in our previous paper.[4] The metabolism of 3,4-benzpyrene was determined according to the method of Kuntzman *et al.*[16] and the metabolism of aniline by the method of Kato and Gillette.[17] Activities were expressed as nano- or picomoles of substrate metabolized per gram of tissue fresh weight per hour.

Results are shown in Table 1. As can be seen, 3,4-benzypyrene was metabolized by all ten livers studied and the activities ranged from 40 to 170 nmole/g/hr. These values are lower than those obtained previously, they ranged from 100 to 380 nmoles/g/hr, the mean about 200 nmole/g/hr, yet are clearly higher than the blank values for the assay. We have shown that after 8 weeks of fetal age, drug metabolism in fetal liver increased and attained almost constant levels at 12–13 weeks of fetal age. During the same period the liver morphology and its function change,[18,19] and with regard to the smooth endoplasmic reticulum, Koga[19] was able to show its presence at 6 weeks of fetal age, but not at 4 weeks. It is believed that drug-metabolizing enzymes are mainly located in smooth endoplasmic reticulum and it is interesting to notice that both smooth endoplasmic reticulum and drug-metabolizing enzymes are present in livers from human fetuses aged 6 to 7 weeks.

TABLE 1. METABOLISM OF 3,4-BENZPYRENE AND ANILINE BY LIVERS FROM HUMAN FETUSES AGED 6 TO 7 WEEKS

Patient	Age (yr)	Cigarettes smoked daily	Medication during pregnancy	Fetal age (days)	Liver weight (mg)	Benzpyrene hydroxylase (pmole/g/hr)	Aniline hydroxylase (nmole/g/hr)
RO	30	*	*	43	6	40	N.D.†
MK	24	5	N.K.‡	43	10	59	N.D.
SL	18	10	Amobarbital	45	10	95	N.D.
EJ	30	*	*	46	15	167	N.D.
SK	23	10	N.K.	49	32	109	N.D.
SH	30	10	*	50	20	100	N.D.
AO	27	*	N.K.	51	44	136	67
LR	24	N.K.	N.K.	52	140	40	72
EL	42	N.K.	N.K.	52	115	126	77
BI	40	8	*	54	23	108	N.D.

* Patient, according to history, did not smoke or use any drugs during the 2 months before abortion.
† N.D. indicates, not determined.
‡ N.K. indicates, not known.

Aniline hydroxylase activity was detected in three livers studied but it was at a lower level than later in the pregnancy. Placentas between 5 and 8 weeks of fetal age did not metabolize 3,4-benzpyrene. Incubation of aniline with placental homogenates indicated trace hydroxylation which was too weak to warrant further study.

Comparison of 3,4-benzypyrene hydroxylase and aniline hydroxylase activities in the early fetal liver with those in livers from older fetuses and adults is shown in Table 2. Activity in livers from small fetuses is very low and it could be suggested that at about 6 weeks of fetal age drug-metabolizing enzymes, in concomitant with the appearance of smooth endoplasmic reticulum, are appearing in the human fetal liver.

TABLE 2. COMPARISON OF 3,4-BENZPYRENE HYDROXYLASE AND ANILINE HYDROXYLASE ACTIVITIES BETWEEN LIVERS FROM HUMAN FETUS AND ADULT

		Benzpyrene hydroxylase (pmole/g/hr)			Aniline hydroxylase (nmole/g/hr)		
Source		Mean	Range	*n*	Mean	Range	*n*
Fetus	Age < 8 weeks	98	40–167	10	72	67–77	3
Fetus*	Age > 8 weeks	194	100–380	40	168	48–342	25
Adult†		8460	1650–15000	18	524	240–1566	9

* Data from Pelkonen *et al.*[4] (3,4-benzypyrene) and from unpublished observations (aniline).

† Data from an unpublished study.

This study clearly demonstrates that human fetal liver obtained at 6- to 7-weeks after conception is capable of hydroxylating 3,4-benzypyrene and aniline, whereas the ability of the placenta to metabolize the same compounds is insignificant. The potential role of this ability in chemical teratogenesis and metabolic activation of foreign compounds needs further evaluation.

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