Aryl Hydrocarbon Hydroxylase Activity and Microsomal Cytochrome Content of Human Fetal Tissues

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ABSTRACT

Aryl hydrocarbon hydroxylase (AHH) and microsomal cytochromes were measured in tissues of human fetuses aborted by prostaglandins. Cytochrome P-450 concentrations and AHH activity were about 4 times higher in adrenal glands than in liver. AHH was present in testes, ovaries, and vagina and uterus at levels equal to or greater than those in the liver. Mean hepatic AHH and hepatic and adrenal cytochromes P-450 and b, were not significantly different in prostaglandin and hysterotomy abortuses; mean adrenal AHH was significantly lower in prostaglandin abortuses, but the ranges in both groups were overlapping. Neither fetal sex nor maternal cigarette smoking affected hepatic or adrenal AHH activity or microsomal cytochrome concentrations or difference spectra. Hepatic and adrenal AHH activities were concentrated in microsomes and were correlated with microsomal P-450 content. These findings are consistent with P-450 mediation of AHH in human fetal tissues. The data demonstrate the utility of prostaglandin abortuses for studies of fetal tissue mixed-function oxidase activity and point to the endocrine glands and target tissues in addition to the liver as potential sites for activating chemical carcinogens and cytotoxins in the human fetus.

INTRODUCTION

The same drug-metabolizing enzymes can catalyze chemical inactivations and activations to carcinogens and cytotoxins. Metabolic activation is a precondition for the action of most chemical carcinogens and many cytotoxins (7, 17). The activity of the body's drug-metabolizing enzyme systems will, therefore, be an important determinant of susceptibility to chemical carcinogenesis and toxicity.

Many highly reactive metabolites are short lived (7, 17) and may be formed in or close to the tissues in which they are harmful. During transplacental chemical carcinogenesis and cytotoxicity, for example, some injurious chemicals and intermediates may be transported to the fetus from the mother, but active metabolites generated in fetal tissues may also participate in cytotoxic injury or tumor initiation.

Drug-metabolizing enzyme activity in the human fetus is less active than in the human adult but much more active than in fetuses of lower mammalian species (21, 27, 33). and there is beginning evidence that the human fetus can carry out carcinogen activations (10, 21). Progress in research on fetal drug metabolism has recently been slowed partly because hysterotomy is now rarely used as a mid-trimester abortion procedure, and hysterotomy abortuses are consequently less available for study.

Suction curettage, i.a.2 0.9% NaCl solution instillation, and prostaglandins, the midtrimester abortion procedures currently used, all result in intrauterine fetal death. This is in contrast to the results of hysterotomy. After prostaglandin abortion, however, the tissues of the abortus are at least grossly intact. Tissues from prostaglandin abortuses have been used successfully for cell culture studies (5) and for studies of hepatic lymphocyte ontogeny (6) and thymidine and amino acid metabolism (9). Studies of mixed-function oxidase activity in prostaglandin abortuses have not yet been reported. In view of the potentially important role of human fetal drug-metabolizing enzyme activity in transplacental chemical carcinogenesis and toxicity, we examined the suitability of prostaglandin abortuses for the study of mixed-function oxidase activity. As an index of mixed-function oxidation, we used AHH activity, which can also serve as an indirect indicator of tissue capacity to activate polycyclic hydrocarbons (4, 34) and microsomal cytochrome content.

MATERIALS AND METHODS

Tissues were obtained from fetuses aborted by (a) i.a. prostaglandin F 20 (40 mg), (b) i.m. prostaglandin 15-methyl-F 20 (250 μg followed by 500 μg every 2 hr until abortion), (c) vaginal suppositories containing prostaglandin E 2 (20 mg every 2 hr until abortion), and (d) intravaginal Silastic devices containing prostaglandin 15(S)-15-methyl-F 20 (11 mg). Data are also included from our previous studies on AHH in 6 fetuses aborted by hysterotomy (27) and from studies on 2 other fetuses aborted by hysterotomy for medical reasons. All abortuses weighed less than 500 g and were less than 22 weeks gestational age as estimated from crown-rump measurements (20).

Maternal drug ingestion and cigarette-smoking histories were obtained. Abortuses were included only from women who had not ingested drugs other than vitamins or aspirin during the 2 weeks prior to abortion. Drugs received during the abortion procedure were 4 tablets of Lomotil (2.5 mg diphenoxylate hydrochloride and 0.025 mg atropine sulfate per tablet) and 10 mg Compazine (prochlorperazine) i.m. just before and 2 tablets of Lomotil 2 hr after the prostaglandins were administered. Drugs given for hysterotomy abort-

1 Supported by Grant BC-98 from the American Cancer Society, Grant 1-427 from the National Foundation, Grant 710 from the New York State Health Research Council, and grants from The New York Community Trust and the Revlon Foundation.

2 The abbreviations used are: i.a., intraamniotic; AHH, aryl hydrocarbon hydroxylase.

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tion were 100 mg secobarbital about 10 hr before and 100 mg sodium thiopental i.v. 0.5 hr before the procedure. Only abortuses with grossly intact tissues were used. Tissues were stored at 4°C until assay (between 0.5 and 19 hr for prostaglandin abortuses and usually within 1 hr for hysterotomy abortuses).

Tissues were homogenized in 3 volumes 0.1 M potassium phosphate buffer, pH 7.4. AHH was measured in triplicate in homogenates and sometimes also in microsomes (18). Incubation time (10 min) and the tissue concentrations used were within the linear range. Routinely, each 1-ml reaction mixture included tissue homogenates or microsomes equivalent in wet weight to 25 mg for liver, lung, kidney, and intestine; 10 mg for adrenal; and up to 25 mg for testes, vagina and uterus, and ovaries. The assay sensitivity was increased 4-fold by making the final extraction in 0.5 ml rather than in 2.0 ml 1 N sodium hydroxide. The recovery of hydroxylated benzo(a)pyrene was complete in the smaller extraction volume. A quinine sulfate standard previously standardized against 3-hydroxybenzo(a)pyrene was used to quantitate the hydroxylated benzo(a)pyrene formed. Activity was deemed measurable when fluorescence after incubation was at least twice the zero time blank. AHH activity is expressed as pmol phenols produced per mg protein per hr unless otherwise indicated.

Microsomes were prepared by centrifuging a 9,000 × g supernatant of the homogenate at 104,000 × g for 60 min. Microsomal pellets were suspended in 0.1 M potassium phosphate buffer, pH 7.4, for AHH determinations or in the same buffer containing 30% glycerol for determinations of cytochrome b₅ (19) and cytochrome P-450 (3, 19) (with a Cary Model 15 spectrophotometer) and of protein (14). Cytochrome P-450 and b₅ concentrations are given in nmol cytochrome per mg microsomal protein.

Statistical analyses included Student's t tests, linear regression analyses, and measurements of correlation coefficients by the use of standard procedures. p values less than 0.05 were required for statistical significance.

NADH, NADPH, and benzo(a)pyrene were purchased from Sigma Chemical Co., St. Louis, Mo. Benzo(a)pyrene was dissolved in benzene and recrystallized with cold methanol before use. The 3-hydroxybenzo(a)pyrene used as a standard in the AHH assay was a kind gift of Dr. Harry Gelboin, NIH. Other reagents were reagent grade or better and were purchased from domestic commercial suppliers.

RESULTS

AHH in Tissues of Abortuses Aborted by Different Prostaglandins. The mean values for AHH in the livers and adrenals of abortuses aborted by the different prostaglandins are shown in Table 1. The group means for hepatic and adrenal AHH activity, respectively, were not significantly different. Therefore, the 4 groups were combined for further analyses. The variation between the highest and lowest individual values was wide (23-fold for the livers and 21-fold for the adrenals).

The mean values ± S.E. for AHH in 8 fetuses aborted by hysterotomy were 42.1 ± 8.1 for the livers and 228.4 ± 33.1 for the adrenals. Mean hepatic AHH values for the hysterotomy and prostaglandin abortuses (see Table 2) did not differ significantly. Adrenal AHH was significantly higher in the hysterotomy abortuses (p < 0.001). However, the ranges of AHH activities in prostaglandin and hysterotomy abortuses overlapped both for the liver and the adrenal.

Effect of Intra- and Extratruterine Storage Time on AHH Activity. The mean times from prostaglandin administration to abortion for the different prostaglandin groups ranged from 11.6 to 12.9 hr; from abortion to dissection, mean times ranged from 6.4 to 8.7 hr, with no significant differences among the group means.

The coefficients (r) for the correlation between AHH activity in tissues from individual abortuses and the time of adminis-

Table 2

Effect of Intra- and Extratruterine Storage Time on AHH Activity

In vitro AHH activities are given for hepatic and extrahepatic organs of human abortuses. Data for tissues of fetuses aborted by different prostaglandins are combined. AHH was assayed in tissue homogenates as described in "Materials and Methods" and is expressed as pmol phenols produced per mg protein per hr.

<table>
<thead>
<tr>
<th>Organ</th>
<th>AHH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>27.4 ± 2.0* (71)</td>
</tr>
<tr>
<td>Adrenal</td>
<td>95.1 ± 9.1* (65)</td>
</tr>
<tr>
<td>Vagina and uterus</td>
<td>35.4 ± 3.6 (4)</td>
</tr>
<tr>
<td>Testis</td>
<td>33.4 ± 9.6 (13)</td>
</tr>
<tr>
<td>Ovary</td>
<td>16.6 ± 4.5* (6)</td>
</tr>
<tr>
<td>Intestine</td>
<td>11.1 ± 3.2* (8)</td>
</tr>
<tr>
<td>Kidney</td>
<td>5.1 ± 0.8* (11)</td>
</tr>
<tr>
<td>Lung</td>
<td>2.7 ± 0.5* (10)</td>
</tr>
</tbody>
</table>

a Mean ± S.E.
br Number of abortuses per group.
c Significantly different from liver (p < 0.05).

Table 1

AHH in livers and adrenals of fetuses aborted by different prostaglandins

AHH was measured in vitro in homogenates of liver and adrenal from fetuses aborted by prostaglandins as described in "Materials and Methods." AHH activity is expressed as pmol phenols produced per mg protein per hr.

<table>
<thead>
<tr>
<th>Prostaglandin</th>
<th>Route of administration</th>
<th>Liver (Mean ± S.E.)</th>
<th>Range</th>
<th>Adrenal (Mean ± S.E.)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGF₁₀</td>
<td>i.a.</td>
<td>22.5 ± 3.6 (17)</td>
<td>8.3-60.0</td>
<td>67.6 ± 19.4 (16)</td>
<td>16.5-305.9</td>
</tr>
<tr>
<td>15-Methyl-PGF₁₀</td>
<td>i.m.</td>
<td>23.7 ± 4.0 (21)</td>
<td>3.9-92.4</td>
<td>118.2 ± 20.8 (19)</td>
<td>19.5-311.5</td>
</tr>
<tr>
<td>E₂</td>
<td>Intravaginal</td>
<td>31.6 ± 3.8 (22)</td>
<td>6.6-78.9</td>
<td>104.1 ± 11.9 (20)</td>
<td>14.5-205.2</td>
</tr>
<tr>
<td>15(S)15-Methyl-E₂</td>
<td>Intravaginal</td>
<td>33.8 ± 4.8 (11)</td>
<td>11.6-57.9</td>
<td>81.0 ± 19.1 (10)</td>
<td>16.6-224.8</td>
</tr>
</tbody>
</table>

a Numbers in parentheses, number of abortuses per group.
b None of the differences between group means for the liver was statistically significant (p > 0.05).
c None of the differences between group means for the adrenal was statistically significant (p > 0.05).
between (a) administration of prostaglandins to abortion, (b) abortion to dissection, or (c) administration of prostaglandins to dissection were not statistically significant (range, 0.00 to 0.10). Therefore it is unlikely that the wide individual variation observed in AHH activity from different abortuses was attributable to differences in the length of intra- or extraterine storage prior to assay.

**AHH in Extrahepatic Tissues.** AHH activity was present in the vagina and uterus, ovaries, testes, intestine, kidney, and lung as well as in the liver and adrenals (Table 2). The mean adrenal specific activity (activity per mg protein) was 3.5 times higher than that in the liver. AHH was higher in the adrenal than in the liver in 60 of the 62 abortuses in which AHH was measured in both tissues.

Although the specific AHH activity of testes, vagina and uterus, and adrenal was similar to or higher than that of the liver, the liver had the greatest total hydroxylation capacity because of its overall size, i.e., total organ AHH of the liver was about 3 times higher than that of the adrenals and about 150 times higher than that of the testes.

**AHH Activity with Respect to Fetal Sex, Maternal Cigarette Smoking, and Fetal Age.** The mean AHH activities ± S.E. for males and females, respectively, were: liver, 23.1 ± 1.8 (n = 32) and 30.2 ± 3.3 (n = 39); adrenal, 105.3 ± 45.4 (n = 29) and 87.2 ± 10.0 (n = 36). The differences in AHH for males and females were not significant. Maternal cigarette smoking also did not affect the AHH activity of fetal tissues significantly. The mean AHH activities ± S.E. for abortuses of smokers and nonsmokers, respectively, were: liver, 25.4 ± 2.7 (n = 36) and 28.5 ± 3.0 (n = 35); adrenal, 94.6 ± 12.4 (n = 34) and 96.1 ± 13.7 (n = 31).

No differences were observed in extrahepatic AHH with respect to fetal sex or maternal cigarette-smoking history.

There were low but statistically significant inverse correlations for AHH activity and fetal age for both the fetal liver and the adrenal; r = -0.46 (p < 0.001) and -0.38 (p < 0.005) for the liver and adrenal, respectively. Age-related changes in AHH were not observed in the other extrahepatic tissues.

**Hepatic and Adrenal Microsomal Cytochromes.** As shown in Charts 1 and 2, peaks in the NADH-reduced difference spectra for liver and adrenal microsomes were at 424 nm, and troughs were at 409 to 410 nm, as is characteristic of cytochrome b₅, in other species (3, 19).

The dithionite difference spectrum of microsomes through which carbon monoxide was first bubbled (3) was used for liver cytochrome P-450 measurements because it largely eliminated the interference of hemoglobin. As shown in Chart 1, the carbon monoxide-binding peaks were at 448 to 449 nm and about 424 nm. Elimination of the cytochrome b₅ difference spectrum shifted the 420 nm region peak from 424 to about 420 nm and produced a small decrease in the height of the 450 nm region peak. Since the 420 nm peak was only partially decreased, molecular species other than b₅ and P-450 (probably methemoglobin and/or cytochrome P-420) were present in the liver microsomes.

Adrenal microsomes (Chart 2) were only minimally contaminated by hemoglobin and had a well-defined carbon monoxide-binding peak at 447 to 448 nm in both the carbon...
monoxide difference spectra of dithionite-reduced microsomes and the dithionite difference spectra of carbon monoxide-treated microsomes. The 424 nm peak was largely eliminated by the addition of NADH to the reference cuvet, which indicates that the 424 nm peak in adrenal microsomes was principally due to cytochrome b₅.

The mean cytochrome P-450 and b₅ concentrations ± S.E. in the liver (n = 24) were 0.14 ± 0.01 and 0.10 ± 0.01, and in the adrenal (n = 16) they were 0.62 ± 0.04 and 0.16 ± 0.01. Thus the mean cytochrome P-450 and b₅ concentration were 4.4 and 1.6 times higher, respectively, in the adrenal than in the liver.

Neither fetal sex nor maternal cigarette smoking affected the cytochrome P-450 concentration of the liver or the adrenal. Cytochrome P-450 content and fetal age were not significantly correlated in the liver but were inversely correlated in the adrenal (r = -0.62; p < 0.02), which echoes the inverse relationship between AHH and fetal age. The location of the spectral peak for P-450 in the liver and adrenal was not affected by fetal age or maternal cigarette-smoking history.

AHH activity in adrenal homogenates and the cytochrome P-450 content of the microsomes prepared from those homogenates were significantly correlated (r = 0.55; p < 0.05). In contrast, liver homogenate AHH activity and microsomal cytochrome P-450 content were not significantly correlated. However, liver microsomal AHH activity and cytochrome P-450 content were significantly correlated (r = 0.84; p < 0.005) in the 9 abortuses in which AHH was measured in both the microsomes and homogenates (Table 3).

Specific AHH activity was higher in microsomes than in homogenates, which indicates that AHH activity was concentrated in the microsomal fraction. However, the recovery of microsomes (AHH activity per g of tissue in microsomes/AHH activity per g of tissue in homogenates) was highly variable, ranging from 18% to 100%. The mean recovery of 43% is higher than the 10 to 15% recoveries reported by Ackermann et al. (1) and is comparable to the 40 to 60% microsomal recoveries in fetal liver reported by Pelkonen (21). Fetal age did not affect microsomal recovery. In contrast to that in the liver, microsomal recovery in the adrenals usually approached 100% as shown in Table 3, and as we also found in adrenals from a group of drug-exposed abortuses (not reported here). The variable recovery of AHH in liver microsomes explains the lack of correlation between liver homogenate AHH and microsomal P-450 and indicates that the microsomal enzymes in the liver are more susceptible to degradation during preparation of the microsomal fraction and are less stable than are the microsomal enzymes of the adrenal.

### DISCUSSION

These studies show that in the human fetus at midgestation: (a) the endocrine glands and tissues responsive to sex hormones, including the testes, ovaries, and vagina and uterus as well as the adrenal (35), can have AHH activities equal to or greater than those in the liver; (b) there is wide individual variation in AHH levels of tissues from different abortuses, comparable to the variation found in livers and lymphocytes of human adults (2, 24); (c) there are no sex differences in AHH activity of liver and adrenal.

### Table 3

<table>
<thead>
<tr>
<th>Organ</th>
<th>Fetal age (wk)</th>
<th>Homogenate</th>
<th>Microsomes</th>
<th>Recovery of AHH in microsomes (%)</th>
<th>P-450</th>
<th>b₅</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>nmol phenols/g/ hr</td>
<td>pmol phenols/mg protein/ hr</td>
<td>nmol phenols/g/ hr</td>
<td>pmol phenols/mg protein/ hr</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>11.5</td>
<td>4.1</td>
<td>34.2</td>
<td>2.6</td>
<td>303.5</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>2.5</td>
<td>25.2</td>
<td>2.5</td>
<td>237.5</td>
<td>100</td>
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<tr>
<td></td>
<td>14</td>
<td>4.0</td>
<td>43.8</td>
<td>0.9</td>
<td>62.1</td>
<td>23</td>
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<tr>
<td></td>
<td>14.6</td>
<td>1.6</td>
<td>11.3</td>
<td>0.5</td>
<td>23.6</td>
<td>31</td>
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<td></td>
<td>15.2</td>
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<td>78.9</td>
<td>1.5</td>
<td>168.2</td>
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<tr>
<td></td>
<td>16.5</td>
<td>2.8</td>
<td>22.9</td>
<td>0.5</td>
<td>36.5</td>
<td>18</td>
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<tr>
<td></td>
<td>16.8</td>
<td>5.8</td>
<td>48.2</td>
<td>1.6</td>
<td>118.2</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>18.7</td>
<td>4.1</td>
<td>29.8</td>
<td>2.9</td>
<td>222.0</td>
<td>71</td>
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<tr>
<td></td>
<td>20</td>
<td>4.7</td>
<td>38.1</td>
<td>0.9</td>
<td>69.8</td>
<td>19</td>
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<tr>
<td>Adrenal</td>
<td>15.2</td>
<td>13.5</td>
<td>205.2</td>
<td>13.8</td>
<td>552.0</td>
<td>102</td>
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<tr>
<td></td>
<td>18.7</td>
<td>19.2</td>
<td>176.5</td>
<td>19.3</td>
<td>960.2</td>
<td>101</td>
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<td></td>
<td>20</td>
<td>5.9</td>
<td>70.0</td>
<td>5.8</td>
<td>315.0</td>
<td>96</td>
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</table>

* Mean ± S.E.
differences in hepatic or extrahepatic AHH or P-450; (d) AHH is correlated with cytochrome P-450 concentrations, which supports the likelihood that aryl hydrocarbon hydroxylation is a cytochrome P-450-mediated reaction in the human fetal liver and adrenal, as it is in adult rat liver (28); and (e) hepatic mixed-function oxidase enzymes of the liver are less stable than are mixed-function oxidase enzymes of the adrenal.

We also show that previous findings in hysterotomy abortuses apply to fetuses aborted by prostaglandins, which indicates that prostaglandin abortuses can be useful for studies of fetal mixed-function oxidase activity. Thus our findings confirm that during midgestation AHH is present in lung, kidney, intestine, adrenal, and liver (11, 27); that both AHH and cytochrome P-450 content are about 4 times higher in the adrenal than in the liver (27, 35); that the carbon monoxide-binding peak for the hemoprotein in adrenal microsomes is at 448 nm rather than at 450 nm (21, 27, 35); and that maternal cigarette smoking does not increase AHH activity in human fetal liver (22). It is further shown that cigarette smoking also does not affect extrahepatic AHH activity or hepatic or adrenal microsomal cytochrome P-450 or b5 content.

The mean cytochrome P-450 and b5 concentrations in the liver and adrenal of the prostaglandin abortuses fall within the ranges previously reported for hysterotomy abortuses (1, 11, 21, 27, 33, 35). The cumulative evidence indicates that the cytochrome P-450 and b5 concentrations of human fetal liver are about one-half of the concentrations of adult livers, whereas the P-450 concentrations are about the same in human fetal and adult adrenal glands.

AHH values from the 2 other laboratories reporting data on AHH in human fetal tissues vary over 2 orders of magnitude (11, 22). Our values fall between the 2. The differences in AHH values between laboratories may be attributable to the use of different standards for phenolic fluorescent products of benzo(a)pyrene. Our laboratory’s values for AHH in human adult liver and rat liver (A. B. Rifkind, unpublished data) are comparable to the values reported by Kuntzman et al. (12). Our data agree with Pelkonen’s (21) that AHH in the fetal liver is about 2% of the activity in the human adult liver.

Although the differences in mean adrenal AHH activity in prostaglandin and hysterotomy abortuses may have been apparent only, because the hysterotomy group was small and the range of activity in the 2 groups was overlapping, other possible explanations include (a) postmortem decline of AHH activity in the prostaglandin abortuses, (b) inhibition of mixed-function oxidase activity by drugs administered during the prostaglandin abortion procedure, or (c) induction of mixed-function oxidase activity by drugs administered prior to the hysterotomy.

With respect to a, although AHH may have been lower than it would have been in the fresh state for some abortuses, the lack of significant correlations between AHH activity and the duration of intra- or extraterine tissue storage, or between AHH activity and the time between the administration of prostaglandins and abortion or between abortion and assay, indicates that there was no regular postmortem decline in AHH activity during the period in which tissues were obtained.

With respect to b, narcotic analgesics, phenothiazines, and prostaglandins can interact with the liver mixed-function oxidase system (13, 30, 31). Species differences in responses to those drugs, however, preclude predicting their effects on the human fetus. For example, phenothiazines increase AHH and other mixed-function oxidase activities in rat liver (31) but depress AHH in chick embryo liver (A. B. Rifkind, unpublished observations). Prostaglandins F20 and E2 produce spectral changes in guinea pig but not in rat liver microsomes (13). Prostaglandin 15-methyl-F20, but not F20, depressed AHH activity in chick embryo liver (A. B. Rifkind, unpublished observations), but AHH activity and microsomal cytochrome content of human fetal tissue were not significantly different after maternal exposure to prostaglandins 15-methyl-F20 and F20. Moreover, if the drugs were to account for the lower adrenal AHH activity, they would have had to inhibit adrenal activity much more than hepatic activity.

With respect to c, it is unlikely that mixed-function oxidase activity was induced by drugs given to the women prior to hysterotomy, first because the drugs were first administered about 10 hr before hysterotomy, and induction of mixed-function oxidase activity appears to require a longer period. Second, although near the end of gestation chemicals administered to the mother can induce AHH and other mixed-function oxidases in fetal tissues (15, 32), it is not yet determined whether mixed-function oxidase activity of human fetal tissues is inducible even in the liver during midgestation. While there is evidence that AHH activity may be inducible by polycyclic hydrocarbons in cultured human fetal liver cells (25), the data reported here and the other available data (22, 23) have not demonstrated induction of fetal tissue drug metabolism during the first half of gestation following maternal exposure to known inducers such as cigarette smoking and barbiturates.

The presence of mixed-function oxidase activity in the fetal liver, endocrine glands, and endocrine target organs suggests that those tissues may be able to activate chemicals to carcinogenic or cytotoxic intermediates. Fetal activation may participate in transplacental carcinogenesis. With respect to the transplacental production of cancer of the reproductive tract by diethylstilbestrol (8), for example, the presence of mixed-function oxidase activity in the human fetal vagina and uterus opens the possibility that diethylstilbestrol could be metabolized to carcinogenic or cytotoxic intermediates at the target organ (the vagina and uterus).

Similarly, recent reports of neuroblastomas occurring in the offspring of women who ingested phenytoin during pregnancy (26, 29) suggest that neuroblastoma, a common cancer of childhood, may have a chemical etiology. Since neuroblastomas are primarily of adrenal origin and phenytoin tends to concentrate in fetal as well as in adult adrenal glands (18), the fetal adrenal might serve as a site for activation of phenytoin. Accordingly, it would be interesting to examine the capacity of the fetal adrenal to activate phenytoin to mutagenic or cytotoxic products. While the above examples point to the potential production of carcinogenic or toxic metabolites at the tissue sites at which
cancer occurs, the wide distribution of AHH in fetal tissues also opens the possibility that some chemicals might be activated in one fetal organ and produce injury in another organ.

REFERENCES

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