was 50 msec, and the intensity of the illumination of the exposure field was adjusted to keep an overall mean average accuracy of about 70 percent. The order of presenting the stimuli was random.

On the average, the target line was reported correctly on 86 percent of the presentations when it was a part of a connected and closed whole. But, when it was presented alone, only 55 percent were reported correctly [$t(3) = 6.85$, $P < .01$]. This result indicates clearly that the connected and closed structure can facilitate the detection of the target line that is a part of it.

Another distinction made in topology is whether in a plane a line is contained in a closed curve or not. If the idea about the topological structure of form vision is right, this kind of topological property should also be able to facilitate the identification of target lines.

In a third experiment, two pairs of stimuli (Fig. 3) were used. The two target lines contained in set A differed both in position and slope. Set B contained both the same target lines and an additional circle in each stimulus, so that one target line was in the circle and the other one outside. Because the additional circle was located in the same position, this context gave no clue about which of the two target lines was presented (*9*).

The procedure was similar to that of experiments 1 and 2, except that the two stimuli of each pair were presented successively on the same trial in random order. The eight subjects were simply required to indicate which target line was first and which second. With set A, mean accuracy was 59.2 percent and with set B, 79.1 percent [$t(7) = 7.17$, $P < .001$].

The data of these three experiments are difficult to interpret in terms of traditional feature detector models or spatial frequency filter models (*10*). But it is direct, natural, and consistent to explain all of them in terms of early detection of global topological properties, defined in terms of the invariant properties under topological transformations. These experimental facts are therefore relevant to Gibson's theory of invariance detection.

From the perspective of the general theory of computation, the nature of topological invariants makes their computation difficult (*11*). How should we treat the contradiction of these experimental results with the computational account of perception? The results are consistent with Gibson's insight that "The perceptual system simply extracts the invariants from the flowing array; it resonates to the invariant structure or is attuned to it" (*12*), although now we do not know how this resonance to topological invariants is generated. This kind of question lies at the core of issues in perception (*13*).

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1. With the aid of the mathematics of tolerance spaces [E. C. Zeeman, *Topology of 3-Manifolds*, K. Fort, Ed. (Prentice-Hall, Englewood Cliffs, N.J., 1962), p. 240], we can describe global properties on a discrete set. Thus, numerous facts of visual perceptual organization, for example, the Gestalt laws of proximity and similarity, may be described mathematically by the global topological (or tolerance) properties (L. Chen, paper presented at the 4th Biophysical Academic Conference of China, Beijing, May 1979; paper presented at the 14th Annual Mathematical Psychology Meeting, Santa Barbara, August 1981). Some of the configural superiority effects (*6*) and global precedence [D. Navon, *Cognit. Psychol.* **9**, 353 (1977)] can also be considered as evidence that visual systems are superior at perceiving topological properties before perceiving more detailed geometrical properties of stimuli.
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8. The target line was about 3 minutes of visual angle wide and 53 minutes long at the viewing distance of 90 cm. The line segments consisted of the context, 6 minutes wide and 2°40 minutes long at the same viewing distance.
9. The target lies were about 3 minutes wide and 53 minutes long at the viewing distance of 90 cm. The width of the curved line of the circle was 5 minutes and its diameter 56 minutes at the same view distance.
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Maternal Ethanol Exposure Induces Transient Impairment of Umbilical Circulation and Fetal Hypoxia in Monkeys

Abstract. *When ethanol was administered intravenously to pregnant monkeys, a transient but marked collapse of umbilical vasculature was observed uniformly within about 15 minutes. The ethanol-induced impairment of umbilical circulation produced severe hypoxia and acidosis in the fetus; recovery occurred during the succeeding hour. This striking interruption of feto-placental circulation may explain one of the mechanisms of mental retardation, a frequent manifestation in children afflicted with fetal alcohol syndrome.*

Alcohol abuse throughout the world is on the rise (*1*). Among women of reproductive age, ethanol consumption is increasingly prevalent. Epidemiological studies have shown that ethanol consumption during pregnancy causes increased perinatal mortality and morbidity (*2*). One out of 750 infants born in the United States manifests some characteristics of fetal alcohol syndrome (FAS), resulting from maternal consumption of ethanol during pregnancy (*3*). Psychomotor retardation in FAS children has been demonstrated—their average IQ was 67 with a dispersion of 50 to 83 (*4*). Specifically, FAS is composed of four major anomalies: (i) craniofacial dysmorphism, (ii) intrauterine and postnatal growth retardation, (iii) retardation of psychomotor development, and (iv) nonspecific malformations (*5, 6*).

While conducting laboratory studies (with monkeys as the test animals) on the kinetics of ethanol transfer across the placenta to the fetus, we observed that 10 to 15 minutes after ethanol was administered to the mother the vasculature of the umbilical cord collapsed. Subsequent recovery of umbilical function from this flacid state occurred during the next hour. The present study was designed to investigate the concurrent metabolic consequences to the fetus of this observed ethanol-induced transient impairment of umbilical circulation.

Rhesus (*Macaca mulatta*) and cynomolgus (*Macaca fascicularis*) monkeys at 120 to 147 days of gestation (term is 167 days) were used in all experiments. These primates had no exposure to ethanol or other exogenous agents prior to these experiments. Maternal body

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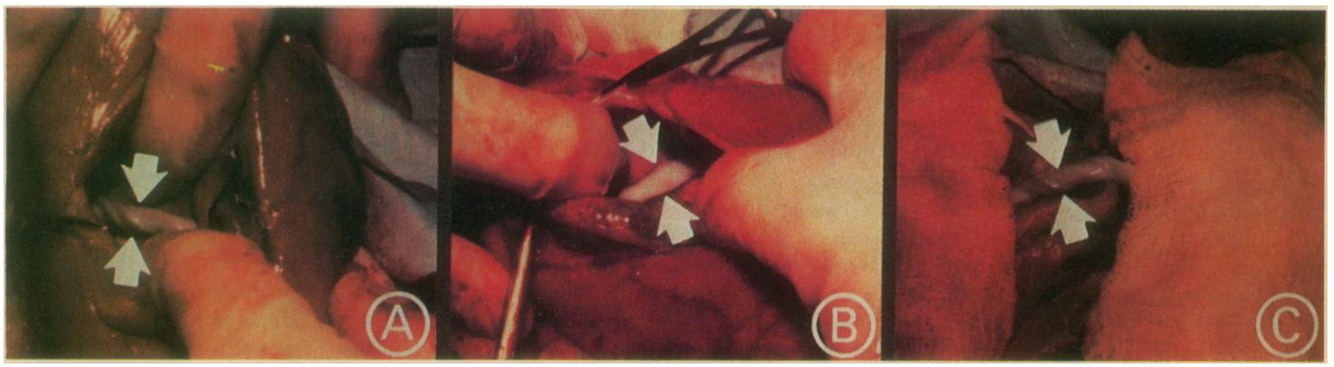

Fig. 1. Transient collapse of umbilical circulation after the intravenous administration of ethanol to the mother. (A) Umbilical cord as visualized prior to injection of ethanol (arrows). (B) Pale, flacid cord (arrows) 15 minutes after injection of ethanol. (C) Recovery of umbilical cord, 1 hour after ethanol injection. Note the return of turgidity and color (arrows).

weight varied from 4.5 to 9 kg. All surgeries were performed with ketamine as the anesthesia (100 mg for rhesus and 80 mg for cynomolgus) (Parke, Davis & Company, Detroit).

The ethanol solution was prepared in sterile 5 percent dextrose in normal saline and administered as a bolus (1 to 2 minutes) into the femoral vein of the mother (35 percent ethanol; 3.0 g per kilogram of body weight). Five primates received ethanol treatments, two control monkeys were injected with dextrose-saline only, and two others were used as absolute controls without any injections. After injection of ethanol or vehicle only, heparinized blood samples were obtained from the uterine artery of the mother and the umbilical vein of the fetus at 15-minute intervals from time zero to 90 minutes. Blood ethanol and acetaldehyde levels were determined by gas chromatography, according to the method of Murad *et al.* (*7*). Arterial blood gases (oxygen and carbon dioxide) were measured by standard procedures, using an automatic Corning-175 blood gas machine. Statistical analysis utilized Student's *t*-test for grouped or paired data to delineate whether the observed deviant points in *p*H, PO_2 and PCO_2 are significantly different from the control values.

Although there were slight individual variations in response time, the predominant pattern was an ethanol-induced collapse of umbilical circulation with rapid onset. In the five experiments, collapse of all three umbilical vessels began within 10 to 15 minutes after administration of ethanol to the mother (Fig. 1B), and maximal effects were found at about 20 minutes after ethanol treatment. Gradual recovery of umbilical vessels was noticeable after approximately 30 minutes (Fig. 1C). Confirmation of these visual assessments is derived from blood gas values of arterial blood taken before, during, and after the ethanol injection. In contrast, not one control monkey manifested loss of umbilical turgidity during the 90-minute interval of study.

The metabolic concomitants of these visual cues were reflected in the maternal and fetal arterial blood gas values (mean ± standard deviation of the mean) throughout the experiment (Fig. 2). There were no significant changes in blood gas values among mothers injected with ethanol or in those of either control group. The fetuses in control experiments maintained an uneventful blood gas profile throughout the study. In contrast, markedly adverse effects were observed in fetal blood gas parameters soon after the mothers received the intravenous bolus of ethanol (Fig. 2C). Concurrent with the prompt collapse of the umbilical vessels, the *p*H of fetal blood declined from 7.30 ± 0.08 at 15 minutes to 6.81 ± 0.05 at 30 minutes; gradual recovery from acidosis persisted through 60 minutes. Similarly, PO_2 dropped from 38 ± 2 at time zero to 11 ± 2 at 30 minutes; changes in PCO_2 were not as dramatic, although some values were elevated from 40 ± 3 at time zero to 58 ± 5 at 30 minutes. Concentra-

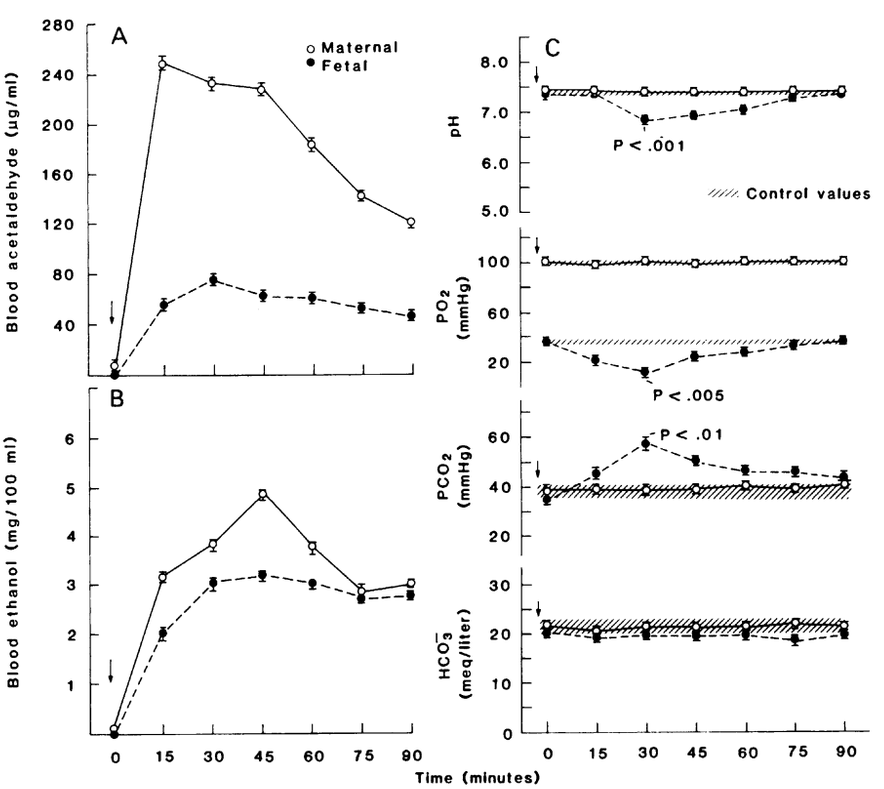

Fig. 2. Ethanol (A) and acetaldehyde (B) in maternal (○) and fetal (●) blood. Results are means ± standard deviation of the mean (N = 5). (C) Maternal and fetal blood gas values. Results are means ± standard deviation of the mean (N = 5) and of the control groups (N = 4). The shaded areas represent normal control values.

tions of ethanol in blood from mothers reached a peak near 250 ± 8.2 mg/100 ml at 15 minutes and declined steadily thereafter. There was only a slight delay in achieving maximum transfer of ethanol from the maternal to the feto-placental compartment (Fig. 2A). The highest concentrations of ethanol in feto-placental circulation were only one-third of those in maternal blood at 30 minutes after administration of ethanol. The rates of disappearance of ethanol from blood were clearly different in mother and fetus, reflecting either different rates of metabolism or continued distribution of ethanol pools after recovery of the umbilical circulation. An ethanol equilibrium in circulation between mother and fetus was not obtained during the 90 minutes of the study. Conversely, concentrations of circulating acetaldehyde peaked at 45 minutes in both mother and fetus (5 and 3 μg/ml, respectively). That this equilibration persisted after 75 minutes (Fig. 2B) raises the question of whether the fetus itself is able to metabolize ethanol or acetaldehyde and whether detoxification is dependent on the restoration of umbilical circulation. Note that the state of fetal hypoxia developed in concert with rising concentrations of blood ethanol in the conceptus. Furthermore, gradual restoration of umbilical circulation was observable between 30 and 60 minutes after ethanol administration (Fig. 1) and was temporally consistent with normalization of feto-placental blood gas values (Fig. 2C).

Even one brief exposure (24 hours) of fetal mice to ethanol can produce striking morphological aberrations in the developing brain (*8*). That brain cells are extremely susceptible to low oxygen tensions, with significant brain damage occurring despite a short duration of severe hypoxia, is well established (*9*). The vulnerability of neuronal cells to fetal hypoxia is not fully understood. Here, our results show that severe, transient, acute hypoxia of the fetus can be provoked by administration of ethanol into the maternal circulation. We wonder about the consequences of repetitious ethanol insults on fetal brain development, whereby transient hypoxia within the fetus may take a cumulative toll on fetal brain development and maturation. We suspect that similar fetal hypoxia may develop within human fetuses after moderate or heavy alcohol consumption. The sequelae of repeated exposure to intermittent ethanol toxicity throughout pregnancy may include brain damage in utero, manifest as mental retardation among FAS babies.

Horiguchi *et al.* (*10*) reported adverse effects of ethanol infusion in pregnant monkeys during labor, including progressive acidosis, hypotension, respiratory depression, and hypercapnia. Although we did not infuse ethanol during labor, we observed similar effects upon the fetus. In contrast, Dilts (*11*) did not observe such changes in acid-base balance in either the fetus or the pregnant ewe after ethanol infusion. This discrepancy may be due to different responses when ethanol is infused over a prolonged interval versus a bolus injection; species differences and gestational ages may be important variables as well.

In proposing the ethanol-induced transient impairment of umbilical circulation and resultant fetal hypoxia may lead to irreversible brain damage, we acknowledge that a single brief insult may or may not have discernible consequences. However, our findings demonstrate that the fetal brain of these primate surrogates remains vulnerable to ethanol-induced hypoxia in the third trimester, after organogenesis has been completed. Recently, it has been suggested that exposure of the human fetus to ethanol may cause behavioral teratogenesis (*12*) even though structural malformations are not apparent.

The present investigation has several limitations that must be acknowledged: (i) Whether intravenously administered and orally administered ethanol produce equivalent adverse effects on the feto-placental circulation must be determined; (ii) data relating ethanol dosage (consumption) in the mother to the degree of fetal hypoxia is needed; (iii) the pharmacologic mechanism of ethanol-induced collapse of umbilical circulation requires scrutiny; and (iv) an assessment of changing feto-placental capacity to compensate for such ethanol insults, as a function of gestational age or an acquired tolerance due to repeated exposure, must be evaluated.

Although fetal organogenesis advances beyond overt susceptibility to the teratogenic effects of ethanol, even in late gestation the unborn child remains at risk to acute ethanol-induced hypoxia. This hazard is prompted by severe, transient impairment of umbilical circulation, as demonstrated here in monkeys. Indeed, repetitive ethanol insults may compromise fetal brain development by cumulative impairment of developing neuronal tissues. Based on these experimental results obtained in laboratory primates, we offer a prudent recommendation that pregnant women consider total abstinence from ethanol throughout pregnancy.

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