production and to correlate amount and pattern of smoking with the concentration of nicotine in milk throughout the lactating cycle.

Experimental Studies

Studies in Animals

Nicotine

Influence on the Lactation Process. Blake and Sawyer (*17*) studied the influence of subcutaneously injected nicotine (4 mg total over a 5-minute period) upon lactation in the rat. They found that nicotine inhibited the suckling-induced rise in prolactin. No effect of injected nicotine was demonstrated for oxytocin secretion since milk release was not blocked. In essence, these findings suggest that nicotine can cause a malfunction in milk production but not in its release mechanism. This phenomenon was examined by Terkel, et al. (*184*) in terms of pups' survival. Most of those pups born to females given a high dose of nicotine throughout pregnancy and lactation died of starvation before weaning. Their mothers' mammary glands contained very little milk, and plasma prolactin levels were very low. The mechanism by which nicotine may affect prolactin release is not yet clarified.

Hatcher and Crosby (*68*) found that injection of 4.0 mg/kg nicotine into nursing cats suppressed lactation for several hours. This was also observed in a cow.

Wilson (*202*) examined the effects of nicotine supplied through drinking water (0.5, 1.0, and 2.0 mg daily) on the weight gain of nursing rats. Apparently, the nicotine had been available throughout gestation as well, because the author commented on a reduction in litter size among the experimental groups, more or less proportionate to the dose of nicotine; hence, a prenatal effect could not have been distinguished from a postnatal one. Average birth weight was similar for experimental and control groups. No difference in weight gain was seen for any of the groups. The lack of impact on birth weight suggests that the dose was lower than that used in other studies. Indeed, Becker and Martin (*13*) observed a significant decrease in weight in the offspring of rats receiving 3.0 mg/kg twice daily during gestation. If the treatment continued throughout the nursing period, the young had a poorer survival chance than when exposed only *in utero* or when subjected daily to hypoxic stress in a special environmental chamber.

Presence of Nicotine in the Milk and its Effect Upon the Nursing Offspring. Hatcher and Crosby (*68*), using a frog bioassay, reported traces of nicotine in cow's milk 24 hours after the intramuscular injection of 5.0 mg/kg. They also reported that 0.5 mg/kg nicotine injected into nursing cats had no apparent harmful effect upon the kittens. Kittens fed the milk from the cow that had been injected with 5.0 mg/kg nicotine were apparently unaffected.

Nitrosamines. Mohr and Althoff (*121*) found that diethylnitrosamine and dibutylnitrosamine, when administered to lactating hamsters, were associated with the development of typical tracheal papillary tumors in the young, suggesting passage of those compounds in the milk. Although diethylnitrosamine and dibutylnitrosamine have not been identified in cigarette smoke, many N-nitrosamines are potent carcinogens, and some of them are present in cigarette smoke (*82, 160*).

Studies in Humans

Nicotine and Tobacco Smoke

Influence on the Lactation Process. Emanuel (*45*) noted no reduction in milk production among 10 wet nurses who were encouraged to smoke 7 to 15 cigarettes daily; some were observed to inhale the smoke. Hatcher and Crosby (*68*) noted that after a mother smoked seven cigarettes within 2 hours, it was difficult to obtain a specimen of breast milk. Perlman, et al. (*149*) found that, of 55 women smokers with an adequate milk supply at the beginning of his study, 11 (20 percent) had an inadequate supply at the time of discharge from the hospital. No relationship was reported between the number of cigarettes smoked and the likelihood of developing an inadequate milk supply. The authors' impression was that there was no greater proportion with an inadequate milk supply among smokers than among nonsmokers, but no corroborating data were supplied. Thompson (*186*) relates the fact that a young primipara who consumed 14 cigarettes secreted only 35 cc of milk obtained at two pumpings. He states that although the evidence is minimal, he has yet to observe a patient averaging eight or more cigarettes daily whose lactation was adequate at 3 months postpartum.

Presence of Nicotine in the Milk. Using a frog bioassay, Hatcher and Crosby (*68*) found that the milk of a woman collected after she had smoked seven cigarettes in 2 hours contained approximately 0.6 mg/liter nicotine. Emanuel (*45*), using a leech bioassay, studied excretion of nicotine in the milk of wet nurses who were encouraged to smoke for the experiment. After the subjects had smoked 6 to 15 cigarettes over a 1- to 2-hour period, the author found nicotine in their milk 4 to 5 hours after smoking, with a maximum concentration of 0.03 mg/liter. Bisdom (*16*) demonstrated nicotine in the milk of a mother who smoked 20 cigarettes a day. Thompson (*186*) found approximately 0.1 mg/liter of nicotine in the milk of a mother who smoked nine cigarettes a day and attempted three "pipesful." Perlman, et al. (*149*), using a Daphnia bioassay, demonstrated nicotine in the milk of all women in their study who smoked. Moreover, they found a direct dose-relationship between concentrations of nicotine and the number of cigarettes smoked. No comment was made by the authors on the possible inaccuracy introduced by examining only the residual milk

following nursing, but it is well known that the composition of the fore milk and the hind milk is different, and perhaps the concentration of nicotine also differs.

These ingenious bioassay methods have now been replaced by modern technology. Ferguson, et al. (*50*) measured by gas chromatography nicotine in a total of 34 samples of human milk from 15 donors. No nicotine peaks were found in the chromotograms of the six donors who were nonsmokers. The average nicotine content for the other samples was 91 parts per billion (ppb), ranging from 20 to 512 ppb. Because the sampling was done randomly, the authors could not correlate the amount of smoking with the concentration of nicotine in milk. A well-planned pharmacokinetic study is needed to determine the rate of nicotine secretion and modifying factors.

Evidence for a Clinical Effect Upon the Offspring. Emanuel (*45*) noted that, among the infants in his study, loose stools were observed only in the one infant whose wet nurse had smoked 20 cigarettes in the previous 4 hours. Bisdom (*16*) observed a case of "nicotine poisoning" in a 6-week-old infant whose mother smoked 20 cigarettes a day. The symptoms included restlessness, vomiting, diarrhea, and tachycardia. Nicotine was demonstrated in the milk, and the symptoms abated when smoking was stopped. Greiner (*64*) also described a case of possible nicotine poisoning in a 3-week-old nursling whose mother smoked 35 to 40 cigarettes a day. The symptoms gradually abated over a 3-day period. Perlman, et al. (*149*) noted no effect of smoking on the weight gain of the infants of the smokers in their study. Furthermore, no untoward symptoms were observed. They therefore doubted an effect of smoking on lactation. They noted that the dose received by the infants was beneath the toxic level as computed from adult experience, and this was in accord with their clinical observations. The fact that they studied only women with an apparently adequate milk supply may have affected their results. The authors suggested that perhaps the lack of effect of smoking upon lactation might represent the development of tolerance to nicotine, as both the mother and the offspring had been exposed throughout the pregnancy. Ferguson, et al. (*50*) noted that all infants observed in their study were asymptomatic, with normal feeding habits and behavior. While all authors refer to the presence or absence of immediate toxic effects, no evaluation of subtle effects has been done. Such effects may develop as a consequence of the infant's double exposure, through milk ingestion and inhalation from a "smoking" environment.

DDT. Bradt and Herrenkohl (*18*) measured DDT content in human milk samples from 10 donors and found that the results were correlated with the number of cigarettes smoked per day. This suggests either that cigarette smoke may be a source of the human body burden of DDT or that it may cause more DDT to be excreted in

the milk. The study was preliminary, however, and further data are needed to evaluate the implications for the health of infants.

Vitamin C. Venulet and Danysz (*195, 196*) demonstrated in a series of studies that the level of vitamin C was reduced in the milk of smoking mothers as compared with nonsmokers. The clinical significance of this observation has not been evaluated.

Physiologic-Experimental Studies

Studies in Animals

Tobacco Smoke

Several investigators have demonstrated that exposure of pregnant rats or rabbits to tobacco smoke leads to a reduction of birth weight in the offspring, as compared to controls (*47, 168, 211*). Apparently Essenberg, et al. (*46*) were the first to study the effects of cigarette smoke on pregnant animals. These authors reported that in female rats exposed to smoke from cigarettes the incidence of sterility, reabsorption of the young *in utero,* abortions, and newborn deaths prior to weaning increased significantly as compared to controls. Wagner, et al. (*197*) reported that, in albino mice exposed to tobacco smoke, maternal weight gain during pregnancy was significantly less than in control animals. Shoeneck (*168*) exposed rabbits to tobacco smoke for several generations. The original doe weighed 3.5 kg. A female of the first generation weighed 2.8 kg, that from the second generation weighed only 1.5 kg, and all attempts to breed the doe were either totally unsuccessful or resulted in stillbirths or neonatal deaths.

Of course, factors other than carbon monoxide in tobacco smoke may also cause fetal growth retardation. Younoszai, et al. (*211*) reported data from studies in rats which indicated that some agent present in cigarette smoke other than nicotine was responsible for the reduction in birth weight observed. These workers exposed rats to several types of smoke, including the smoke of tobacco leaf, smoke from lettuce leaves plus nicotine, and smoke from lettuce leaves alone. The body weight of rat fetuses exposed to lettuce leaf smoke decreased 9 percent, body weight of the fetuses exposed to lettuce leaf smoke plus nicotine decreased about 12 percent, and body weight of fetuses exposed to tobacco smoke decreased about 17 percent. The reported carboxyhemoglobin concentrations varied from 2 to 8 percent in all animals, but the data were not given. Although the authors suggested that carbon monoxide might not be responsible for the retardation of fetal growth, the evidence presented was inadequate to support a firm conclusion.

In an attempt to determine whether the decrease in fetal weights of smoking mothers results from smoking per se or from decreased food intake, Haworth and Ford (*69*) compared fetal body and organ weights

in pregnant rats exposed to tobacco smoke for 6 to 8 minutes, five times a day, from days 3 to 20 of gestation. These rats were compared with another group whose food intake was restricted to the amount actually consumed by the tobacco-exposed rats, and both were compared to a well-fed control group. The animals in both experiments were killed on the 21st day of gestation, and weights of the entire body, the liver, and the kidney of each fetus were recorded. The total average fetal weight of the group exposed to tobacco smoke was significantly lower than that of both the food-restricted and control groups. The fetal weights of the latter two groups were quite similar. Protein and DNA analyses were performed separately on the entire forebrains and hindbrains of the fetuses and on the entire carcass. Both DNA and protein were significantly and proportionately reduced in the carcass and hindbrains of the animals exposed to tobacco smoke. This implies that cell number was reduced and cell size was normal, suggesting that the exposure to tobacco smoke either inhibited cellular proliferation or accelerated cellular destruction.

Another study of smoking in animals that is quoted for its relatively negative results is that of Kirschbaum, et al. (*85*). These researchers attempted to simulate maternal smoking in 12 near-term pregnant sheep by having the ewe inspire cigarette smoke periodically so that 8 to 9 cigarettes were consumed in one hour. The authors reported only minor changes in maternal and fetal blood pressures, heart rates, and blood gases. However, on the basis of the blood carbon monoxide contents (and assuming a normal blood hemoglobin concentration), one can calculate that the maternal blood carboxyhemoglobin concentration during smoking equaled only 0.6 percent, a concentration not significantly greater than that obtained under normal control conditions in most reports (*99*). Thus, one must conclude that in fact the carboxyhemoglobin concentrations did not approach those levels seen even in one-pack-a-day smokers.

In one of the few studies on simulated marijuana smoking in animals, Singer, et al. (*173*) reported that in guinea pigs exposed to marijuana smoke the maternal heart rate increased during the "smoking" period, and the maternal electroencephalogram changed to a pattern of low-frequency and high-amplitude activity. The fetal electroencephalogram changed to a low-frequency, high-voltage activity pattern during the smoking period; after cessation of maternal smoking, it changed to a lower-voltage and higher-frequency activity.

Nicotine

Following the studies of Essenberg, et al. (*46*), several workers have demonstrated that chronic injections of large doses of nicotine into pregnant rats result in a reduction of birth weight of the offspring (*11-13, 46, 84, 122*). For example, Becker, et al. (*12*) demonstrated that the fetuses of mothers who received nicotine not only weighed less for

their age, but had a shorter crown-rump length, a smaller transverse head diameter, less ossification of forelimb bones, shorter vibrassae, and shorter claw length in relation to fetal age. Nishimura and Nakai (*136*) reported numerous malformations, particularly of the skeletal system of fetal mice (strain S) whose mothers received injections of nicotine. These developmental anomalies included delayed osteogenesis and malformation of major joints, polydactyly, syndactyly, spinal curvature, etc. The critical period for producing these abnormalities was longer than for many other drugs tested, extending from the 6th through the 14th day of gestation. In a subsequent study, Geller (*57*) showed that doses of nicotine, about 15 percent of that used by Nishimura and Nakai, resulted in no fetal abnormalities. Landauer (*91*) also noted multiple congenital abnormalities in white leghorn chicks in which the eggs were injected with varying concentrations of nicotine sulfate at several stages of incubation. The predominant lesion noted was shortening and twisting of the neck, secondary to abnormal development of the cervical spine.

Several groups have shown that nicotine administration to pregnant rats resulted in prolonged gestation (*11, 13, 75, 79*). For instance, in Sprague-Dawley rats receiving daily injections of 3 mg of nicotine per kg of body weight throughout the 21 days of gestation, the onset of labor was delayed 1 day in 40 percent, delayed 2 days in another 40 percent, and the remainder delivered on the third day (*13*). Maternal weight gain in nicotine-treated rats is also significantly less (*12, 78, 79*). Damage to the placental capillaries of nicotine-treated dogs was reported by Fischer (*52*).

That nicotine definitely crosses the placenta into the fetus has been demonstrated by a number of workers (*66, 187*). Nicotine and its metabolic product, cotinine, are also found in amniotic fluid (*194*). The question of the rate at which nicotine and its metabolites cross the placenta is of some interest. Tjalve, et al. (*187*) showed that, following maternal injection of C^{14}-labeled nicotine, radioactivity appeared rather quickly in the placenta and fetal tissues, reaching a peak in both in about 30 minutes. In studies of rhesus monkeys with catheters in maternal and fetal blood vessels and amniotic fluid, Suzuki, et al. (*182*) measured nicotine levels following a single injection of 0.5 to 1.0 mg ^{3}H-nicotine into the maternal circulation. The decrease in maternal nicotine concentration was a double exponential process. Initially there was a rapid decrease as nicotine became distributed in various maternal body compartments. Then there was a slow decrease due to the metabolism of nicotine and its crossing the placenta. Fetal nicotine concentration increased rapidly; then a plateau developed, followed by a slow decrease as nicotine was metabolized and re-entered the maternal circulation. It was noted that the fetal adrenal glands, heart, and kidneys tended to accumulate the nicotine.

While the fetal liver metabolizes nicotine (presumably in the microsomal fraction), it is less efficient than maternal liver (*187*). Stalhandske, et al. (*179*) quantitated this relation by measuring the formation of labeled cotinine after incubation of C^{14}-labeled nicotine with liver slices from fetal and newborn mice. These workers showed an almost linear increase in the rate of metabolism of nicotine from about 1 day prior to birth, which is normally 19 days in the strain of mice used, until a week following birth.

The effects of nicotine on the fetal circulation may vary somewhat. Nicotine is similar to acetylcholine in its action on both sympathetic and parasympathetic ganglia, on skeletal muscles, as well as on the central nervous system. It acts at all three sites, first stimulating, then depressing them. Minute doses of nicotine stimulate the chemoreceptors of the carotid and aortic bodies, causing reflex hypertension, cardiac acceleration, and increased respiratory rate. Nicotine also releases epinephrine from the adrenal medulla, thereby producing cardiovascular changes. Thus, nicotine can produce widely differing effects, depending on the dosage and the particular site that is most sensitive to stimulation or depression.

Suzuki, et al. (*181*) studied the effects of nicotine injection on heart rate and arterial blood pressure in rhesus monkeys. Following infusion of nicotine into the mother for 20 minutes (at a rate of 100 mg/kg for a total maternal dose of 2 mg/kg), maternal arterial pressure rose and heart rate fell by about 15 percent. Changes in blood pressure and heart rate of the fetus were less marked and more variable than those of the mother. There was relatively slight hypotension and an irregular delayed tachycardia. Mature fetuses (greater than 120 days gestation) also developed significant acidosis, hypercarbia, and hypoxia. On the other hand, Kirschbaum, et al. (*85*) showed no significant changes in fetal blood pressure or umbilical blood flow following injection of 3 mg/kg nicotine tartrate into a pregnant sheep. However, these negative findings may have resulted from the ewes being anesthetized with the fetuses exteriorized, an experimental condition resulting in altered cardiovascular responses. Suzuki, et al. (*181*) also administered nicotine directly to the fetus *in utero*. The fetal blood pressure immediately rose and heart rate decreased, both values returning to control values within 10 minutes. The fetal responses showed a significant age dependency. The changes were more marked in the older fetuses in contrast to the younger fetuses, despite a larger dose for the latter. These differences in response of the fetuses as a function of gestational age imply differences in the development of the autonomic nervous system, with the more mature fetuses being more sensitive than less mature ones.

In a preliminary study, Resnik, et al. (*158*) report that injection of 1 to 1.5 mg/min of nicotine reduced uterine blood flow 40 percent in pregnant sheep. This decreased flow was associated with a twofold

increase in blood epinephrine and norepinephrine concentrations, compared with preinjection values. The authors concluded that the uterine vascular response to nicotine was mediated by the release of catecholamines within the maternal circulation.

Several investigators have studied nicotine effects on the fetal and newborn central nervous system. Hudson, et al. (*77*) injected 3 mg of nicotine per kg body weight twice daily in rats during the course of a 21-day pregnancy and attempted to assess nicotine effects on the developing brain from behavioral responses. They compared seizure activity between the offspring of nicotine-treated and untreated animals. Such electrophysiological data have been shown to provide useful information on brain maturation patterns. Although convulsive seizures represent a fundamentally pathologic phenomenon, when used experimentally they offer a measure of interaction occurring between inhibitory and excitatory systems of the central nervous system that manifests as overt motor activity. The researchers utilized the electroshock seizure threshold as a specific index of subcortical brain maturation, showing it to be markedly effected in nicotine-treated animals. In control newborn rats, the electroshock seizure threshold decreased slowly from day 10 to day 18 and remained at this level until day 24, the last day of testing. On the other hand, in the offspring from nicotine-treated mothers, the electroshock seizure threshold increased from days 10 to 14, then dropped below control values on day 16 and continued to decrease until day 24. The differences in electroshock seizure thresholds indicate that nicotine induced a transitory effect on the development of seizure activity, most likely involving subcortical inhibitory and excitatory pathways.

Hudson, et al. (*77*) also utilized maximal electroshock seizure patterns as a specific index of the whole brain maturation and cortical development. They showed that on day 26, the duration of flexion was shorter and the duration of extension longer in offspring of nicotine-treated rats than in their corresponding controls. These responses returned to control levels within 33 days. The responses indicate increased brain excitability, which at this age may indicate immaturity or other disturbances of central nervous system maturation. Thus, nicotine administration during gestation prolonged the normal maturational timetable for excitatory and inhibitory systems, either by delaying the development of excitation or accelerating the development of inhibition. Although these specific electroconvulsive responses normalize with increasing age, even transient abnormalities occurring during critical maturational periods may have functional repercussions because of the complexity of events taking place during central nervous system development. Indeed, these authors point out that continuing studies on the effects of endogenous and exogenous factors on central nervous system development reveal that alterations at critical periods of prenatal and postnatal brain maturation, though not

always immediately observable, are frequently manifest in the onset of specific functions or when a specialized demand is placed on the organism.

Nicotine administration during gestation also may affect newborn psychomotor function. Martin and Becker (*106*) noted that young rats so treated performed less well than control animals on fixed-ratio, variable discrimination, and discrimination reversal.

Carbon Monoxide

Classically, it has been held that carbon monoxide exposure resulting in significant biologic effects on the human organism is produced mainly by poisoning with relatively high concentrations of blood carboxyhemoglobin. During the past decade, it has been appreciated that even relatively low carboxyhemoglobin concentrations, for example, 4 to 5 percent, can result in demonstrable disturbances of mental, visual, and other functions (*26*). Longo (*93*) recently has reviewed numerous aspects of carbon monoxide exposure in the pregnant mother, the fetus, and the newborn infant. Those studies derived from animal experiments may be considered from the standpoint of the rate of buildup or elimination of carbon monoxide from the pregnant mother and fetus, fetal to maternal carboxyhemoglobin concentrations under steady-state conditions, and the effects of carbon monoxide on the fetus *in utero*. For obvious ethical and technical reasons, studies of maternal and fetal carbon monoxide exchange are impossible in human beings, and much of our knowledge of these relations are based on animal studies.

Blood carboxyhemoglobin concentration [HbCO] usually is expressed as percent saturation:

$$\left[\text{HbCO}\right] = \frac{\text{blood CO content}}{\text{blood CO capacity}} \times 100$$

The terms "percent saturation" and "carboxyhemoglobin concentration" are used interchangeably. Both imply the percentage of hemoglobin combined with carbon monoxide. Douglas, et al. (*39*) first showed that the amount of blood carboxyhemoglobin concentration in relation to oxyhemoglobin concentration resulted not only from the ratio of the partial pressure of carbon monoxide, P_{CO}, to the partial pressure of oxygen, P_{O_2}, but in addition, from the relative affinity of hemoglobin for carbon monoxide as compared with oxygen, a factor expressed by the symbol M.

$$\frac{[\text{HbCO}]}{[\text{HbO}_2]} = \frac{P_{CO} \times M}{P_{O_2}}$$

Tc determine the rate at which blood carboxyhemoglobin concentrations in the mother and the fetus change in response to exposure to a given concentration of carbon monoxide in the air, Longo and Hill (*97*) exposed pregnant sheep with catheters chronically implanted in maternal and fetal blood vessels to inspired CO concentrations of 30 to 300 ppm. Figure 9 summarizes the results for changes in maternal and fetal carboxyhemoglobin concentrations. It also compares the experimental results with predictions made using a mathematical model. At all levels of carbon monoxide exposure, the maternal carboxyhemoglobin concentration increased relatively rapidly during the first 2 to 3 hours. It then continued to increase more slowly over the next few hours, reaching a relatively constant level in 7 to 8 hours. The change in maternal carboxyhemoglobin concentration resembled a simple exponential process with a half-time of 2.5 hours.

The increase in fetal carboxyhemoglobin concentrations lagged behind maternal concentrations (*97*). During the first hour of exposure, fetal carboxyhemoglobin concentrations showed little change. During the following 4 to 5 hours they increased, but at a relatively slow rate as compared with the rate of the early carboxyhemoglobin rise in the mother. By 5 to 6 hours, fetal carboxyhemoglobin equaled maternal concentrations, after which the values continued to increase slowly for 24 hours or more. Only after 36 to 48 hours did the fetal blood attain final steady-state carboxyhemoglobin concentrations. The time for fetal carboxyhemoglobin concentration to reach half its final value was about 7 hours. At equilibrium, fetal carboxyhemoglobin concentration exceeded the maternal concentration by about 58 percent. Hill, et al. (*73*) then used a mathematical model to calculate the theoretical relations of fetal-to-maternal carboxyhemoglobin concentrations in humans. Although slightly different in some details, the predicted uptake and elimination curves in pregnant women after exposure to several inspired carbon monoxide concentrations were strikingly similar to the experimental results in animals.

The mechanism by which carbon monoxide crosses the placenta from maternal to fetal blood clearly is by diffusion. Longo, et al. (*99*) showed in sheep and dogs that the half-time for carbon monoxide to diffuse across the placenta is about 2 hours. These workers (*98*) also demonstrated that the resistance to diffusion in the placenta is due equally to the placental membranes per se and to the relative resistance afforded by the chemical combination of carbon monoxide with hemoglobin.

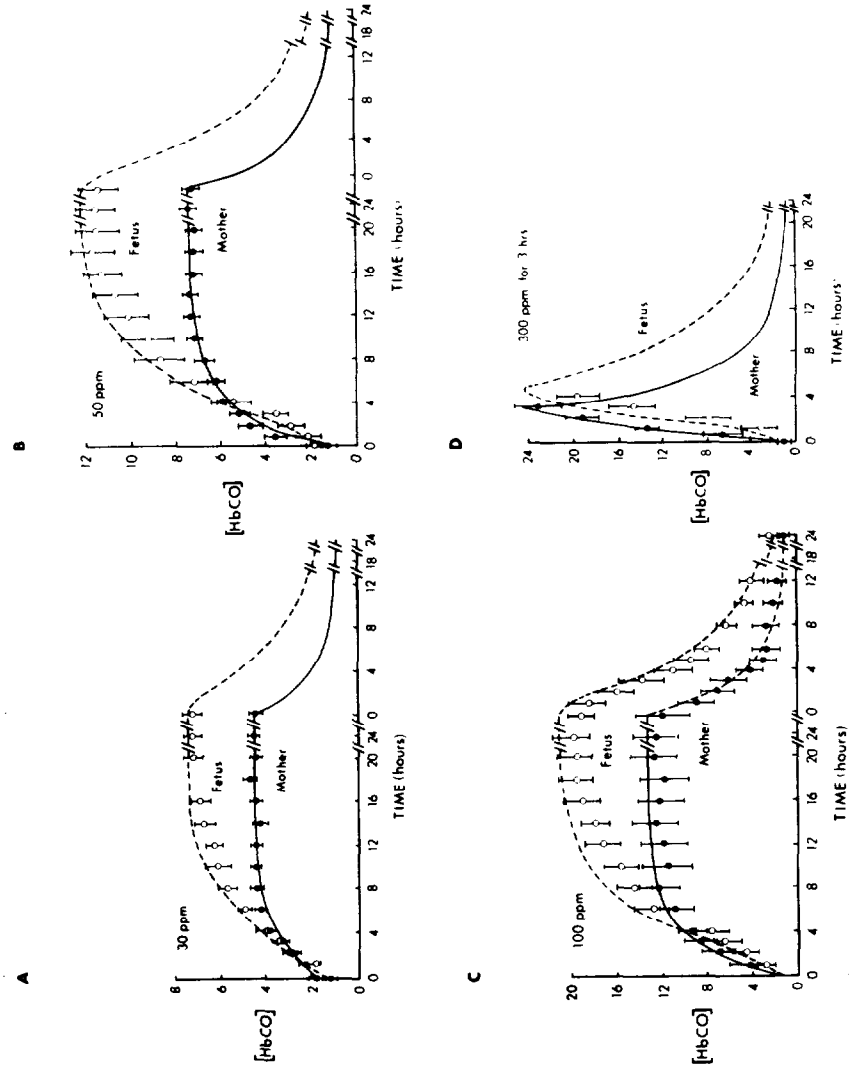

FIGURE 9.—Time course of carbon monoxide uptake in maternal and fetal sheep exposed to varying carbon monoxide concentrations. The experimental results for the ewe (●) and fetal lamb (○) are the mean values (± SEM) of 9 to 11 studies at each inspired carbon monoxide level, except in the case of 300 ppm, at which only three studies were performed. The theoretical predictions of the changes in maternal and fetal carboxyhemoglobin levels for the ewe and lamb are shown by the solid and interrupted lines, respectively

SOURCE: Longo, L.D. (97).

Effects on Fetal Growth and Development

Only a few studies have reported the effects of carbon monoxide on fetal growth and development. Wells (*200*) exposed pregnant rats to 1.5 percent (15,000 ppm) CO for 5 to 8 minutes 10 times on alternate days during the 21-day pregnancy. This resulted in maternal unconsciousness and abortion or absorption of most fetuses. The surviving newborns failed to grow normally. Similar exposure to 5,900 ppm affected only a small percentage of animals. This brief report lacks quantitative data on the number of experimental animals and number and weight of the fetuses. Williams and Smith (*201*) exposed rats to 0.34 percent (3,400 ppm) carbon monoxide for 1 hour daily for 3 months. Peak carboxyhemoglobin concentrations in these animals varied from 60 to 70 percent. Among seven female animals, only one-half the control number of known pregnancies occurred. The number of young per litter was reduced and only 2 out of 13 newborns survived to weaning age. No pregnancies resulted in five females exposed for 150 days.

Astrup, et al. (*5*) reported quantitative data on fetal weights following exposure of pregnant rabbits to carbon monoxide continuously for 30 days. Exposure to 90 ppm resulted in maternal carboxyhemoglobin concentrations of 9 to 10 percent. Birth weights decreased 11 percent from 57.7 to 51.0 g, and neonatal mortality increased to 10.0 percent from a control value of 4.5 percent. Mortality of the young rabbits during the following 21 days increased to 25 percent from a control value of 13 percent. Following exposure to 180 ppm CO, with resulting maternal carboxyhemoglobin concentrations of 16 to 18 percent, birth weights decreased 20 percent from 53.7 to 44.7 g, and neonatal mortality was 35 percent compared with 1 percent for the controls. Three of seventeen newborns in this group had limb deformities. Mortality during the following 21 days was 27 percent, the same value as for the controls.

Fechter and Annau (*48*) exposed pregnant Long-Evans rats to 150 ppm CO throughout gestation. The newborns of the CO exposed rats weighed slightly less at birth than controls (5.55 [$\pm$0.05 SEM]g versus 5.74 [$\pm$0.06]g). During the newborn period this difference increased. By day 21, the weights were about 42 ($\pm$ 1) and 46 ($\pm$ 1)g, respectively. Behavioral tests disclosed less spontaneous and L-dopa-stimulated activity as compared with controls. Garvey and Longo (*56*) exposed pregnant Long-Evans rats to 30 or 90 ppm CO throughout gestation. Although fetal total body weight was unaffected by these concentrations, the brain weights increased 14 percent and lung weight decreased 24 percent in those fetuses exposed to 90 ppm CO. This brain enlargement was attributed to an increased water content as the concentrations of brain protein, DNA, norepinephrine, and serotonin were decreased, as was the brain wet-dry weight ratio. Schwetz, et al. (*170*) reported that mice and rabbit fetuses exposed to 250 ppm CO

from days 6 to 15 of pregnancy (mice) and days 6 to 18 of pregnancy (rabbits) developed minor skeletal alterations.

Carbon Monoxide Effects on Tissue Oxygenation

Several mechanisms probably account for the effects of carbon monoxide on developing tissue. Undoubtedly the most important of these is the interference with tissue oxygenation (*10, 53*). Claude Bernard in 1857 first observed that carbon monoxide decreases the capacity of blood to transport oxygen by competing with it for hemoglobin. Carbon monoxide binding to hemoglobin increases the oxygen affinity of the remaining hemoglobin (Figures 10 and 11). This shift of the oxyhemoglobin saturation curve to the left means that the oxygen tension of blood must decrease to lower than normal values before a given amount of oxygen will release from hemoglobin. This effect may be particularly significant for the fetus because the oxygen partial pressure in its arterial blood is normally relatively low, about 20 to 30 torr as compared to adult values of about 100 torr. Carbon monoxide also interferes with oxygen transport by displacing oxygen from the hemoglobin in arterial blood, thus decreasing the blood oxygen transport capacity. To the pregnant woman these effects on blood oxygenation pose a special threat. Not only is her oxygen consumption increased 15 to 25 percent during pregnancy (*150*), but her blood oxygen capacity is decreased 20 to 30 percent or more because of the decreased concentration of hemoglobin. The woman with a significant anemia faces an even more severe compromise of her oxygen delivery.

Aerobic metabolic processes depend upon the maintenance of tissue oxygen partial pressure above some critical level, which varies among different tissues. Intracellular gas tensions are difficult, if not impossible, to measure directly. However, changes in capillary P_{O_2} values reflect tissue oxygen tensions, other things being equal. In the absence of arteriovenous shunts, the P_{O_2} of venous blood draining a tissue equals the P_{O_2} at the venous end of its capillaries. Thus, venous P_{O_2} roughly indicates the adequacy of tissue oxygenation.

Longo (*94*) and Longo and Hill (*97*) have examined the changes in maternal and fetal oxygen tension in response to various carboxyhemoglobin concentrations in sheep with catheters chronically implanted in maternal and fetal vessels. Figure 12 shows the decreasing oxygen partial pressures in the fetal descending aorta and inferior vena cava below the ductus venosus as the concentration of carboxyhemoglobin increases (*97*). In contrast to the adult, whose arterial oxygen tension remains relatively unaffected by changes in carboxyhemoglobin concentrations, the fetus has arterial oxygen tensions which are particularly sensitive to increases in maternal or fetal carboxyhemoglobin concentrations. In the illustration, the oxygen partial pressure

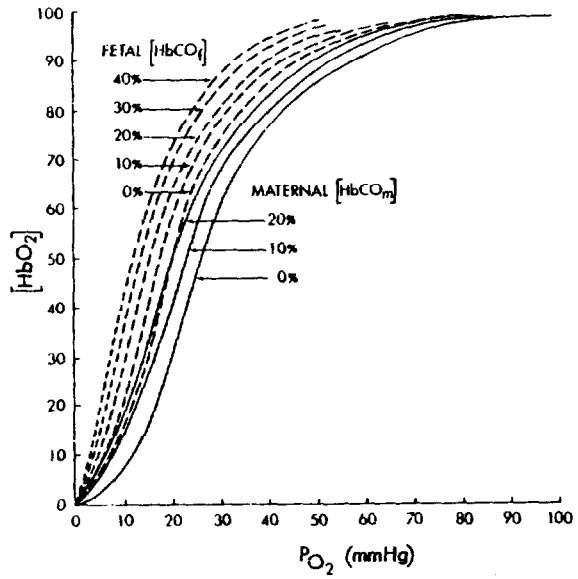

FIGURE 10.—Human maternal and fetal oxyhemoglobin saturation curves showing carbon monoxide effect. The effect of varying concentrations of carboxyhemoglobin [HbCO] is calculated by the method of Roughton and Darling (1944). The oxyhemoglobin saturation [HbO_2] is that percentage of hemoglobin not bound as carboxyhemoglobin

SOURCE: Longo, L.D. (*93*).

in the fetal descending aorta decreased from a control value of about 20.0 torr to 15.5 torr at 10 percent fetal carboxyhemoglobin concentration. (The regression equation for this relation was $P_{O2}=20.1-0.4$ [$HbCO_f$], ($R=-0.094$).) This figure also shows the relation of oxygen tension of the inferior vena cava below the ductus venosus to carboxyhemoglobin concentration in the fetus. At 10 percent carboxyhemoglobin concentration, inferior vena cava oxygen tension decreased from a control value of about 16.0 to 12.5 torr. (The regression equation for this relation was $P_{O2}=-0.3$ [$HbCO_f$], ($R=-.096$).)

As noted above, the fetus, which normally has a relatively low oxygen tension in relation to that of the adult, is particularly vulnerable to these decrements in blood oxygen tension with increased carboxyhemoglobin concentration. In the above-mentioned study (*97*), 57 percent of the fetuses died when fetal carboxyhemoglobin values increased above 15 percent for 30 minutes or longer (5 of 11 died at 100 ppm, and 3 of 3 died at 300 ppm). These deaths presumably resulted from hypoxia of vital tissues. Probably two major reasons account for

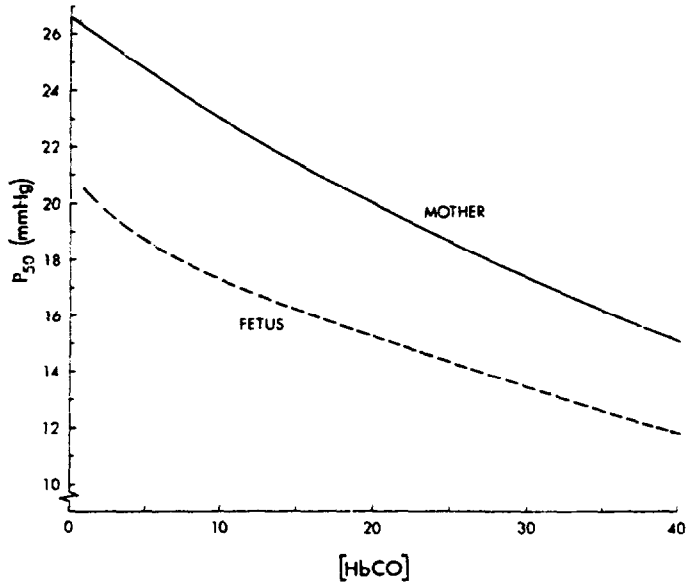

FIGURE 11.—The partial pressure at which the oxyhemoglobin saturation is 50 percent, P50, for human maternal and fetal blood as a function of blood carboxyhemoglobin concentration
SOURCE: Longo, L.D. (*93*).

this. First, in the adult, elevation of carboxyhemoglobin concentration to 15 to 20 percent results in a 6 to 10 torr decrease in venous P_{O2} values. Although this decrease is substantial, the resultant oxygen partial pressures probably remain well above critical values for maintaining tissue oxygen delivery (*178*). In contrast, the fetus with normal arterial and venous P_{O2} values probably close to the critical levels would develop tissue hypoxia or anoxia with substantial decreases in oxygen tension. Furthermore, adult subjects and animals subjected to carbon monoxide hypoxia show increases in cardiac output (*6*) and presumably coronary and tissue blood flow. Apparently such compensatory adjustments are not available to the fetus to any great extent. The decreases in blood oxygen tension measured experimentally followed those predicted, assuming no increase in tissue blood flow. In addition, the fetus probably cannot increase its cardiac output significantly, as the output normally is about two to three times that of the adult on a per weight basis (*154*). Thus, the fetus probably normally operates near the peak of its cardiac function curve.

In an attempt to determine to what extent the fetus *in utero* responds to carbon monoxide hypoxia as compared with hypoxia induced by the mother breathing air or gas with a low oxygen content,

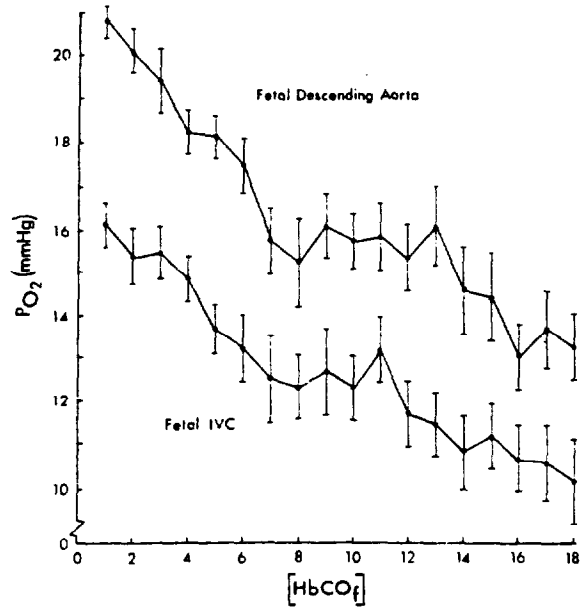

FIGURE 12.—Fetal values of oxygen partial pressure as a function of carboxyhemoglobin concentrations during quasi-steady-state conditions. Fetal inferior vena caval oxygen tension is a function of both maternal and fetal carboxyhemoglobin concentrations. The oxygen partial pressure of fetal arterial blood is chiefly a function of maternal carboxyhemoglobin concentrations. During steady-state conditions, however, it will also be related to the fetal carboxyhemoglobin concentration level. Each point represents the mean ±SEM (vertical bars) of 6 to 20 determinations at each level of blood carboxyhemoglobin

SOURCE: Longo, L.D. (97).

Longo, et al. (*100*) measured the cardiac output and distribution of blood flows to various organs of the fetus. These investigators used chronically-catheterized fetal lambs in near-term pregnant sheep and measured blood flow using radioactive-labeled microspheres. They found that the fetal response to carbon monoxide induced hypoxia was indistinguishable from its response to so-called hypoxic hypoxia. Under both sets of conditions, the output of the fetal heart showed no significant increase during hypoxia, a compensatory adjustment that occurs in adults in an attempt to maintain adequate tissue oxygenation. On the other hand, the fetus demonstrated a redistribution of its peripheral circulation such that blood flow increased somewhat to the brain, heart, and adrenal glands. Presumably this increased flow

occurred in an effort to maintain oxygenation of these "survival" organs.

Ginsberg and Myers (*59*, *60*) studied the effects of CO exposure on near-term pregnant monkeys and their fetuses. When they exposed acutely-anesthetized animals to 0.1 to 0.3 percent carbon monoxide, resulting maternal carboxyhemoglobin concentrations were about 60 percent. During the 1- to 3-hour studies, fetal blood O_2 content decreased to less than 2 ml/100 ml blood, from control values of 9 to 15 ml/100 ml blood. Fetal heart rates decreased in proportion to the blood oxygen values. These fetuses also developed severe acidosis (pH less than 7.05), hypercarbia (P_{CO2}=70 torr or greater), hypotension, and electrocardiographic changes, such as T-wave flattening and inversion (*60*).

Effects on Newborn Animals

The effect of CO on newborn survival has been studied by several groups. Smith, et al. (*174*) exposed rats to mixtures of illuminating gas in air with carbon monoxide concentrations equaling 0.43 percent. For 22 newborn rats, 12 to 48 hours old, exposed to carbon monoxide, the average survival time was about 195 minutes, in contrast to an average survival time of about 36 minutes in mature animals. McGrath and Jaeger (*111*) noted that 50 percent of newly hatched chicks could withstand exposure to 1 percent (10,000 ppm) carbon monoxide for about 32 minutes. This initial resistance to carbon monoxide decreased rapidly. By day 1, mean survival time decreased to about 10 minutes, by day 4 it was 6 minutes, and by day 8 it was 4 minutes, where it remained for all ages tested up to 21 days. Subsequently Jaeger and McGrath (*80*) showed that decreasing the body temperature increased the time to last gasp from a mean value of 9.8 ± 0.5 min at 40°C to 20.7 ± 0.1 at 30°C. They noted that hypothermia caused markedly reduced heart and respiratory rates and suggested that its major benefit was a reduction in energy-requiring functions.

In an attempt to develop an animal model for hyperkinesis, Culver and Norton (*32*) and Norton, et al. (*139*) exposed 5-day-old Sprague-Dawley rats to 1 percent (10,000 ppm) CO until breathing ceased for 20 seconds. This required about 2 hours. Hyperactivity was present when the rats were tested at 4 to 8 weeks of age, but not when they were tested at 3 to 5 months of age. Incidentally, a similar type of hyperactive behavior developed following X-irradiation and bilateral stereotaxic lesions of the globus pallidus (*139*).

Polycyclic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) such as benzo(*a*)pyrene (B*a*P) are constituents of cigarette smoke which have been implicated in the generation of cancers in many animal species (*200*). No studies

presently available relate benzo(*a*)pyrene to a reduction in birth weight of exposed offspring. Evidence suggests, however, that BaP does reach and cross the placenta. Aryl hydrocarbon hydroxylase (AHH) is a part of the cytochrome P-450-containing microsomal enzyme system present in many tissues of different species. This enzyme system is induced to hydroxylate polycyclic aromatic hydrocarbons after exposure of cells to PAH. Several investigators have utilized the inducibility of the enzyme system to demonstrate indirectly that benzo(*a*)pyrene and other polycyclic hydrocarbons reach the placenta and fetus.

Welch, et al. (*199*) extended this work by administering the polycyclic hydrocarbon, 3-methylcholanthrene (3-MC) to rats during late gestation. The metabolism of benzo(*a*)pyrene was studied *in vivo*, using tritium-labeled benzo(*a*)pyrene, and *in vitro*. AHH activity was increased in fetal livers to adult levels by pretreatment with 3-MC. Since a relatively high dose of polycyclic hydrocarbon was required to stimulate enzyme activity in the fetus, compared to the dose which stimulated placental enzyme activity, the authors suggested that the placenta may protect the fetus from exposure to polycyclic hydrocarbons. However, immaturity of the fetal enzyme system might also account for its apparent relative insensitivity to polycyclic hydrocarbons. Therefore, an exposure of the fetus to levels of polycyclic hydrocarbon similar to those experienced by the mother cannot be ruled out by the available data. Nebert, et al. (*133*) and Pelkonen, et al. (*148*) also correlated the activity of this enzyme, which was readily induced in placental tissue with maternal smoking.

Schlede and Merker (*167*) have studied the effect of benzo(*a*)pyrene administration on aryl hydrocarbon hydroxylase activity in the maternal liver, placenta, and fetus of the rat during the latter half of gestation. The pregnant animals were treated with large oral doses of benzo(*a*)pyrene 34 hours prior to sacrifice. Control rats had no detectable levels of aryl hydrocarbon hydroxylase in their placentas. Treatment with benzo(*a*)pyrene resulted in barely detectable placental levels at gestation day 13, but steadily rising values until day 15, and then constant levels thereafter. No activity was detected in the fetuses of untreated controls. In the treated animals, the fetal enzyme activity rose steadily from the 13th to the 18th day of gestation. The authors concluded that the stimulatory effect of benzo(*a*)pyrene treatment on aryl hydrocarbon hydroxylase activity in the fetus demonstrates that benzo(*a*)pyrene readily crosses the rat placenta. The placenta is involved in complex hormonal interrelations between mother and fetus, and oxidative enzyme pathways in the placenta are important in maintaining hormonal balance for normal fetal development. The hydroxylation of polycyclic hydrocarbons and the active transport of various compounds by trophoblast cells may share common enzyme

systems. Thus, the induction of various enzymes by maternal smoking may interfere with the transport systems.

The effect of maternal administration of benzo(*a*)pyrene as a carcinogenic risk for progeny was examined by Nikonova (*135*). Pregnant mice (strains A and C 57 BL) were injected with a single dose of either 4 or 6 mg benzo(*a*)pyrene on the 18th or 19th day of gestation. In both strains, the offspring, when examined 1 year later, showed a markedly higher incidence of neoplasms of the lungs, liver, and mammary glands.

Studies in Humans

Tobacco Smoke

Sontag and Wallace (*175*) first reported an increase in fetal heart rate during maternal smoking. These authors concluded that the response was secondary to the passage of nicotine across the placenta, although this was not demonstrated. Hellman, et al. (*70*) studied several factors affecting the fetal heart rate. These workers asked habitual smokers not to smoke for 24 hours, then to smoke one to two cigarettes. Typically, a gradually increasing maternal tachycardia developed within 3 minutes of the onset of smoking. Fetal tachycardia with a flattening of the normal beat-to-beat variation occurred in about 3.5 minutes. In contrast, a similar response to maternal atropine injection did not occur for about 12 minutes. The authors reported short bursts of fetal tachycardia during the time that the mother was being given the cigarette, but before the lighting of the cigarette. They called this an "anticipatory response" and concluded that it probably resulted from some vasomotor change in the uterine placental vessels. Cloeren, et al. (*25*) reported that in 22 pregnant women studied during the last half of pregnancy fetal tachycardia usually followed maternal smoking, and in two-thirds of the cases the fetal heart rate showed a loss of beat-to-beat variability.

Recent reports indicate that "breathing" movements by the fetus are a normal component of intrauterine development. Both the proportion of time the fetus makes breathing movements and the character of these movements appear to reflect fetal condition. In women with normal pregnancies, cigarette smoking abruptly and significantly decreased the proportion of time that the fetus made breathing movements to 50 percent from a control value of 65 percent (*58, 105*). These acute changes may not result from nicotine or carbon monoxide, however, since marked decreases in breathing failed to occur in the fetuses of women who smoked non-nicotine cigarettes (*104*).

These changes in fetal heart rate and breathing movements can result directly from effects on the fetus per se, or indirectly from effects on the placental circulation, or both. Haberman (see Longo (*96*)) used thermography to assess utero-placental blood flow. In this

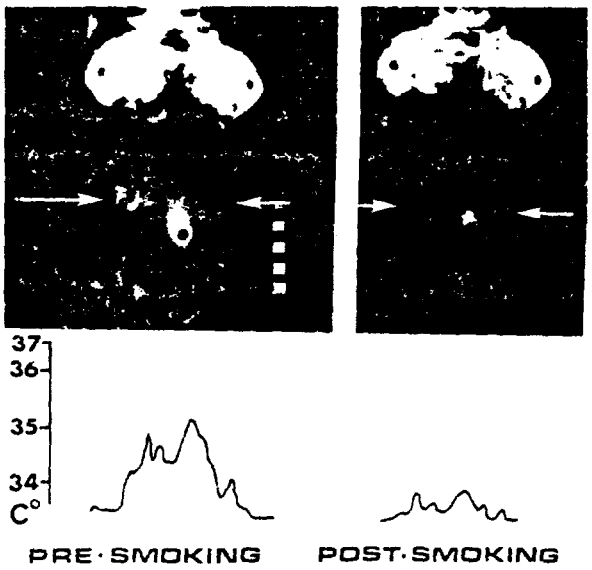

FIGURE 13.—Thermogram from a near-term pregnant patient before and after smoking. The normal thermal imprint of the placenta is shown on the left as a white area between the arrows. The right panel shows decreased heat emission after the mother smoked a single cigarette for 8 minutes. Below are the temperature profiles across the abdomen at the level of the arrows. The small squares in the left panel are the temperature calibrations (Courtesy of Dr. JoAnn D. Haberman)

SOURCE: Longo, L.D. (*96*).

technique, infrared sensors record the heat distribution from a given area of the body. Figure 13 shows a thermogram from a near-term pregnant patient before and after smoking and inhaling from a single cigarette for 8 minutes. The thermal imprint of the placenta (white area between arrows) in the panel on the left markedly decreased following smoking (panel on right). While there is a question as to whether this technique measures blood flow or blood volume in a given area, it is evident that maternal smoking results in changes in heat emission from the pregnant uterus. Cloeren, et al. (*25*) have reported that the utero-placental blood pool, as measured with radioactive Indium, increased during maternal smoking; however, these investigators failed to present any quantitative data.

An additional consideration is the effect of maternal smoking on placental metabolism. Tanaka (*183*) used a Warburg apparatus to measure oxygen consumption of placental slices from nonsmoking and smoking mothers. The oxygen consumption of placental tissue from

normal nonsmoking mothers equaled 1.9 microliters (μl) per mg of placenta per hour. The rate of oxygen consumption from the placentae of smoking mothers decreased in proportion to the carboxyhemoglobin concentration in maternal blood. For instance, it decreased about 30 percent to 1.3 μl/mg/hr at 8 percent maternal carboxyhemoglobin concentration. By energy-dependent processes, placental cells play an important role in metabolizing hormones and other compounds and in actively transporting amino acids, vitamins, and other substances. The components of tobacco smoke may adversely affect fetal development by interfering with these metabolic and transport functions.

Asmussen and Kjeldsen (*4*) used the human umbilical artery as a model to evaluate vascular damage caused by tobacco smoking. In comparison with the vessels from babies of nonsmoking mothers, the umbilical arteries from 13 smoking mothers showed marked changes of the vascular intima. Scanning electronmicroscopy disclosed swollen and irregular endothelial cells with a peculiar cobblestone appearance and cytoplasmic protrusions or blebs on their surface. Transmission electronmicroscopy showed degenerative changes, including endothelial swelling, dilation of the rough endoplasmic reticulum, lysosomes abnormal in appearance, and extensive subendothelial edema. In addition, the basement membrane was markedly thickened, a change probably indicating reparative change. Finally, the vessels showed focal opening of intercellular junctions and loss of collagen fibers. This study underscores the probable vulnerability of the fetus to the effects of smoking by the mother. Subsequently, Asmussen (*3*) noted that in comparison with the placentae of nonsmoking mothers, the placentae of four mothers who smoked disclosed changes similar to those seen in the umbilical arteries; namely, broadening of the basement membrane of the placental villi, increased collagen content of the villi, decreased vascularization, and intimal changes of the villous capillaries and arterioles with pronounced intimal edema. Loehr, et al. (*92*) reported similar changes in placental morphology. In addition, Spira, et al. (*177*) observed that the placentae of smoking mothers show a higher frequency of abnormal trophoblast cells and clumping of the nuclei of the syncytiotrophoblast.

Heron (*71*) reported a delayed onset of crying immediately after birth in the infants of smoking mothers. Several infants showed definite evidence of asphyxia with irregular respiration and cyanosis. Younoszai, et al. (*210*) found, in addition to elevated carboxyhemoglobin levels among the infants of smoking mothers, significant elevation of mean capillary hematocrits and significant reduction of standard bicarbonate levels, as compared to the infants of nonsmoking mothers. As no evidence for nicotine effects upon blood glucose, serum-free fatty acid levels, urinary catecholamines, or hypoxia was present, they concluded that the higher hematocrit levels in the infants of smoking mothers may have represented a compensatory response to the

decreased oxygen-carrying capacity of the blood due to the presence of carboxyhemoglobin.

As noted elsewhere in this chapter, mothers who smoke have a higher incidence of complications such as abruptio placenta with resulting stillbirth, placenta previa, and other causes of bleeding during pregnancy (*2, 63, 89, 101, 102, 115, 116, 189*). The incidence of premature rupture of the fetal membranes also increases (*116, 189*), while the incidence of the hypertensive disorders of pregnancy decreases (*2, 20, 89, 165, 189*). Unfortunately, the physiologic basis for these disorders is not known. It can be postulated that abruptio placenta may follow spasm of uterine vessels such as the spiral arterioles secondary to nicotine and other compounds. It is of interest that abruptio placentae and other disorders occur more frequently in women whose pregnancies are complicated by the hypertensive disorders of pregnancy. On the other hand, the decreased incidence of hypertensive disorders among pregnant women who smoke may result from the vasodilating action of the thiocyanate present in tobacco smoke.

Carbon Monoxide

Although there are few studies of carbon monoxide effects on human pregnancy, those reports of maternal and fetal blood carboxyhemoglobin concentrations during maternal smoking will be considered in this section.

The blood carboxyhemoglobin concentration of normal nonsmoking pregnant women, [$HbCO_m$], normally is 0.5 to 1.0 percent while that in the fetus is about 10 to 20 percent higher, that is, 0.6 to 1.2 percent. Figure 14 depicts the steady-state fetal and maternal carboxyhemoglobin concentrations as a function of the carbon monoxide concentration. Several studies have reported carboxyhemoglobin concentrations in the blood of smoking mothers and their newborns (Table 14). Reported fetal carboxyhemoglobin concentrations range from 2 to 10 percent and maternal concentrations range from 2 to 14 percent. These blood samples, obtained at the time of vaginal delivery or Cesarean section, probably fail to reflect accurately the normal values of carboxyhemoglobin. For instance, the number of cigarettes smoked during labor might have been less than the number normally consumed; blood samples were collected at varying time intervals following the cessation of smoking, and many samples were probably taken in the morning before the carboxyhemoglobin concentrations had built up to the values reached after prolonged periods of smoking. Therefore, the average values for normal smoking mothers and their fetuses could be well above the concentrations reported in maternal and fetal blood.

Using a mathematical model, Hill, et al. (*73*) calculated the theoretical relations of fetal and maternal carboxyhemoglobin concen-

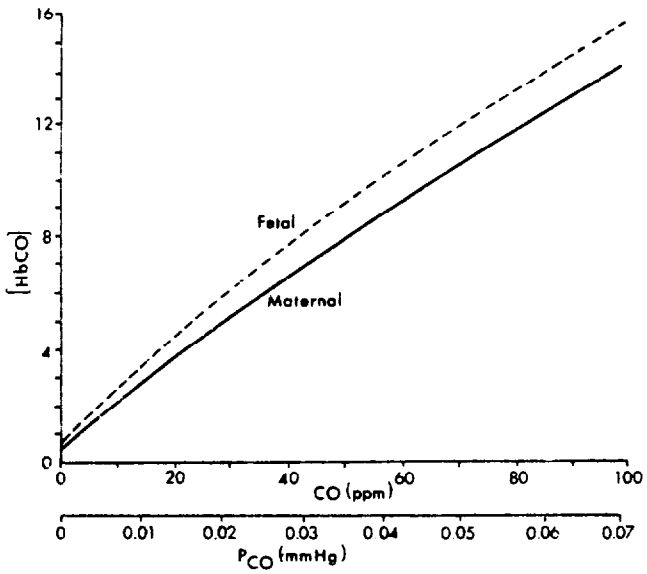

FIGURE 14.—Percent carboxyhemoglobin in maternal and fetal blood as a function of carbon monoxide partial pressure and concentration (parts per million) in inspired air. These carboxyhemoglobin concentrations were calculated from the Haldane relation correcting for the carbon monoxide effect on the oxyhemoglobin saturation curves

SOURCE: Hill, E.P. (*75*).

trations in human subjects. During carbon monoxide uptake, fetal carboxyhemoglobin concentrations would lag behind the maternal concentrations for the first few hours. After 14 to 24 hours they would equal maternal carboxyhemoglobin concentrations. Eventually the fetal carboxyhemoglobin would equilibrate at concentrations 10 to 15 percent higher than the maternal concentrations. During the washout phase, fetal carbon monoxide elimination would lag behind the maternal elimination and the carboxyhemoglobin concentration in the fetus would be significantly greater than that of the mother. The time required to reach one-half of the final value would average about 2 hours for the mother and 7 hours for the fetus. The pattern of carbon monoxide uptake and elimination in this theoretical analysis (*73*) is similar to that of the experimental results in sheep (*97*).

Carbon monoxide markedly shifts the oxyhemoglobin saturation curve to the left and alters the shape of the curve toward a more hyperbolic form. Figure 10 shows this effect for several concentrations of human maternal and fetal carboxyhemoglobin (*93*). The oxyhemoglobin saturation is for that percentage of hemoglobin not bound as

TABLE 14.—The relation of the concentrations of fetal to maternal carboxyhemoglobin in mothers who smoke during pregnancy

Fetal carboxyhemoglobin concentration	Maternal carboxyhemoglobin concentration	Fetal/maternal carboxyhemoglobin ratio	reference
7.5†	4.1	1.8	(27)
7.6(SEM ± 1.14)*	6.2(±0.75)*	1.2(±0.2)*	(65)
3.1(±0.84)**	3.6(±1.06)**	0.7(±0.14)	
5.0(±0.48)	6.7(±0.61)	0.7(±0.04)	(71)
3.6(±0.7)	6.3(±1.7	0.7(±0.15)	(95)
5.3(±0.22)	5.7(±0.24)	0.9(±0.06)	(183)
2.4(±0.30)	2.0(±0.31)	1.2(±0.08)	(209)
7.3	8.3	0.9	(211)

*One or more cigarettes 1 hr or less prior to delivery.
**One or more cigarettes 1 to 24 hrs. prior to delivery.
†Calculated from $[HbCO_m]$ and the ratio of $[HbCO_f]$ to $[HbCO_m]$.
SOURCE: Longo L.D. (*93*).

carboxyhemoglobin. Figure 11 shows the change in the oxygen partial pressure corresponding to 50 percent oxyhemoglobin saturation, the P50, for maternal and fetal blood as a function of blood carboxyhemoglobin concentration. For instance, at 10 percent carboxyhemoglobin concentration, the P50 for maternal blood decreases to 23.0 torr from a control value of 26.5 torr. At this same carboxyhemoglobin concentration, the fetal P50 decreases to 17.3 torr from a normal value of 20.5 torr.

In a theoretical analysis of the effects of elevated blood carboxyhemoglobin on fetal oxygenation, Longo, et al. (*73, 93*) have shown that either markedly increased tissue blood flow or considerably reduced oxygen tensions are the price that must be paid to maintain normal oxygen delivery. The upper part of Figure 15 shows the predicted decrease in oxygen tension as carboxyhemoglobin concentrations increase. The lower portion shows the compensatory or equivalent change in fetal blood flow necessary to maintain a steady-state oxygen exchange in the placenta, assuming no drop in umbilical artery oxygen tension. A 10 percent carboxyhemoglobin concentration would be equivalent to a drastic reduction in blood flow. Fetal blood flow would have to increase 62 percent (from 350 to 570 ml/min) to maintain normal oxygen exchange. Higher levels of fetal carboxyhemoglobin require even more dramatic compensations. However, it seems doubtful that much, if any, compensatory increase in blood flow occurs in the presence of carbon monoxide in the fetus (*97*). Therefore, the

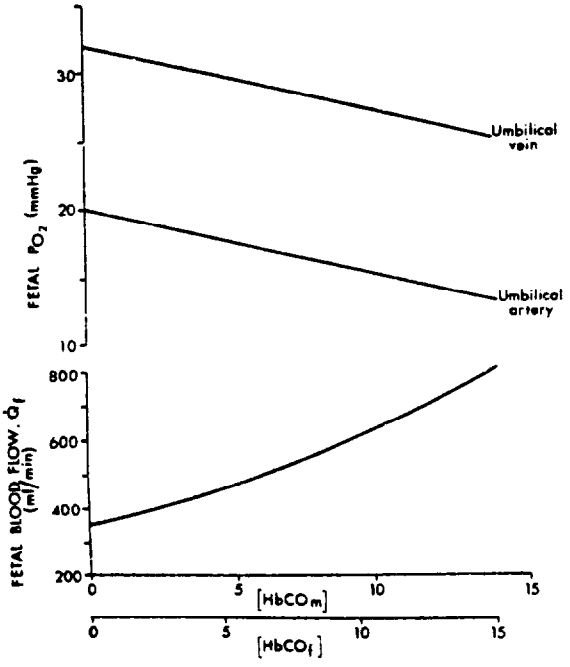

FIGURE 15.—The degree of compensation necessary to offset the effects of elevated fetal carboxyhemoglobin concentrations. Upper portion: Decrease in umbilical artery P_{O_2} and umbilical vein (placental end-capillary) P_{O_2} necessary to maintain normal oxygen exchange across the placenta in the presence of increasing amount of fetal carboxyhemoglobin. Lower portion: Increase in fetal blood flow (Qf) which would be required to maintain the normal O_2 exchange in the placenta with no change in umbilical artery P_{O_2}

SOURCE: Longo, L.D. (*95*).

changes in P_{O_2} values probably illustrate the *in vivo* situation more closely than do the equivalent changes in blood flow.

Vitamin B_{12} and Cyanide Detoxification

McGarry and Andrews (*110*) determined serum vitamin B_{12} levels in 826 women at their first prenatal clinic visit. They found that the serum levels for smokers were significantly lower than for nonsmokers. After adjustment for gestational age, parity, social class, hemoglobin level, hypertension, and maternal weight, smokers still had significantly lower levels of B_{12}. They also found a direct, statistically significant dose-response relationship between cigarettes smoked and serum vitamin B_{12} level. They again confirmed the relationship between smoking and low birth weight. The authors suggested that the lower