somatic complaint score between smokers and nonsmokers. However, when smokers were compared with nonsmokers of the same parity, education, work history, and psychosomatic complaint score, cigarette smokers still had a significantly higher proportion of small infants than did nonsmokers. As previously mentioned, whenever other factors known or suspected to influence birth weight have been controlled, cigarette smoking has always been demonstrated to have an independent and significant effect.

Ounsted (*69*) offered evidence that the best predictor of the birth weight of a mother's future offspring was the birth weight of her previous children. Herriott, et al. (*35*) found prematurity rates for previous pregnancies among smokers to be markedly higher than among nonsmokers, independent of parity, height, and social class. Evidently a woman whose previous infants have been small tends to continue to have relatively smaller than average infants in subsequent pregnancies. The question is, will those infants be even smaller than expected if she smokes?

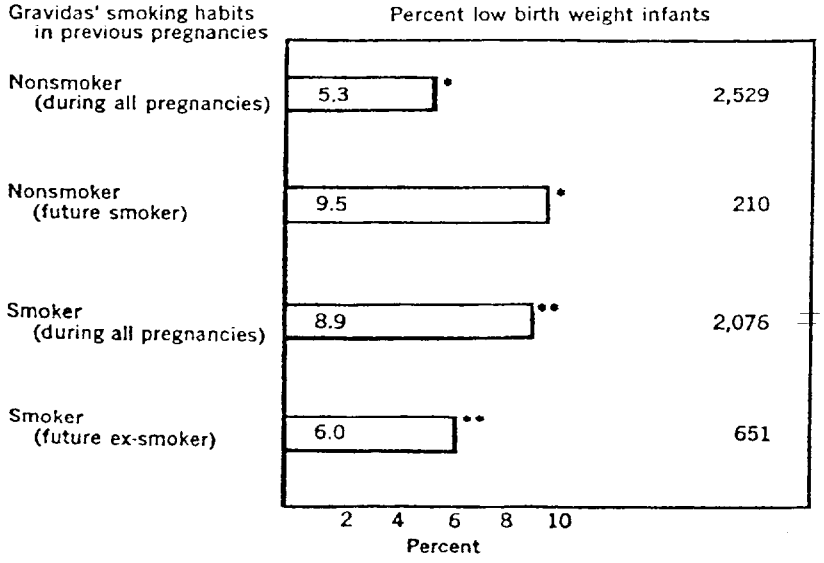
Goldstein, et al. (*28*), in a comprehensive review, proposed a research design in which a woman would serve as her own control to compare outcomes of pregnancies during which she smoked with those during which she did not with consideration of the effect of parity on the outcome. Yerushalmy (*112*) has recently tested this type of research design, using data from his Oakland Growth Study. With information on the age at which a woman began to smoke cigarettes, her smoking status during the pregnancy actually studied, her prior reproductive experience, and the outcome of her present pregnancy, the author compared the outcomes of pregnancy during periods of smoking and nonsmoking using the woman as her own control. As the author noted, "If smoking *causes* the increase in low-birth-weight infants, then the incidence of low birth weight for infants born to smoking mothers during the period before they acquired the smoking habit, should be relatively low. If, on the other hand, the high incidence of low birth weight is due to the *smoker*, then it should be high for infants of future smokers also when they were born before their mothers started to smoke."

Yerushalmy then proceeded to compare the reproductive experiences of four groups of women: (a) Those who smoked in none of their pregnancies, (b) those who smoked in all of their pregnancies, (c) those who were smoking now but previously had not smoked during some pregnancies (future smokers), and (d) those who were ex-smokers now but had previously smoked during some pregnancies. These outcomes are shown in figure 5. The incidence of low-birth-weight infants in the pregnancies of the future smokers, before they started to smoke, was similar to that for women who smoked in every pregnancy, which was significantly higher than that of infants from

mothers who had never smoked. He also noted that ex-smokers, during the period before they quit, gave birth to relatively few low-birth-weight infants; the incidence was significantly lower than for mothers who smoked during all of their pregnancies. He concluded that the findings cannot be easily reconciled with a cause-effect basis for smoking and birth weight. He said, "Rather the evidence appears to support the hypothesis that the higher incidence of low-birth-weight infants is due to the *smoker*, not the *smoking*."

There are several considerations which limit the interpretations which can be drawn from this study. The information on smoking behavior of the women during past pregnancies was apparently derived from the woman's age when she began to smoke, her smoking behavior early in the study pregnancy, and the age at which she had her prior pregnancies. Thus, if the woman reported that she began smoking at a certain age, and that she was still smoking at the time of the study, it was apparently inferred that she had smoked during all of her pregnancies. Since no questions were specifically asked about actual smoking behavior during each previous pregnancy, it is possible that the woman indeed had not smoked during every pregnancy or that the amount or way she smoked had differed from current smoking

Figure 5.—Percent of low birth weight white infants by smoking status of their mothers.



*Difference is statistically significant (P <0.01).
**Difference is statistically significant (P <0.02).

SOURCE: Adapted from Yerushalmy, J. (112).

habits. This would be important to know given the strong dose-response relationship which has been established between cigarette smoking and low birth weight, and would tend to make the reproductive outcomes for ex-smokers similar to those of nonsmokers, and different from those of women who smoked in all pregnancies.

For ex-smokers, the age at which smoking began was not elicited. Hence, some of the infants of ex-smokers may have been born before their mothers acquired the smoking habit. This would also tend to make the reproductive experiences of ex-smokers more like those of nonsmokers and different from those of women who smoked in all pregnancies.

No direct adjustment for age, parity, and other variables was reported, although Yerushalmy stated that the study population was limited to the births that occurred to women at age 25 years or less. He noted that, "In order to adjust for parity, the same comparisons were performed for firstborn infants only. The numbers were reduced considerably, but the same tendencies as found above were noted." However, no data were presented. Primiparous births and births in teenagers are strongly associated with the delivery of low-birth-weight infants. If the pregnancies which occurred among future smokers included a predominance of very young women and primiparous births, the reproductive experiences of future smokers would tend to be similar to those of women who smoked during all pregnancies, and different from those of nonsmokers. In the absence of more precise information on actual smoking behavior during pregnancy and more rigorous adjustment for maternal age, this study does not provide a critical test of the hypothesis that it is the smoking during pregnancy which is responsible for the high proportion of small-for-dates infants born to women who smoke.

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 (*23, 87, 117*). Younoszai, et al. (*117*) 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. The authors suggested that carbon monoxide might also not be responsible for the retardation of

fetal growth; however, the evidence presented was inadequate to support a firm conclusion.

Haworth and Ford (*33*) recently extended the experiments of Younoszai. A group of pregnant rats was exposed to cigarette 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, and suggests that the exposure to tobacco smoke either inhibited cellular proliferation or accelerated cellular destruction.

Nicotine

Several workers have demonstrated that chronic injections of large doses of nicotine into pregnant rats resulted in a reduction of birth weight of the offspring (*7*, *8*, *9*, *23*, *40*). Other investigators have determined that tritium-labelled nicotine injected into pregnant rabbits and C^{14}-labelled nicotine injected into pregnant mice crossed the placenta to the developing embryo and fetus (*89*, *98*). Kirschbaum, et al. (*41*) found no significant acute effects of small doses of nicotine, injected intravenously into near-term sheep, on blood gas composition, pH, blood pressure, or heart rate in either the ewes or their fetuses. The authors concluded that the influence of maternal smoking upon the fetus must result from chronic effects or through the effects of other variables which they did not study.

Recently, Suzuki, et al. (*94*) evaluated the short-term effects of injected nicotine on the cardiovascular performance, acid-base status, and oxygenation of pregnant female Rhesus monkeys and their infants during the second half of gestation using the mothers as their own controls. Nicotine was administered either as a single intravenous dose of 0.5 to 1.0 mg. or as a continuous infusion of 100 μg./kg. over

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a 20-minute period. The injection of nicotine in the larger, single dose into the mother produced a rise in maternal blood pressure and a fall in maternal heart rate, and an immediate fall in both fetal blood pressure and fetal heart rate followed by persistent hypotension and tachycardia in the fetus. Subsequent to the injection of 1.0 mg./kg. of nicotine into pregnant monkeys, in a single dose, significant changes in the arterial blood of the older fetuses included a fall in pH, a rise in base deficit, and a fall in oxygen tension. Carbon dioxide tension remained unchanged. Nicotine injected directly into the fetus prompted an immediate rise in fetal blood pressure and a fall in fetal heart rate. These responses were similar to those previously seen in the mothers following a direct injection of nicotine. The changes were more prominent in older rather than in younger fetuses. The authors summarized their findings by stating that: (a) fetuses in different gestational stages are differentially responsive to a given dose of nicotine, probably because of the different stages of development of the autonomic nervous system; (b) diminished intervillous space perfusion resulting from vasoconstriction in the uterine circulation appears to be mainly responsible for the fetal asphyxia following the injection into the mother, because fetal hypotension and bradycardia were not preceded by the transient hypertension seen following the direct administration of nicotine to the fetus; (c) the differences between the results obtained by Kirschbaum and by Suzuki, et al. may reflect either the considerable dosage differences or species differences; and (d) the doses which the authors employed were much larger than those which a human mother would absorb from usual cigarette smoking, but that differences in tolerance to nicotine between the Rhesus monkey and humans would imply that the dosages were, in fact, comparable and that, "Hence, it can be envisaged that the concentration of nicotine which could be reached in the organism of a smoking mother would reduce oxygen availability to the fetus."

Carbon Monoxide

Longo (*45*) has reviewed the work of several investigators which has demonstrated the transplacental passage of carbon monoxide from mother to fetus in animals. A recent study which related CO to birth weight was published by Astrup (*2*). He found that continuous exposure throughout gestation of pregnant rabbits to different levels of ambient carbon monoxide resulted in a statistically significant dose-related reduction in birth weight (table 2). The actual significance level was not reported.

TABLE 2.—*Effect of carbon monoxide exposure of pregnant rabbits on birth weight*

	Group 1, 0 percent COHb	Group 2, 8 to 10 percent COHb	Group 3, 16 to 18 percent COHb
Number of pregnant rabbits	17	14	17
Total number of babies	116	81	123
Average weight of babies in grams	53.7	51.0	44.7

SOURCE: Astrup, P. (*6*).

Polycyclic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) such as benzo(a)pyrene (BAP) are constituents of cigarette smoke which have been implicated in the generation of cancers in many animal species (*111*). 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. (*108*) 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-labelled 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.

Schlede and Merker (*86*) 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 24 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 on 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.

Studies in Humans

Carbon Monoxide

Smokers and their newborn infants have significantly elevated levels of carbon monoxide as compared with nonsmokers and their infants (*31*, *34*, *88*, *116*). Recently, Baribaud, et al. (*5*) studied 50 nonsmokers and 27 cigarette smokers and their newborns. All smokers inhaled. The authors found that the mean level of CO content in the blood of nonsmokers was 0.211 volumes percent compared with 0.672 volumes percent in the blood of smokers. The values for blood samples from the umbilical cords of their newborns were 0.352 and 0.949 volumes percent, respectively. Moreover, a definite dose relationship was found between CO levels and number of cigarettes smoked.

Younoszai, et al. (*116*) found, in addition to elevated carboxyhemoglobin levels among the infants of smoking mothers, significant elevation of mean capillary hemotocrits and significant reduction of standard bicarbonate levels, as compared to the infants of nonsmoking mothers. Since no evidence for nicotine effects upon blood glucose, serum FFA levels, or urinary catecholamines, or for 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.

Longo (*45*) pointed out that a level of 9 percent carboxyhemoglobin in the fetus is the equivalent of a 41 percent decrease in fetal blood flow or fetal hemoglobin concentration. In reviewing the studies of CO levels in human mothers and their newborns, he made the follow-

ing comments: "These samples were obtained at the time of vaginal delivery or Cesarean section and may not accurately reflect the normal values of $(COHb)_F$ for several reasons. The number of cigarettes smoked by the mothers during labor may be less than their normal consumption and was not specified in these studies. The blood samples were collected at varying time periods following the cessation of smoking. In addition, many of the samples were probably taken early in the day before COHb levels had built up to the levels reached after prolonged periods of smoking. Thus actual levels of $(COHb)_M$ and $(COHb)_F$ may be higher than the reported values."

Polycyclic Hydrocarbons

The results of several studies concur that cigarette smoking is strongly associated with the induction of aryl hydrocarbon hydroxylase in the human placenta (*18*, *38*, *61*, *99*, *109*). This finding implies that benzo(a)pyrene or other polycyclic hydrocarbons reach the placenta. To date, evidence to support the passage of polycyclic hydrocarbons through the placenta to the human fetus has not been published.

Vitamin B_{12} and Cyanide Detoxification

McGarry and Andrews (*48*) 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 lowered vitamin B_{12} levels reflect a disorder of cyanide detoxification. Cyanide is a demonstrable ingredient in cigarette smoke (*39*, *60*, *62*, *64*, *68*, *74*, *91*).

Vitamin C

Venulet (*105*, *106*, *107*) has demonstrated that the vitamin C level is significantly lower in the serum of women who smoke cigarettes during pregnancy, compared to values for their nonsmoking counterparts.

Possible Mechanisms

The following mechanisms have been proposed for the production of low birth weight and other unfavorable outcomes of pregnancy following exposure to cigarette smoke:

1. A direct toxic influence of constituents of cigarette smoke upon the fetus (*2*, *45*, *50*, *51*, *117*).
2. Decreased placental perfusion (*94*).
3. Decreased maternal appetite and diminished maternal weight gain with secondary effects upon the fetus (*6*, *33*, *36*, *65*, *75*, *99*-*117*).
4. A direct effect upon the placenta (*36*, *57*, *65*, *110*).
5. An oxytocic effect on uterine activity (*44*).
6. A disturbance of vitamin B_{12} metabolism (*48*).
7. A disturbance of vitamin C metabolism (*105*, *106*, *107*).

Of the potential mechanisms, available evidence suggests that neither decreased maternal appetite and decreased maternal weight gain nor a direct effect upon the placenta are responsible for a significant reduction in birth weight. Existing evidence does not permit firm conclusions concerning the relative significance of the remaining mechanisms.

Timing of the Influence of Cigarette Smoking on Birth Weight

Several investigators have published results which bear on the time period during which exposure to cigarette smoke most affects fetal growth. Lowe (*46*) and Zabriskie (*118*) have offered evidence which suggests that cigarette smoking influences fetal growth most during the second half of pregnancy. Butler, et al. (*15*) found that the birth weights of infants of women who did not smoke after the fourth month of pregnancy were essentially the same as those of the infants of nonsmokers. This implies that the influence is most probably exerted after the fourth month of pregnancy. Herriott, et al. (*35*), however, found that women in lower socioeconomic classes who gave up smoking early in pregnancy tended to have intermediate weight babies as compared with nonsmokers and persistent smokers, but his numbers of women were small and the results were not statistically significant. Underwood, et al. (*100*) found that cigarette smoking in any single trimester was associated with a lower birth weight of the infant, although the difference between the birth weights of infants of women who smoked only during a single trimester and infants of nonsmokers was not statistically significant because of small numbers. Several investigators have detected a nearly constant difference between the birth weights of the infants of smokers and nonsmokers, delivered during the last month of pregnancy, following gestations of comparable length [fig. 1, (*11*)]. Although this observation is

compatible with the suggestion that the influence of cigarette smoking upon the fetus occurs prior to the last month of pregnancy, it is based upon data derived from cross-sectional rather than longitudinal studies. The results of many human epidemiological studies suggest that maternal smoking prior to pregnancy does not influence fetal weight gain (*15*, *25*, *46*, *49*, *113*).

Site of Action at the Tissue and Cellular Level

The use of labelled nicotine (*98*) and the preparations of autoradiograms have permitted the localization of nicotine within the tissues of the fetus and mother. Tjalve, et al. (*98*) found high levels of nicotine in the respiratory tract, adrenal, kidney, and intestine of 16- to 18-day mice fetuses. The use of other labelled constituents during various parts of gestation might further the understanding of how certain ingredients in cigarette smoke produce an impact upon birth weight. Haworth and Ford (*33*) have reported data which suggest that the reduction of birth weight of rat fetuses caused by the action of the ingredient(s) of tobacco smoke results from a reduction in cell number, but not in cell size.

Significance of the Association

Among all women in the United States, cigarette smokers are nearly twice as likely to deliver low-birth-weight infants as are nonsmokers. Assuming that 20 percent of pregnant women in the United States smoked cigarettes through the entire pregnancy (extrapolated from data on changes in smoking behavior during pregnancy collected for the British Perinatal Mortality Study), taking into account the apparently different risks of delivering a small-for-dates infant for Caucasian and non-Caucasian women who smoke during pregnancy, and considering the number of infants with a birth weight less than 2,500 grams born to Caucasian and non-Caucasian women, an excess of nearly 43,000 occurred in the 286,000 low-birth-weight infants among the 3,500,000 infants born in the United States in 1968, because of the increased risk among women who smoke of having small-for-dates infants.

Since neonatal mortality is higher for low-birth-weigth infants, with gestational age held constant, the excess of small-for-dates infants among smoking mothers would imply a significant excess mortality risk as well.

A causal association between cigarette smoking and fetal growth retardation is supported by the following evidence:

1. The results of all 42 studies in which the relationship between smoking and birth weight was examined have demonstrated a strong association between cigarette smoking and delivery of small-for-dates infants. On the average, the smoker has nearly twice the risk of delivering a low-birth-weight infant as that of a nonsmoker.
2. This association has been confirmed by both retrospective and prospective study designs.
3. A strong dose-response relationship has been established between cigarette smoking and the incidence of low-birth-weight infants. Available evidence suggests that the effect of smoking upon fetal growth reflects the number of cigarettes smoked daily during a pregnancy, and not the cumulative effect of cigarette smoking which occurred before the pregnancy began.
4. When a variety of known or suspected factors which also exert an influence upon birth weight have been controlled for, cigarette smoking has consistently been shown to be independently related to low birth weight.
5. The association has been found in many different countries, among different populations, and in a variety of geographical settings.
6. New evidence suggests that if a woman gives up smoking by the fourth month of pregnancy, her risk of delivering a low-birth-weight infant is similar to that of a nonsmoker.
7. The infants of smokers experience a transient acceleration of growth rate during the first 6 months after delivery, compared to infants of nonsmokers. This finding is compatible with viewing birth as the removal of the smoker's infant from a toxic influence.
8. The results of experiments in animals have shown that exposure to tobacco smoke or some of its ingredients results in the delivery of low-birth-weight offspring. New evidence demonstrates that chronic exposure of rabbits to carbon monoxide during gestation results in a dose-related reduction in the birth weight of their offspring.
9. Data from studies in humans have demonstrated that smokers' fetuses are exposed directly to agents within tobacco smoke, such as carbon monoxide, at levels comparable to those which have been shown to produce low-birth-weight offspring in animals.

Cigarette Smoking and Fetal and Infant Mortality

Introduction

Several previous studies of the relationship between cigarette smoking and higher fetal and infant mortality among the infants of smokers have been reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*). In many of these studies, the authors combined two or more categories of fetal and infant mortality. Different mortality outcomes, such as spontaneous abortion, stillbirth, and neonatal death, are influenced by different sets of factors. Among other factors, the frequency of abortion is influenced by congenital infections, hormonal deficiencies, and cervical incompetency. In addition to other factors, the frequency of stillbirth is influenced by premature separation of the placenta, uterine inertia, and dystocia. Along with other factors, the frequency of neonatal death is influenced by gestational maturity, birth injuries, and delivery room and nursery care. Separate analysis of the relationship of cigarette smoking to each different mortality outcome, with control of the unique set of factors which influences it, may facilitate understanding of the relationship.

Spontaneous Abortion

Previous epidemiological and experimental studies of the relationship between spontaneous abortion and cigarette smoking reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*) form the basis of the following statements:

The results of several studies, both retrospective and prospective, have demonstrated a statistically significant association between maternal cigarette smoking and spontaneous abortion (*43*, *65*, *70*, *99*, *118*). Data from some of these studies have documented a strong dose-response relationship between the number of cigarettes smoked and the incidence of spontaneous abortions (*70*, *99*, *118*). In general, variables other than cigarette smoking (e.g., maternal age, parity, health, desire for the pregnancy, and use of medication), which may influence the incidence of spontaneous abortions, have not been controlled. The results of the one study, in which adjustment for the woman's desire for the pregnancy was performed, indicated that after such adjustment cigarette smoking during the pregnancy retained an association with spontaneous abortion of borderline significance (*43*). The time period during which cigarette smoking might exert an influence on the incidence of spontaneous abortions has not been determined. Abor-

tions have been produced in animals only with large doses of nicotine (*23*, *96*, *104*); the relevance of these studies for humans is uncertain.

Spontaneous Abortion Summary

Although several investigators have found a significantly higher, dose-related incidence of spontaneous abortion among cigarette smokers as compared to nonsmokers, the lack of control of significant variables other than cigarette smoking does not permit a firm conclusion to be drawn about the nature of the relationship.

Stillbirth

Epidemiological studies of the association between cigarette smoking and stillbirth previously reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*) form the basis for the following statements:

In one group of retrospective and prospective studies, a higher stillbirth rate was found for the infants of smokers as compared to those of nonsmokers (*14*, *25*, *43*). In another group of retrospective and prospective studies, no significant difference was detected in the stillbirth rate among the infants of smokers and nonsmokers (*16*, *20*, *85*, *99*, *100*). Differences in study size, numbers of cigarettes smoked, or the presence or absence of control of variables, such as age and parity, which may influence stillbirth rates, were probably not sufficient to explain the differences in results obtained.

Several recent epidemiological studies have added to our understanding of the relationship between cigarette smoking and stillbirth. Niswander and Gordon (*63*) have reported data from 39,215 pregnancies followed prospectively and collected between 1959 and 1966 at 12 university hospitals in the United States. A random sample of women who presented to hospital prenatal clinics were enrolled in the study. The authors reported no increase in stillbirths among white smokers as compared with white nonsmokers. A higher incidence of stillbirths was found among black women who smoked than among nonsmoking black women, and a dose-response relationship with cigarettes smoked was suggested, although the findings did not attain statistical significance. The results were not adjusted for other variables. Rush and Kass (*82*) found, in a prospective study of 3,296 pregnancies at Boston City Hospital, a nonsignificant increase in

stillbirths among white women who smoked, but a statistically significant increase in stillbirths among black women who smoked ($P<0.02$). These findings are consistent with those previously outlined by Frazier, et al. (*25*) and Underwood, et al. (*99*).

Rumeau-Roquette (*81*), in a prospective study of 4,824 pregnancies in Paris, demonstrated that the risk of stillbirth was significantly higher for cigarette smokers than for nonsmokers ($P<0.001$). The authors also presented evidence that a woman with either a previous stillbirth or at least one prior infant weighing less than 2,500 grams at birth was significantly more likely to have a future stillborn infant than a woman without such an obstetrical history. After previous obstetrical history was controlled, smokers still retained a statistically significant increased risk of subsequent stillbirth as compared to nonsmokers ($P<0.01$). Of further interest was the finding that among women who previously had delivered only living infants, weighing over 2,500 grams, cigarette smoking had no influence on the stillbirth rate.

Previous experimental studies were reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*). The authors demonstrated that exposure of pregnant rabbits to tobacco smoke and pregnant rats tc large doses of injected nicotine resulted in a significant increase in stillbirths (*7*, *8*, *23*, *87*).

Stillbirth Summary

1. The results of recent studies suggest that cigarette smoking is most strongly associated with a higher stillbirth rate among women who possess less favorable socioeconomic surroundings or an unfavorable previous obstetrical history. In the United States, black women have higher stillbirth rates than white women. The finding that cigarette smoking is associated with an even greater difference between the stillbirth rates of the two groups merits special attention. These findings may provide at least a partial explanation for the lack of a significant difference in stillbirth rates between smokers and nonsmokers, which some investigators have found.
2. The results of experiments in animals demonstrate that exposure to tobacco smoke and some of its ingredients, such as nicotine, can result in a significant increase in stillbirth rate.

Late Fetal and Neonatal Deaths

Considerable variation has occurred in the definition of the study population among the studies in which the relationship of cigarette smoking to fetal mortality (other than abortion) and early infant mortality was examined. The most commonly identified study populations have been perinatal deaths, neonatal deaths, and late fetal plus neonatal deaths. Perinatal deaths are a combination of late fetal deaths (i.e., stillborn infants) and deaths occurring within the first week of life. Neonatal deaths include all deaths of liveborn infants within the first 28 days of life.

Epidemiological Studies

Most of the earlier epidemiological studies of the association between cigarette smoking and late fetal plus neonatal mortality were reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*). A review of previously unreported studies (*67*, *76*), as well as reexamination of previously cited studies, forms the basis of the following statements:

The results of several prospective and retrospective studies indicate a statistically significant higher late fetal and/or neonatal mortality for the infants of smokers compared to those of nonsmokers (*14*, *17*, *25*, *43*). The results of other prospective and retrospective studies identified no significant difference in the mortality rates between the infants of smokers and nonsmokers (*20*, *65*, *72*, *85*, *100*, *115*).

If mortality rates were compared for those infants of smokers and nonsmokers weighing less than 2,500 grams, the infants of nonsmokers apparently had a considerably higher risk than did those of smokers.

The results of recent studies, coupled with a critical review of the design and analysis of previous studies, and a reexamination of existing data, may provide at least a partial explanation of discrepancies between the results of previous studies.

Comparisons of the Mortality Risks of Low-Birth-Weight Infants Born to Smokers and Nonsmokers

The perinatal mortality risk for infants weighing less than 2,500 grams appears to be lower for those infants born to women who smoke during pregnancy than for those born to nonsmokers (table

3). However, available evidence shows that cigarette smokers' infants tend to be small-for-gestational age rather than gestationally premature. Hence, within a given birth weight group, the infants of smokers are, on the average, gestationally more mature than those of nonsmokers. Data collected by the National Center for Health Statistics (*103*) demonstrate that within a given birth weight group, the more gestationally mature an infant, the lower is its mortality risk (fig. 6). Thus, the difference in perinatal mortality risks experienced by the infants of cigarette smokers and nonsmokers, within comparable birth weight classes, reflects the facts that the two sets of infants are not of the same average gestational age, and that gestational age is a major factor influencing late fetal and neonatal mortality. An accurate estimate of comparative mortality risks for the infants of cigarette smokers and nonsmokers requires adjustment for gestational age.

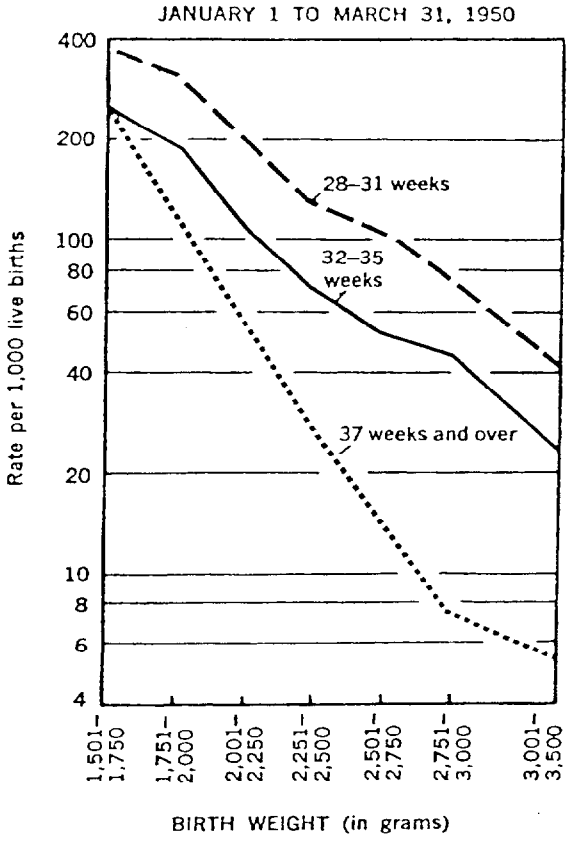
For infants of comparable gestational age, lower birth weight is associated with higher mortality (fig. 6). Since infants of cigarette smokers have, on the average, lower birth weights than the infants of nonsmokers, within groups of comparable gestational age, cigarette smokers' infants should experience higher mortality rates than nonsmokers' infants of similar gestational ages. In a recent review, Meyer and Comstock (*51*) provided a more extensive discussion of these points.

TABLE 3.—*Comparison of the perinatal mortality for infants weighing less than 2,500 grams, of smokers and nonsmokers*

Author, reference	Perinatal mortality rate (deaths per 1,000 live births)	
	Smokers	Nonsmokers
Underwood, et al. (*100*)	187	269
Ontario Department of Health (*67*)	232	300
Kullander and Källen (*43*)	129	139
Rantakallio (*76*)	288	344
Yerushalmy [1] (*112*):		
Black women	114	202
White women	114	218
Butler and Alberman (*14*)	269	284

[1] Reported neonatal mortality rates only.

Figure 6.—Neonatal mortality rates among single white births in hospitals (by detailed birth weight and specified gestation groups: United States).

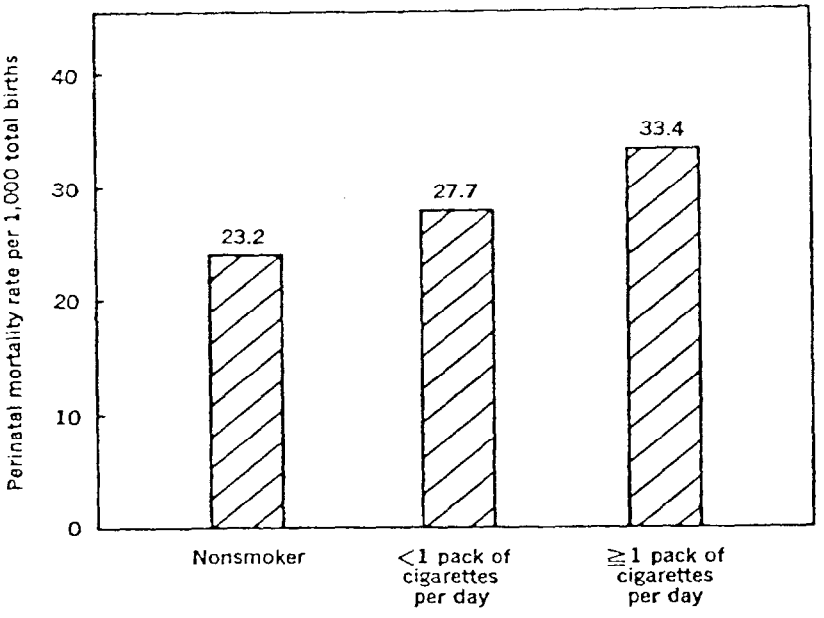


SOURCE: U.S. Public Health Service, National Center for Health Statistics *(103)*.

Recent Studies

The Ontario Perinatal Mortality Study (*66*, *67*) was conducted among 10 teaching hospitals during 1960 and 1961. In this retrospective study of 51,490 pregnancies, a statistically significant increase in the perinatal mortality rate was demonstrated for smokers' infants as compared with those of nonsmokers; the infants of smokers experienced an overall relative risk of 1.27 ($P<0.001$). Moreover, the investigators found a statistically significant dose-response relationship between the amount of cigarettes smoked and the perinatal mortality rate ($P<0.001$) (fig. 7).

Figure 7.—Perinatal mortality rate per 1,000 total births by cigarette smoking category.



	Nonsmoker	<1 pack of cigarettes per day	≥1 pack of cigarettes per day
Number of perinatal deaths:	659	425	220
Total births:	28,358	15,328	6,581

($P < 0.001$)

SOURCE: Ontario Department of Health (66).

Recently Butler, et al. (*15*) further analyzed the British Perinatal Mortality Study. They found a highly significant association between maternal smoking after the fourth month of pregnancy and both late fetal and neonatal deaths. Infants of smokers had an increase in the late fetal mortality rate of 30 percent, and an increase in the neonatal mortality rate of 26 percent, compared to the infants of nonsmokers. The overall mortality ratio of late fetal plus neonatal deaths was 1.28 ($P<0.001$). Given the large number of women in the study, and the significant changes in smoking behavior which occurred, they found it possible to consider the effect of a change in smoking

behavior between the beginning of pregnancy and the fourth month on late fetal and neonatal mortality. A statistically significant and dose-related increase in mortality occurred among the infants of mothers who continued to smoke after the fourth month of pregnancy, as compared with the infants of nonsmokers and those of women who smoked prior to the pregnancy but gave up smoking by the fourth month of gestation.

Niswander and Gordon (*63*) reported data from the prospective Collaborative Perinatal Study of the National Institute of Neurological Disease and Stroke. The 39,215 pregnancies registered at 12 university hospitals in the United States were almost equally divided between black and white women. They found a nonsignificant increase in perinatal mortality among the infants of white smokers as compared to those of white nonsmokers; the overall mortality ratio was 1.13 ($P>0.1$). The infants of black smokers, however, had a significantly higher mortality risk than did those of black nonsmokers; the mortality ratio was 1.18 ($P<0.02$). Moreover, a definite dose-response relationship between cigarettes smoked by pregnant mothers and mortality risk was shown for black infants. Black women were noted to smoke significantly fewer cigarettes, on the average, than white women.

Rush and Kass (*82*) found, in a prospective study of 3,276 pregnancies followed at Boston City Hospital, a nonsignificant increase in late fetal plus neonatal mortality rate among the infants of white women who smoked as compared to those of white nonsmokers. However, the infants of black women who smoked had a statistically significant increase in mortality rate compared to the infants of black nonsmokers ($P<0.01$). The overall mortality ratio for black women who smoked was 1.86. The difference in frequency of stillbirth among the infants of smokers and nonsmokers was the primary factor which contributed to the significance of the difference in mortality rates.

Analysis of Previously Reported Studies

Previously reported studies can be divided into two groups: A group in which the late fetal plus neonatal mortality rates for infants born to cigarette smokers were significantly higher than those for the infants born to nonsmokers, and a group in which no significant differences were detected in the mortality rates for the infants born to smokers and nonsmokers. The results of several studies (*14*, *17*, *25*, *42*, *43*, *55*, *84*, *92*) yielded mortality ratios ranging from 1.38 to 1.78. The results of other studies (*20*, *65*, *76*, *85*, *100*, *115*) yielded mortality ratios ranging from 1.01 to 1.06. Both groups contained retrospective and prospective studies of comparable size. The two groups did differ

significantly, however, with regard to control of variables other than cigarette smoking which influence perinatal mortality.

Factors Which Influence Perinatal Mortality Other Than Smoking

Butler and Alberman (*13*), on data from the British Perinatal Mortality Study, employed a logit transformation analysis of variance, and demonstrated that maternal height, age, parity, social class, and severe preeclampsia all had a significant independent effect on late fetal and neonatal mortality. Rumeau-Roquette (*81*) provided evidence that a previous stillbirth or low-birth-weight infant significantly increased the risk of a future stillbirth. Meyer and Comstock (*51*) provided examples of how the differential distribution of smoking and other factors which are related to perinatal mortality, in a population of women, can bias data (e.g., black women have higher perinatal mortality rates than do white women, but black women smoke less than white women do. Hence, nonsmokers will tend to include more black women, and smokers more white women. This will tend to reduce any differences between the groups in mortality rates.) Meyer and Comstock concluded, "Comparisons of mortality rates of smokers' and nonsmokers' babies should be made within subgroups according to parity, socioeconomic status, and other appropriate risk factors, and not separated by birth weight."

In three of the studies in which a significantly higher mortality risk was demonstrated for the infants of smokers, adjustment for other variables was performed. The results indicated that, after such adjustment, a significant independent association between cigarette smoking and infant mortality persisted (*13* and *15*, *17*, *81*). Of the studies which revealed no significant increase in mortality risks for smokers' infants, one (*115*) controlled for race alone. Hence, at least part of the discrepancy in results between the two groups of studies may be explained by a lack of control of variables other than smoking.

Another possible, at least partial, explanation of the discrepancy in results obtained by the two sets of studies is that cigarette smoke may be more harmful to the fetuses of certain women than others. Several developing lines of evidence suggest that this may be the case:

1. Cigarette smoking and socioeconomic background.

Butler, et al. (*15*) noted that when data from the British Perinatal Mortality Study are grouped by social class of the mother's husband, the late fetal plus neonatal mortality ratio for infants of smokers and nonsmokers in the upper social classes I and II is 1.10; the mortality ratio for the entire sample was 1.28. Rush and Kass (*82*) reviewed the British Perinatal Mortality Study, along with several other studies, and noted that all have shown the strongest association between excess infant mortality and cigarette smoking among the infants of those

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mothers with lower socioeconomic status. Comstock and Lundin (*16*) found excess mortality among smokers' infants almost entirely confined to those whose fathers had a grammar school education or less. Several of the studies which revealed no significant difference in mortality among the infants of smokers and nonsmokers were conducted in predominately middle class populations (*20*, *100*, *115*).

2. Cigarette smoking and previous obstetrical experience.

Peterson, et al. (*72*) had rigid criteria for entry into his study population of 7,740 women. He included only those women who previously had healthy infants with a birth weight greater than 2,500 grams. He found a significant decrease in birth weight among smokers' infants, but no significant increase in mortality rates. Rumeau-Roquette (*81*) found that among women who previously had delivered only healthy infants weighing more than 2,500 grams, cigarette smoking was not associated with an increased risk of stillbirth; among those women with a previous stillbirth, smoking was significantly associated with increased risk of a future stillbirth.

3. Cigarette smoking and genetic differences.

The consistent finding that the mortality risk for the infants of black smokers is higher than the risk for the infants of white smokers, even when the socioeconomic background for both is ostensibly similar, suggests that genetic factors also may interact with smoking to produce enhanced risk (*82*, *99*, *115*).

Available evidence suggests that if those women, who are already likely to have small infants for reasons other than smoking, smoke during pregnancy, their infants will be most unfavorably affected. This means that the women in the United States whose infants will be most affected by cigarette smoking are those who have an unfavorable socioeconomic situation, have a history of previously unsuccessful pregnancies, and are black.

Experimental Studies

Studies in Animals

Studies previously reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*) demonstrate that exposure of rabbits and rats to tobacco smoke and to injections of large doses of nicotine resulted in significantly increased late fetal and neonatal mortality. Astrup (*2*) has recently studied the effect of continuous exposure of pregnant rabbits to carbon monoxide on stillbirth rates. He found a significantly higher, dose-related incidence of stillbirths and deaths within the first 24 hours of life among the offspring of the experimental rabbits (table 4).

TABLE 4.—*Effect of carbon monoxide exposure of pregnant rabbits on birth weight and neonatal mortality*

	Group 1, 0 percent COHb	Group 2, 8 to 10 percent COHb	Group 3, 16 to 18 percent COHb
Number of pregnant rabbits	17	14	17
Total number of babies	116	81	123
Stillborn and babies died within first 24 hours	[1] 1	[2] 8	[3] 44
		(P<0.001)	

[1] 1 percent.
[2] 10 percent.
[3] 36 percent.
Source: Astrup, P. (*2*).

Studies in Humans

Some investigators have examined the causes of death among the infants of smokers as compared with those of nonsmokers. Comstock, et al. (*17*) found that infants of smokers died more frequently of asphyxia, atelectasis, and immaturity. Kullander and Källen (*43*) found abruptio placentae significantly increased as a cause of death among smokers' infants. Butler and Alberman (*14*) found little difference in the death rates for the infants of smokers and nonsmokers from isoimmunization and malformations, but higher rates were found for smokers' infants in the groups in which death occurred before or during labor, or in which death resulted from massive pulmonary hemorrhage, or pulmonary infection. As the authors noted, "The latter three are conditions known to be associated with small-for-dates babies." They pointed out that distribution of causes of death in the smoking group could be accounted for almost entirely by the excess of low-birthweight babies. This supports the conclusion that the mechanism which affects birth weight also influences mortality.

SIGNIFICANCE OF THE ASSOCIATION

The following calculation is offered to give some idea of the order of magnitude of increased late fetal and neonatal mortality associated with cigarette smoking during pregnancy. If women who smoked dur-

ing pregnancy in the United States had an elevation in risk of 28 percent for late fetal and neonatal mortality, as demonstrated by Butler, et al. (*15*) for Britain, Scotland, and Wales, and if 20 percent of pregnant women smoked throughout the pregnancy,[1] the higher risk of stillbirth and neonatal death for the infants of mothers who smoke cigarettes during pregnancy would account for approximately 4,600 of the 87,263 stillbirth and neonatal deaths in the United States in 1968.

Late Fetal and Neonatal Death Summary

A strong, probably causal association between cigarette smoking and higher late fetal and infant mortality among smokers' infants is supported by the following evidence:

1. Twelve retrospective and prospective studies have revealed a statistically significant relationship between cigarette smoking and an elevated mortality risk among the infants of smokers. In three of these studies, of sufficient size to permit adjustment for other risk factors, a highly significant independent association between smokng and mortality was established. Part of the discrepancy in results between these studies and those in which a significant association between smoking and infant mortality was not demonstrated may be explained by a lack of adjustment for risk factors other than smoking.
2. Evidence is converging to suggest that cigarette smoking may be more harmful to the infants of some women than others; this may also, in part, explain the discrepancies between the results of the studies in which a significantly higher mortality risk was shown for the infants of smokers compared to those of nonsmokers and the results of those studies in which significant differences in mortality risk were not found.
3. Within groups of similar birth weight, the infants of nonsmokers appear to have a higher mortality risk than do the infants of cigarette smokers. This results from the fact that the infants of nonsmokers within such similar birth weight groups are on the average gestationally less mature than the infants of cigarette smokers. Available evidence indicates that within groups of similar gestational age, infants of lower birth weight experience a higher mortality risk. Since the infants of cigarette smokers are

[1] Based on extrapolation of data on smoking behavior change during pregnancy from the British Perinatal Mortality Study, which probably yields a conservative estimate.

small-for-gestational age, one should expect that if the infants of cigarette smokers and nonsmokers are compared within similar gestational age classes, the infants of cigarette smokers would have the higher mortality rate.

4. The results of recent studies have documented a statistically significant dose-response relationship between the number or amount of cigarettes smoked and late fetal and neonatal mortality.
5. New data suggest that if a woman gives up smoking by the fourth month of pregnancy, she will have the same risk of incurring a fetal or neonatal loss as a nonsmoker.
6. Available evidence strongly supports cigarette smoking as one cause of fetal growth retardation. The causes of excess deaths among the infants of smokers are those associated with small-for-dates babies.
7. Data from experiments in animals have demonstrated that exposure to tobacco smoke or some of its ingredients, such as nicotine or carbon monoxide, results in a significant increase in late fetal and or neonatal deaths.
8. The results of studies in humans have shown that the fetus of a smoking mother may be directly exposed to agents such as carbon monoxide within tobacco smoke, at levels comparable to those which have been shown to produce stillbirth in experimental animals.

Sex Ratio

Although a number of small studies have found a slight, usually statistically nonsignificant, increase in the proportion of female infants born to smokers, the three largest studies of Underwood, et al. (48,505 pregnancies), Butler (15,791 pregnancies), and MacMahon (12,155 pregnancies) have found similar infant sex ratios among both smoking and nonsmoking mothers, with the expected slight excess of males among each (table 5).

Summary

Available evidence strongly indicates that maternal cigarette smoking does not influence the sex ratio of newborn infants.

TABLE 5.—*Proportion of male infants delivered to smoking and nonsmoking mothers*

Author, reference	Pregnancies	Proportion of male infants		Statistical significance
		Smokers	Nonsmokers	
Underwood, et al. (*100*)	48, 505	.518	.519	None.
Butler and Alberman (*14*)	15, 791	.518	.516	Do.
MacMahon, et al. (*49*)	12, 155	.513	.512	Do.
Kullander and Källen (*43*)	6, 363	.515	.501	Do.
Reinke and Henderson [1] (*78*)	3, 156	.498	.517	Do.
Frazier, et al.[1] (*26*)	2, 915	.472	.505	Do.
				(P>0.05)
Kizer (*42*)	2, 095	.502	.493	None.
Herriott, et al. (*36*)	2, 745	.492	.517	Do.
Ravenholt, et al (*77*)	2, 052	.501	.533	P<0.05
Lowe (*46*)	2, 042	.532	.529	None.
Russell, et al. (*83*)	2, 002	.513	.512	Do.

[1] Black women.

Congenital Malformations

Previous epidemiological studies which examined the relationship between cigarette smoking and congenital malformations were reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*). Recently, the authors of the Ontario Perinatal Mortality Study (*66*, *67*), a retrospective study of 51,490 births, reported no difference in malformation rate for the infants of smokers and nonsmokers. The various studies of the association between cigarette smoking and congenital malformation have differed significantly with regard to study design, the type of population sampled, sample size and number of infants with malformations, the definition of malformation, and results (table 6).

Previous experimental work was reviewed in the 1971 and 1972 reports on the health consequences of smoking (*101*, *102*). The chick embryo has been employed in recent studies. The direct application of nicotine to the embryo results in cephalic hematomas (*26*), malformations of the cervical vertebrae (*93*), and anomalies of the heart (*27*), depending upon dose of nicotine and period of incubation in which exposure occurs. Anomalies of the limbs of chicken embryos can also be induced by exposure of the egg to high levels of carbon monoxide (*4*).