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## **Introduction**

Cigarette smoking is a common habit among women of child-bearing age in the United States. In 1970, approximately one-third of American women of child-bearing age were cigarette smokers. The percentage of U.S. women who smoked throughout pregnancy is not definitely known, but is presumably lower, probably in the neighborhood of 20 to 25 percent. With a large fetal population at potential, but preventable, risk, the relationship between cigarette smoking and the outcome of pregnancy has been the focus of considerable and continuing research.

Every investigator who has examined the relationship has confirmed that the infants of women who smoke during pregnancy have a lower average birth weight than the infants of women who do not smoke during pregnancy. Much evidence indicates that cigarette smoking during pregnancy causes this reduction in infant birth weight. Several investigators have demonstrated that the fetal and neonatal mortality rate is significantly higher for the infants of smokers than for the infants of nonsmokers; other investigators have not found higher mortality for smokers' infants. Studies of the association between maternal cigarette smoking and congenital malformations have produced conflicting results.

The following is a review of work previously reported and recent studies which bear on the relationships between cigarette smoking and different outcomes of pregnancy. In addition, the chapter includes a review of the relationship between cigarette smoking and lactation.

## **Smoking and Birth Weight**

### *Epidemiological Studies*

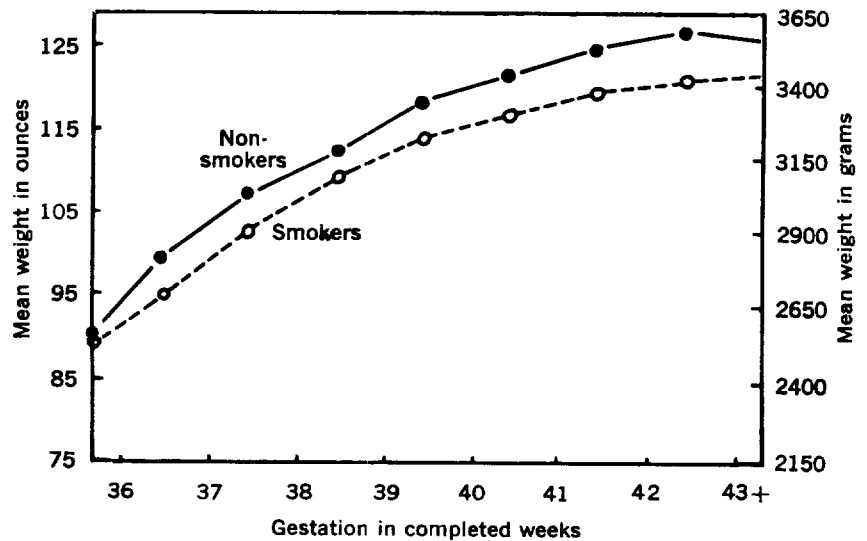
#### **CIGARETTE SMOKING AND THE LOW-BIRTH-WEIGHT INFANT**

In 1957, Simpson (90), using a retrospective study design, determined that among 7,499 women in San Bernardino County, Calif., the delivery of infants weighing less than 2,500 grams was nearly twice as

frequent among cigarette smokers as among nonsmokers. Subsequently, Lowe (46) studied 2,042 women in Birmingham, England, and demonstrated in his retrospective study that the infants of smoking mothers were delivered only slightly earlier (1.4 days on the average) than those of nonsmokers. He further noted that for gestations of 260 days and over, the infants of smokers were consistently lighter in weight during each week of gestation than those of the nonsmokers. This finding has been confirmed since, and figure 1 from the British Perinatal Mortality Study (13) provides illustration of this relationship.

Given the nearly constant disparity present between the birth weights of the infants of smokers and nonsmokers for gestations of 260 days and over, but absent prior to that time, and given the similar birth weights of infants of nonsmokers and of women who gave up smoking early in pregnancy and did not begin to smoke again, Lowe inferred that the influence of smoking upon birth weight might lie mainly in the later months of pregnancy. He emphasized the tentative nature of this conclusion, since the number of infants with a gestation of less than 260 days and the number of women who gave up smoking early in the pregnancy and did not begin to smoke again were both small.

Figure 1.—Mean birth weight for week of gestation according to maternal smoking habit: control week singletons.<sup>1</sup>



<sup>1</sup> This term refers to singleton births in England, Scotland, and Wales occurring during the week of March 3-9, 1958, which are included in the Perinatal Mortality Survey. These comprise 97 percent of all births notified in England and Wales or registered in Scotland during this week.

SOURCE: Butler, N. R., Alberman, E. D. (13).

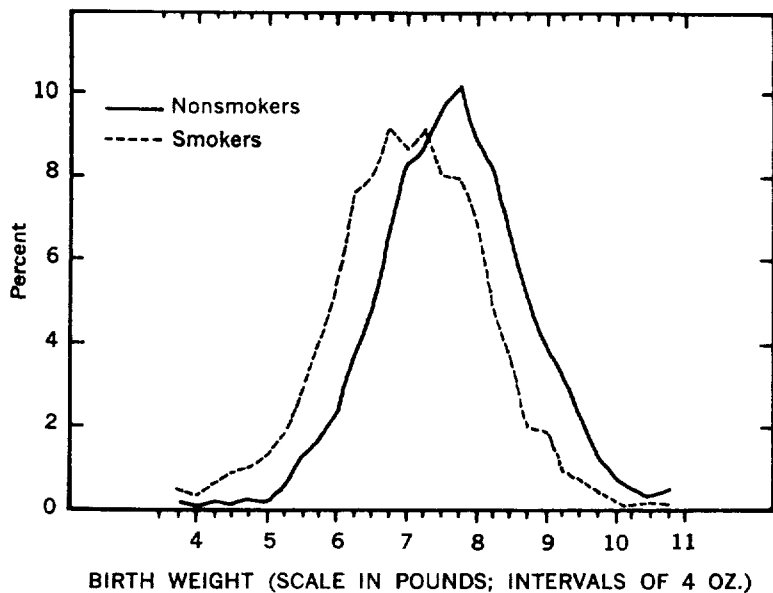
Lowe found that the infants whose mothers smoked throughout pregnancy weighed, on the average, 170 grams less than those whose mothers did not smoke. In addition, he noted that the entire distribution of weights of infants of smokers was shifted to the left (toward lower weights) relative to that for the infants of nonsmokers. This finding, too, has been confirmed by other investigators. Figure 2 offers an illustration from MacMahon, et al. (49).

Given that the infants of smokers and nonsmokers differed only slightly with respect to the duration of gestation. Lowe concluded that the lower birth weight of smokers' infants must be attributed to a direct retardation of fetal growth. In other words, on the basis of his data, the infants of smokers were small-for-dates rather than truly premature.

Many investigators have subsequently confirmed this point (12, 14, 25, 35, 65, 78, 85, 113). Buncher (12), in a study of 49,897 births among U.S. naval wives, in the same population studied by Underwood, et al. (100), found that the infants of smokers were, on the average, delivered only 1 day earlier than those of nonsmokers. This finding accounted for only 10 percent of the discrepancy in birth weight between the two groups of infants. The remainder of the studies resulted in the detection of either similar variations in gestational length or no average difference. In a recent study, Mulcahy and Murphy (56),

Figure 2.—Percentage distribution by birth weight of infants of mothers who did not smoke during pregnancy and of those who smoked 1 pack of cigarettes or more per day.

INFANT WEIGHT AND PARENTAL SMOKING HABITS



SOURCE: MacMahon, et al. (49).

in a sample of 5,099 Irish mothers, concluded that although the babies born to cigarette smokers were delivered slightly earlier than those of nonsmokers, independent of age and parity, the direct effect of smoking in retarding fetal growth was more significant.

The following points, based upon the results from many different studies, can be made about the relationship between cigarette smoking during pregnancy and lower infant birth weight :

1. Women who smoke cigarettes during pregnancy have a higher proportion of low-birth-weight infants than do nonsmokers. This excess of low-birth-weight infants among cigarette smokers predominantly consists of infants who are small-for-gestational age rather than gestationally premature.
2. The entire distribution of birth weights of the infants of cigarette smokers is shifted toward lower weights compared to the birth weights of the infants of nonsmokers.
3. The birth weights of the infants of cigarette smokers are consistently lighter than those of the infants of nonsmokers when the birth weights of the two sets of infants are compared within groups of similar gestational age beyond the 36th week of gestation.

The results of the studies which have been considered so far identify a relationship between cigarette smoking and lower infant birth weight and illustrate some aspects of that relationship, but do not indicate whether the association is causal or indirect. The succeeding two sections of this chapter contain evaluations of the available evidence which bears upon the nature of the association between cigarette smoking during pregnancy and the incidence of small-for-dates infants.

#### EVIDENCE FOR A CAUSAL ASSOCIATION BETWEEN CIGARETTE SMOKING AND SMALL-FOR-DATES INFANTS

Evidence previously reviewed in the 1971 and 1972 reports on the health consequences of smoking (101, 102) suggests that cigarette smoking is causally associated with the delivery of small-for-dates infants. The following is a summary of this evidence :

1. The results from all 30 studies in which the relationship between smoking and birth weight was examined have demonstrated a strong association between maternal cigarette smoking and delivery of low-birth-weight infants. On the average, the smoker has nearly twice the risk of delivering a low-birth-weight infant as that of a nonsmoker

(3, 13, 17, 20, 25, 29, 35, 42, 43, 46, 47, 49, 57, 58, 59, 65, 70, 72, 73, 77, 78, 80, 83, 85, 90, 95, 99, 100, 113, 118).

2. The strong association between cigarette smoking and the delivery of small-for-dates infants first demonstrated with results from studies of retrospective design (3, 13, 17, 35, 46, 47, 49, 57, 58, 59, 65, 70, 72, 73, 77, 80, 85, 90, 95, 99, 100, 118) has been repeatedly confirmed subsequently by data from studies of prospective design (20, 25, 29, 42, 43, 78, 83, 113).

3. A strong dose-response relationship has been established between cigarette smoking and the incidence of low-birth-weight infants (25, 43, 46, 49, 100, 113).

4. When a variety of known or suspected factors which also exert an influence upon birth weight have been controlled for, cigarette smoking has always been shown to be independently related to low birth weight (1, 13, 25, 43, 46, 73, 78, 83).

5. The association has been demonstrated in many different countries, among different races and cultures, and in different geographical settings (13, 17, 25, 29, 36, 42, 43, 59, 73, 78, 80, 113).

6. Previous smoking does not appear to influence birth weight if the mother gives up the habit prior to the start of her pregnancy (25, 46, 49, 113).

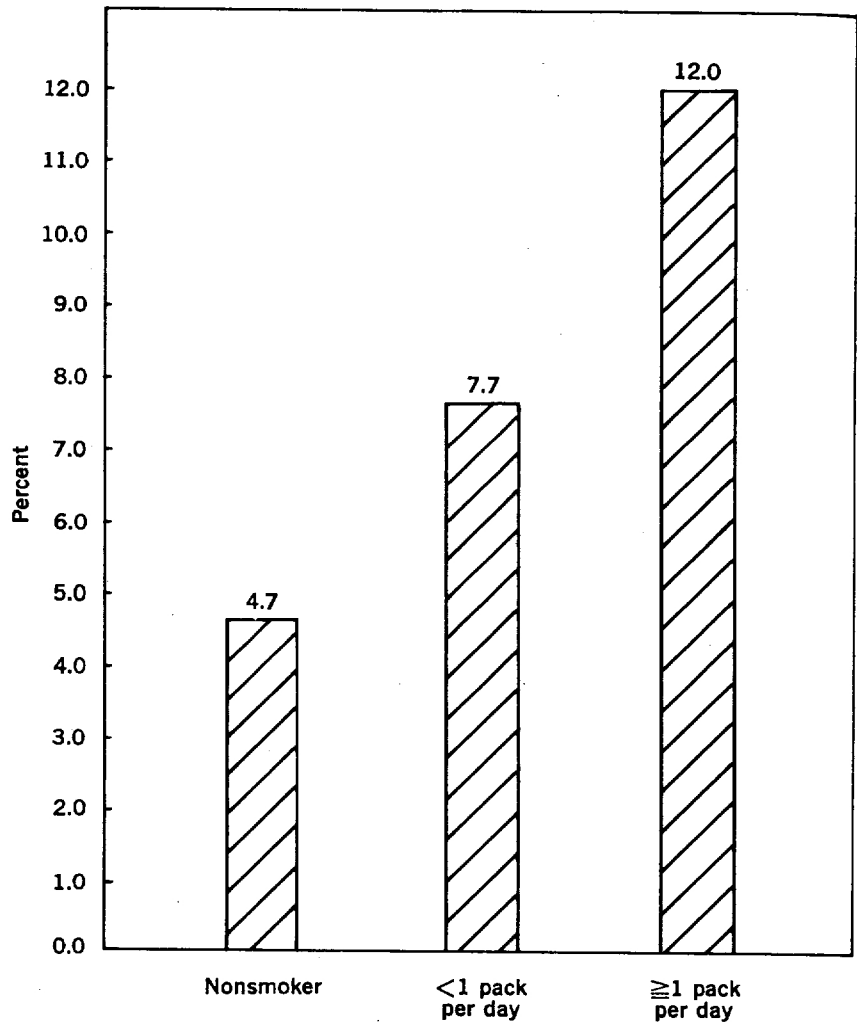
7. The infants of smokers experience an accelerated growth rate during the first 6 months after delivery, compared to infants of nonsmokers. This finding is compatible with viewing birth as the removal of the smoker's infant from a toxic influence (83).

8. Data from experiments in animals have documented that exposure to tobacco smoke or some of its ingredients results in the delivery of low-birth-weight offspring (7, 8, 9, 23, 40, 87, 117).

Several recently published studies have provided additional supporting evidence for a causal relationship between cigarette smoking and small-for-dates infants. The Ontario Perinatal Mortality Study (66) was conducted among 10 teaching hospitals during 1960 and 1961. The authors of this retrospective study of 50,267 births demonstrated a significant excess of infants weighing less than 2,500 grams among cigarette smokers as compared with nonsmokers ( $P < 0.001$ ). Smoking was significantly dose-related to the percentage of pregnancies terminating in the delivery of a low-birth-weight infant (fig. 3).

Niswander and Gordon (63) have recently reported data from the Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. In this prospective study of 39,200 pregnancies, which were nearly equally divided among black and white women, the authors found a significant dose-related excess of low-birth-weight infants among smokers of both groups, compared to nonsmokers of the same race.

Figure 3.—Percentage of pregnancies with infant weighing less than 2,500 grams, by cigarette smoking category.



Number of infants weighing <2,500 grams:	1,322	1,186	793
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Total births:	28,358	15,328	6,581
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(P < 0.001)

SOURCE: Ontario Department of Health (66).

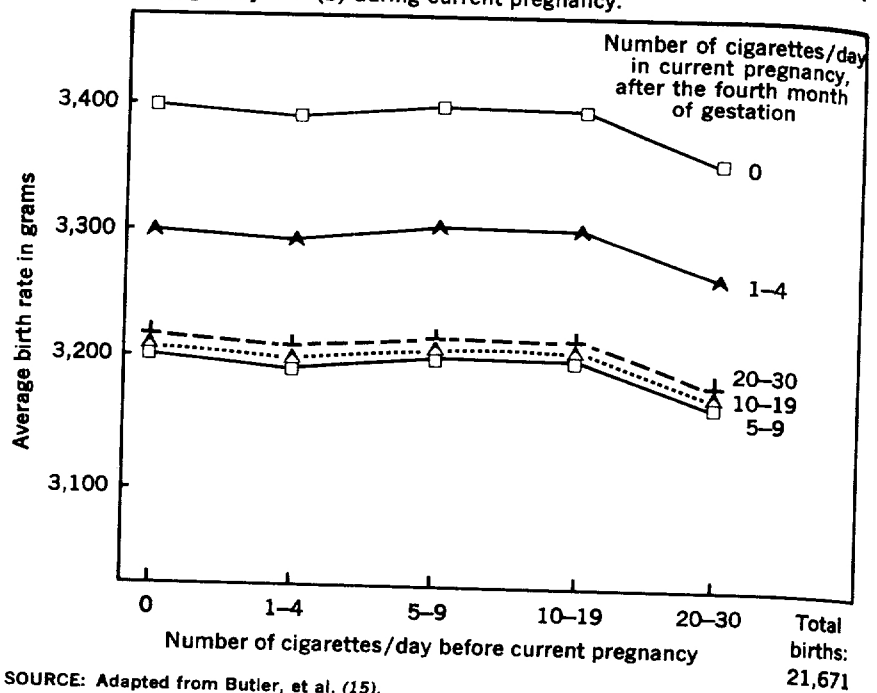
Rantakallio (76) carried out a prospective study of 11,905 single births in Finland. Cigarette smoking mothers had significantly more infants weighing less than 2,500 grams than did nonsmokers ( $P < 0.001$ ).

Rush and Kass (82), in a prospective study of 1,040 pregnancies in Boston, Massachusetts; Domagala, et al. (19), in a retrospective study of 1,832 pregnancies in Poland; and Mukherjee and Mukherjee (54), in a retrospective study of 2,886 pregnancies in India, each found a significantly higher incidence of low-birth-weight infants among cigarette smokers.

Butler, et al. (15) have further analyzed the British Perinatal Mortality Study data. Analysis of the 16,994 questionnaires revealed that 40.8 percent of the women were cigarette smokers before pregnancy. After the fourth month, this percentage had decreased to 27.4 percent. Given the large number of women in the study, and the significant changes in smoking behavior which occurred, Butler, et al. found it possible to consider the effect of a change in smoking behavior on birth weight between the beginning of the pregnancy and the fourth month (after which smoking behavior was reportedly stable). The authors stated, "If smoking itself (rather than the type of woman who smokes) has a deleterious effect on the fetus, it would be reasonable to expect the mothers who gave up smoking during pregnancy to show differences in the birth weight and perinatal mortality of their offspring compared with those who continued to smoke." Their results are presented in figure 4. The birth weights by smoking categories were estimated by using a main effect model without mediating variables. However, the authors reported that when the mediating variables (social class, maternal age, parity, maternal height, sex of infant, gestational age, and perinatal mortality) were allowed for, the results of the analysis were very similar. The effect of cigarette smoking before pregnancy was insignificant compared to that of smoking regularly after the fourth month of gestation. The authors concluded, "The finding that a change in maternal smoking habits during pregnancy had the effect of putting the baby into a birth weight and perinatal mortality category associated with the new smoking habits points toward some kind of cause-effect relationship. \* \* \* This finding is further strengthened by the birth weight analysis which shows that the diminution in birth weight of the offspring of smoking mothers persists and is indeed little changed when allowance has been made for a number of other social and obstetric mediating factors."



Figure 4.—Average birth weight by maternal smoking habit (a) before current pregnancy and (b) during current pregnancy.



SOURCE: Adapted from Butler, et al. (15).

#### EVIDENCE FOR AN INDIRECT ASSOCIATION BETWEEN CIGARETTE SMOKING AND SMALL-FOR-DATES INFANTS

Yerushalmy (113, 114, 115) has suggested that smoking is an index to a particular type of reproductive outcome and thus does not play a causal role in the production of small-for-dates infants. He has developed several lines of support for this hypothesis, from an analysis of data from the prospective investigation of 13,083 mothers in the Oakland Child Health and Development Study. He has emphasized that ineffective randomization and the phenomenon of self-selection complicate the development of appropriate inferences with regard to causality. Such difficulties do not prevent the identification of causal associations, but they demand careful and critical analysis of the data. Yerushalmy has questioned the causal nature of the relationship between cigarette smoking and small-for-dates infants because of: (a) The relationship between the smoking habit of the father and low birth weight of the infant, (b) behavioral differences between smokers and nonsmokers, and (c) comparison of the birth weights

of a woman's infants born during the periods when she smoked cigarettes and when she did not.

Yerushalmy (114) has stated that the smoking habit of the father could not reasonably be related to the birth weight of the infant. From preliminary data derived from the study, however, he determined that there was an increased incidence of low-birth-weight infants when the fathers smoked and, moreover, there was an apparent dose-response relationship as found for maternal smoking. However, he noted that only when both the husband and the wife smoked was the incidence of low-birth-weight babies increased. He felt that these findings supported the conclusion that smoking was a marker of types of individuals and not a causal factor for low birth weight. Other investigators have since examined this relationship (49, 100), but none has confirmed an independent association for paternal smoking. The association between paternal smoking and birth weight appears to be an indirect one. Paternal and maternal smoking behavior are highly correlated and maternal smoking is strongly related to infant birth weight. Underwood, et al. (100) studied 48,505 women, their husbands' smoking behavior, and the relation with birth weight (table 1). If the mother was a nonsmoker, then the father's smoking had no influence on the birth weight of the infant.

TABLE 1.—*Infant birth weight by maternal and paternal smoking habits*

Cigarettes per day	Mothers			Fathers (nonsmoking mothers)		
	Number	Birthweight (grams)		Number	Birthweight (grams)	
		Mean	Difference <sup>1</sup>		Mean	Difference <sup>1</sup>
None	24,865	3,395	0	9,547	3,396	0
1 to 10	7,609	3,286	109	3,493	3,389	7
11 to 30	14,450	3,196	199	10,403	3,391	5
>30	1,570	3,182	213	1,330	3,393	3

<sup>1</sup> Nonsmoker minus smoker.

Source: Underwood, et al. (100).

Yerushalmy (115) pointed out that other investigators had found marked differences between smokers and nonsmokers. In his own study, he found that nonsmokers used contraceptives significantly more frequently than did smokers. Moreover, a significantly higher proportion of smokers drank coffee, beer, and whiskey. However, he did not adjust for these variables in his analysis of the association between cigarette smoking and lower infant birth weight. Other investigators have also found differences between smokers and nonsmokers. For example, Frazier, et al. (25) found significant differences in the distribution of parity, work history, education, and psycho-

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?

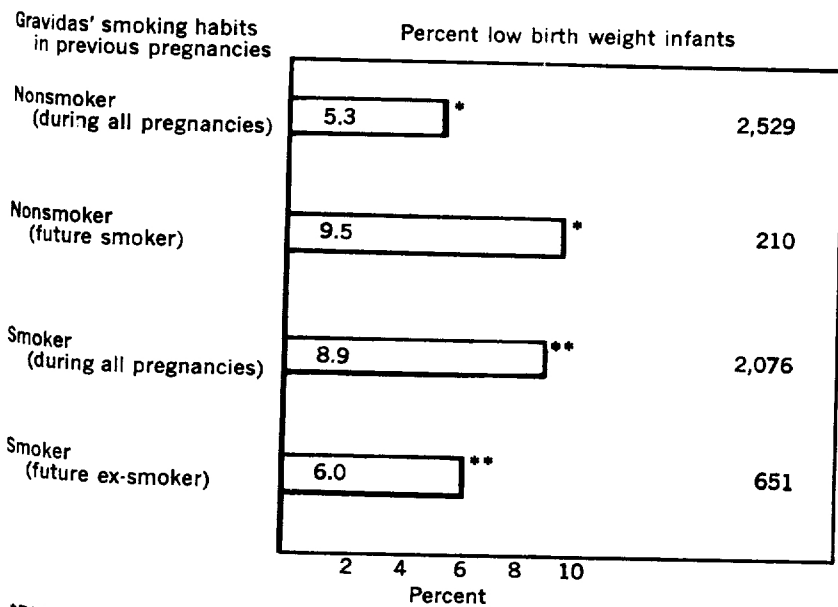
Goldstein, et al. (28), in a comprehensive review, proposed a research design in which a woman would serve as her own control to compare outcomes of pregnancies during which she smoked with those during which she did not with consideration of the effect of parity on the outcome. Yerushalmy (112) has 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<sup>14</sup>-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  $\mu$ g./kg. over

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 (?). 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. (8).

### *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  $(\text{COHb})_F$  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  $(\text{COHb})_M$  and  $(\text{COHb})_F$  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<sub>12</sub> and Cyanide Detoxification

McGarry and Andrews (48) determined serum vitamin B<sub>12</sub> 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<sub>12</sub>. They also found a direct, statistically significant dose-response relationship between cigarettes smoked and serum vitamin B<sub>12</sub> level. They again confirmed the relationship between smoking and low birth weight. The authors suggested that the lowered vitamin B<sub>12</sub> 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<sub>12</sub> 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 non-smokers. 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-weight 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.

### *Birth Weight Summary*

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 to 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.