vitamin B_{12} levels reflect a disorder of cyanide detoxification. Cyanide is a demonstrable ingredient in cigarette smoke (*83, 132, 134, 138, 144, 153, 176*).

Vitamin C

Venulet and Danysz (*195, 196*) have 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.

Research Issues

Nutrients and oxygen provided by the maternal circulation are essential to normal fetal growth and development. It may be anticipated that some alterations may be produced in the developing fetus when the nutrients are accompanied by toxins in the inhaled smoke of burning tobacco and paper and when carbon monoxide is mixed with the oxygen. Some of the observed alterations may be considered innocuous in themselves, but the evidence to date justifies high priority investigation to determine whether they are indicators of processes that are fundamentally dangerous to either the immediate or long-term health of the fetus and the child.

A number of important questions relating to the possible biological effects of tobacco smoke and its constituents on the fetus *in utero* and the newborn infant remain unanswered. The ethical issue of experiments in pregnant human subjects and newborn infants affects further research. The problems of such studies are obvious but will not be resolved in the foreseeable future. Mathematical models, while useful, require considerable data based on human or animal studies. Models, in addition, possess serious limitations and restrictions because any mathematical abstraction encompasses only a very minute portion of the finite world or a given problem. Thus, future progress in our understanding of the effects of tobacco products in these areas of investigation will require appropriate animal studies with extrapolation to humans.

The research objectives are (1) to identify risk of perinatal loss or damage in women who smoke during pregnancy, and (2) to define the effects on the fetus and the new-born infant resulting from maternally-inhaled tobacco smoke.

In considering the epidemiologic, biologic, and pharmacologic facets of the problem of cigarette smoking and its impact on fetal and infant well-being, the following areas of study are suggested:

Fetal Death

1. Do available data sets confirm the evidence that maternal smoking may lead to anoxic death *in utero* of a normal fetus in an uncomplicated pregnancy?

2. Can the risk of such a death be calculated in terms of the mother's capacity to offset the hypoxic stress of smoking by such mechanisms as increasing hemoglobin or hematocrit; increasing cardiac output; increasing placental ratio, surface area, and area of attachment; or by other mechanisms?

3. Are there indications in existing data sets that anoxic fetal deaths occurred in smoking mothers with, for example, anemia, poor cardiac function, poor pulmonary function, poor general health, unfavorable age (older), or low socioeconomic status?

4. Do these deaths occur more frequently in mothers who, besides being heavy smokers, are anemic or live at high altitudes?

5. Do these deaths occur later in pregnancy when there is less reserve capacity to supply oxygen because of the greater oxygen demand of the larger fetus, the reduction of the placental ratio, and the reaching of the natural limits of increase of hematocrit and cardiac output?

6. Can pregnant women at particular risk of anoxic fetal death if they smoke be identified prospectively by measurement of exhaled CO and carboxyhemoglobin, relating these levels to hematocrit, cardiac output, and other tests of reserve capacity to increase oxygen supply to the fetus?

7. Can pregnant women at particular risk of anoxic fetal death if they smoke be identified by use of exercise testing during prenatal care?

8. Do available data sets confirm the evidence that maternal smoking during pregnancy causes fetal death by increasing the incidence of abruptio placentae, other antepartum bleeding, and related complications?

9. Do available data sets confirm the evidence that the above complications occur more frequently among women with other risk factors such as low socioeconomic status, older age, higher parity, unfavorable previous pregnancy history, and more frequently the more the mother smokes?

10. Are the higher incidences of placental complications and fetal deaths among women who smoke due to poorer diet and lower levels of vitamin C, vitamin B_{12}, folic acid, and other substances that help to maintain tissue integrity?

11. Is there a relationship between the increased incidence of vaginal bleeding in the above cases and the pathological changes in placental blood vessels from smoking women observed by Asmussen?

12. If there is a generalized effect of smoking on the integrity of blood vessel linings and other tissues, what role does this play in the bleeding and abruptio placentae observed in such cases?

13. Can fetal death associated with maternal smoking and placental complications be predicted by careful monitoring of any pregnancy with signs of bleeding after 20 weeks of pregnancy?

14. Can these deaths be prevented by cessation of smoking, supplements of vitamins and folic acid, and other treatment to maintain fetal oxygenation?

Neonatal Death

15. Do available data sets confirm the evidence that maternal smoking leads to neonatal death of otherwise normal babies by increasing the occurrence of preterm birth?

16. What proportion of preterm deliveries of smoking mothers is associated with a history of bleeding early in pregnancy?

17. What proportion of preterm deliveries of smoking mothers is associated with premature rupture of membranes?

18. What is the relationship of maternal smoking to the incidence of bleeding early in pregnancy and of premature rupture of membranes, whether or not there is a preterm delivery and whether or not there is a fetal or neonatal death?

19. Through investigation of characteristics such as age, parity, socioeconomic status, and reproductive history, is it possible to identify women who will be at particularly high risk of pregnancy complications and pregnancy loss if they smoke?

20. Besides the warning sign of bleeding, what other measurements will help to identify the woman who must stop smoking in order to maintain the pregnancy?

21. Will measurement of levels of carboxyhemoglobin, vitamin C, vitamin B_{12}, folic acid, and other indices help to elucidate the mechanisms leading to bleeding and to premature rupture of membranes among smoking mothers?

22. Is there evidence that the tensile strength of fetal membranes is reduced if the mother smokes?

23. Is there evidence that amniotic fluid infection plays a part in the smoking-related increase in the incidence of premature rupture of the membranes?

24. Will elucidation of the mechanisms whereby maternal smoking causes complications of pregnancy, early delivery, and neonatal death help to persuade pregnant women to stop smoking—particularly if they have bleeding early or late in pregnancy—and to persuade obstetricians that cessation of maternal smoking is of crucial importance for a successful pregnancy?

25. Will monitoring of exhaled CO levels in all prenatal care clinics help to reverse the recent trend toward more frequent and heavier smoking among young women?

Spontaneous Abortion

26. Can the increased incidence of spontaneous abortion with maternal smoking be confirmed by further studies, allowing for measurement of dose-response relationships and an accurate estimate of risk ratios?

27. Can the mechanisms of action be worked out, using the same approach as has been done for perinatal mortality?

28. To what extent is a previous spontaneous abortion in a smoker related to a subsequent unfavorable outcome of pregnancy if the woman continues to smoke?

29. Is there an overall increase in the risk of spontaneous abortion as a result of maternal smoking, or is the increased risk confined to women already at risk for other reasons?

Preeclampsia

30. What is the mechanism linking smoking during pregnancy to a reduced incidence of preeclampsia and toxemia?

31. Could components of this mechanism, if understood, be applied so that the risk of preeclampsia could be reduced without incurring the risks associated with smoking?

Sudden Infant Death Syndrome

32. Do existing data sets with postnatal follow-up confirm the association of maternal smoking with an increased risk of SIDS?

33. Do the smoking mothers of SIDS victims have other signs of impairment of their oxygen supply system such as anemia, heart trouble, impaired pulmonary function, or high altitude residence, as indicated in prenatal records?

34. Do the smoking mothers of SIDS victims have early or late bleeding, premature rupture of the membranes, abruptio placentae, or preterm delivery?

Long-Term Follow-Up

35. Can studies with long-term follow-up of growth and development identify groups with smoking-related impairment of a serious nature as opposed to very slight changes in overall means?

36. Could case-control studies using prospective long-term follow-up data (such as that from the British Perinatal Mortality Study) identify maternal smoking patterns and other prenatal factors associated with the problems of physical, intellectual, and emotional development of the children?

Birth Weight and Placenta

37. To what extent does the reduction of birth weight of smokers' babies represent a physiological adaptation to reduced oxygen availability?

38. What are the combined effects on birth weight of maternal smoking, anemia, and high altitude?

39. What are the combined effects of maternal smoking, anemia, and high altitude on weight, shape, area and site of attachment, and placental-fetal ratio?

40. How are these relationships affected by other maternal antecedent factors, such as age, socioeconomic status, and previous history?

41. Is the increased incidence of placenta previa with maternal smoking and high altitude related to an adaptive increase in the placental site of attachment?

42. To what extent do placental changes with maternal smoking represent physiological adaptations to hypoxic and other stresses?

43. To what extent do placental changes represent pathological effects of smoking and what is their role in unfavorable pregnancy outcomes?

Experimental Studies

44. Can experimental studies of exposure to cigarette smoke or to the components of cigarette smoke elucidate the mechanism of reduced birth weight?

45. Is the smoking-associated reduction of fetal growth due to a reduction in the rate of mitosis resulting in a decreased number of cells?

46. Is the smoking-associated reduction of fetal growth rate due to a decreased number of cells in some parts of the body but not in others?

47. Is the smoking-associated reduction of fetal growth rate accompanied by deficiencies in learning ability, emotional development, or physical growth?

Lactation and Breast Feeding

48. Does smoking inhibit milk production in humans? This question could be approached through epidemiological and experimental studies. Surveys of a large population of smoking and nonsmoking women are desirable to correlate the number of cigarettes consumed and the pattern of smoking with the amount of milk produced and the concentration of nicotine and other constituents of smoke in milk throughout the lactation cycle.

49. How does nicotine affect prolactin release, and can this phenomenon be reversed? Appropriate experimental animal research

could provide the basis for understanding mechanism(s) of action and the mapping of appropriate interventions.

50. How much nicotine is excreted in breast milk ingested by the nursing infant? A well-planned pharmacokinetic study should be done involving the mother-infant dyad.

51. Is it possible to determine the complete profile of other components of cigarette smoke in breast milk? The answer to this question will permit the identification of potential carcinogenic agents and their degree of ingestion by the infants.

52. Does the interaction between nicotine and other drugs excreted in breast milk affect the physiology of the infants? The presence of DDT and benzo(*a*)pyrene, inducers of the activity of drug-metabolizing enzymes, may cause unexpected, subtle side effects in the growing infant which may manifest at a later date.

Tobacco Smoke

53. To what extent does maternal smoking in humans affect maternal and fetal blood catecholamine concentrations?

54. To what extent does maternal smoking affect uterine and placental blood flow?

55. To what extent does maternal smoking affect fetal heart rate, breathing pattern, electroencephalographic activity, or other parameters that can be monitored (that is, dose-response relationships)?

56. To what extent does smoking marijuana differ in its effects on the mother and fetus as compared with smoking tobacco in cigarettes?

57. To what extent are there interactions between the effects of the major (and perhaps minor) components of tobacco smoke?

58. How can efforts to actively discourage smoking during pregnancy be made more effective?

59. To what extent will smoking withdrawal during pregnancy result in changes in infant weight, perinatal mortality, and long-term sequelae?

Nicotine

60. How does nicotine affect ganglionic development in the embryo and fetus?

61. What is the relationship between development of essential hypertension and nicotine imprint on fetal development?

62. Does nicotine accumulation in the fetal adrenal glands, heart, and kidneys modify development of these organs?

63. What is the effect of nicotine on the hormonal systems of the adrenal and those organs regulating adrenal function?

64. To what extent is nicotine accumulation in the fetal kidney involved in a possible antidiuretic hormone abnormality or other complications in later development?

65. What factors are involved in prolonging gestational length in laboratory animals?

66. Since nicotine modulates neurological function in adults at several areas (central nervous system, skeletal-muscular, ganglia, and so forth), how does it modify development and function?

67. To what extent does the effect of nicotine on neurological function contribute to hyperkinetic syndrome in children?

68. What is the potential for nicotine metabolites being carcinogenic in combination with benzo(*a*)pyrene?

Carbon Monoxide

69. To what extent are embryonic, fetal, or newborn tissues more or less sensitive to the effects of carbon monoxide than those of adults?

70. How does exposure to carbon monoxide physiologically affect the developing fetus or newborn?

71. To what extent do dose-response relationships exist for various carboxyhemoglobin concentrations?

72. Does a "threshold" level result in adverse effects?

73. Does the fetus adapt to low CO concentrations, and if so, by what mechanism?

74. To what extent does CO affect oxygen consumption by the fetus or by individual organs?

75. How does the decrease in blood oxygen tension physiologically affect oxygen availability to the fetal brain, heart, and other vital organs?

76. To what extent do decreases in the mean partial pressures of capillary oxygen affect cellular respiration?

77. How does increased carboxyhemoglobin concentration affect tissue oxygenation?

78. To what extent are the patterns of growth, development, and maturation of the central nervous system and other organ systems interrelated and affected by chronic low-level carbon monoxide exposure?

79. How does carbon monoxide affect developing neuroblasts?

80. To what extent does carbon monoxide increase the risk of prematurity or adversely affect the rate of infant growth?

81. To what extent does the interference with fetal oxygenation result in problems such as mental retardation, cerebral palsy, and perhaps subclinical neurologic, intellectual, or behavioral deficits?

82. Can modifications significantly decrease carbon monoxide levels in tobacco smoke?

83. Do the carbon monoxide concentrations encountered in association with maternal smoking adversely affect the infant's physical or psychomotor development?

84. What are the legal and regulatory considerations concerning the maximum carbon monoxide exposure allowed for pregnant women and newborn infants?

Polycyclic Hydrocarbons

85. To what extent does benzo(*a*)pyrene cross the placenta and enter the fetus?

86. What is its distribution in the fetal organs and tissues?

87. To what extent do the benzo(*a*)pyrene concentrations encountered in smoking mothers affect the growth and development of the fetal brain and other organs?

88. To what extent does benzo(*a*)pyrene have long term effects on the developing embryo and fetus; that is, to what extent are fetuses so exposed subject to the later development of neoplasms or malignancies?

Pregnancy and Infant Health: References

(1) ABERNATHY, J.R., GREENBERG, B.G., WELLS, H.B., FRAZIER, T.M. Smoking as an independent variable in a multiple regression analysis upon birth weight and gestation. American Journal of Public Health and the Nation's Health 56(4): 626-633, April 1966.

(2) ANDREWS, J., MCGARRY, J.M. A community study of smoking in pregnancy. Journal of Obstetrics and Gynaecology of the British Commonwealth 79(12): 1057-1073, December 1972.

(3) ASMUSSEN, I. Ultrastructure of the human placenta at term. Observations on placentas from newborn children of smoking and nonsmoking mothers. Acta Obstetrica et Gynecologica Scandinavica 56: 119-126, 1977.

(4) ASMUSSEN, I., KJELDSEN, K. Intimal ultrastructure of human umbilical arteries. Observations on arteries from newborn children of smoking and nonsmoking mothers. Circulation Research 36(5): 579-589, May 1975.

(5) ASTRUP, P., OLSEN, H.M., TROLLE, D., KJELDSEN, K. Effect of moderate carbon-monoxide exposure on fetal development. Lancet 2: 1220-1222, December 9, 1972.

(6) AYRES, S.M., GIANNELLI, S., JR., MUELLER, H. Myocardial and systemic responses to carboxyhemoglobin. Annals of the New York Academy of Sciences 174: 268-293, October 1970.

(7) BAILEY, R.R. The effect of maternal smoking on the infant birth weight. New Zealand Medical Journal 71(456): 293-294, May 1971.

(8) BAIRD, D. The epidemiology of prematurity. Journal of Pediatrics 65:(6) Part 1: 909-924, December 1964.

(9) BALLANTYNE, J.W. Manual of Antenatal Pathology and Hygiene. The Fetus. Edinburgh, William Green and Sons, 1902, p. 272.

(10) BARTLETT, D., JR. Pathophysiology of exposure to low concentrations of carbon monoxide. Archives of Environmental Health 16: 719-727, May 1968.

(11) BECKER, R.F., KING, J.E. Studies on nicotine absorption during pregnancy. II. The effects of acute heavy doses on mother and neonates. American Journal of Obstetrics and Gynecology 95(4): 515-522, June 15, 1966.

(12) BECKER, R.F., LITTLE, C.R.D., KING, J.E. Experimental studies on nicotine absorption in rats during pregnancy. III. Effect of subcutaneous injection of small chronic doses upon mother, fetus, and neonate. American Journal of Obstetrics and Gynecology 100(7): 957-968, April 1, 1968.

(13) BECKER, R.F., MARTIN, J.C. Vital effects of chronic nicotine absorption and chronic hypoxic stress during pregnancy and the nursing period. American Journal of Obstetrics and Gynecology 110(4): 522-533, June 15, 1971.

(14) BEISCHER, N.A. The effects of maternal anemia upon the fetus. Journal of Reproductive Medicine 6(6): 21-24, June 1971.

(15) BERGMAN, A.B., WIESNER, L.A. Relationship of passive cigarette-smoking to sudden infant death syndrome. Pediatrics 58(5): 665-668, November 1976.

(16) BISDOM, C.J.W. Alcohol en nicotinever giftigung bij zuigelingen (Alcohol and nicotine poisoning in infants (sucklings)). Maandscrift voor Kindergeneeskunde 6: 332-341, 1937.

(17) BLAKE, C.A., SAWYER, C.H. Nicotine blocks the suckling-induced rise in circulating prolactin in lactating rats. Science 177(4049): 619-621, August 18, 1972.

(18) BRADT, P.T., HERRENKOHL, R.C. DDT in human milk. What determines the levels? Science of the Total Environment 6(2): 161-163, September 1976.

(19) BUNCHER, C.R. Cigarette smoking and duration of pregnancy. American Journal of Obstetrics and Gynecology 103(7): 942-946, April 1, 1969.

(20) BUTLER, N.R., ALBERMAN, E.D. (Editors). Perinatal Problems. The Second Report of the 1958 British Perinatal Mortality Survey. London, E. and S. Livingston, Ltd., 1969, pp. 36-84.

(21) BUTLER, N.R., GOLDSTEIN, H. Smoking in pregnancy and subsequent child development. British Medical Journal 4: 573-575, December 8, 1973.
(22) BUTLER, N.R., GOLDSTEIN, H., ROSS, E.M. Cigarette smoking in pregnancy: Its influence on birth weight and perinatal mortality. British Medical Journal 2: 127-130, April 15, 1972.
(23) CAMPBELL, A.M. The effect of excessive cigaret smoking on maternal health. American Journal of Obstetrics and Gynecology 31: 502-508, 1936.
(24) CAMPBELL, A.M. Excessive cigarette smoking in women and its effect upon their reproductive efficiency. Journal of the Michigan Medical Society 34: 146-151, March 1935.
(25) CLOEREN, S.E., LIPPERT, T.H., FRIDRICH, R. The influence of cigarette smoking on fetal heart rate and uteroplacental blood volume. Archiv fuer Gynaekologie 216: 15-22, 1974.
(26) COBURN, R.F. (Editor). Carbon Monoxide. Washington, D.C. National Academy of Sciences, National Research Council, Division of Medical Sciences, 1977, pp. 83-104.
(27) COLE, P.V., HAWKINS, L.H., ROBERTS, D. Smoking during pregnancy and its effects on the fetus. Journal of Obstretrics and Gynaecology of the British Commonwealth. 79(9): 782-787, September 1972.
(28) COMSTOCK, G.W., ABBEY, H., LUNDIN, F.E., JR. The nonofficial census as a basic tool for epidemiologic observations in Washington County, Maryland. In: Kessler, I.I., Levin, M.L. (Editors). The Community as an Epidemiological Laboratory. A Casebook of Community Studies. Baltimore, The Johns Hopkins Press, 1970, pp. 73-99.
(29) COMSTOCK, G.W., LUNDIN, F.E., JR. Parental smoking and perinatal mortality. American Journal of Obstetrics and Gynecology 98(5): 708-718, July 1, 1967.
(30) COMSTOCK, G.W., SHAH, F.K., MEYER, M.B., ABBEY, H. Low birth weight and neonatal mortality rate related to maternal smoking and socioeconomic status. American Journal of Obstetrics and Gynecology 111(1): 53-59, September 1, 1971.
(31) COPE, I., LANCASTER, P., STEVENS, L. Smoking in pregnancy. Medical Journal of Australia 1: 673-677, April 7, 1973.
(32) CULVER, B., NORTON, S. Juvenile hyperactivity in rats after acute exposure to carbon monoxide. Experimental Neurology 50: 80-98, 1976.
(33) DAVIE, R., BUTLER, N., GOLDSTEIN, H. From Birth to Seven. The Second Report of the National Child Development Study (1958 Cohort). London, Longman, in association with the National Children's Bureau, 1972, 198 pp.
(34) DAVIES, D.P., GRAY, O.P., ELLWOOD, P.C., ABERNETHY, M. Cigarette smoking in pregnancy: Associations with maternal weight gain and fetal growth. Lancet 1: 385-387, February 21, 1976.
(35) DE HAAS, J.H. Parental smoking: Its effects on fetus and child health. European Journal of Obstetrics Gynecology and Reproductive Biology. Excerpta Medica 5(5): 283-296, 1975.
(36) DENSON, R., NANSON, J.L., MCWATTERS, M.A. Hyperkinesis and maternal smoking. Canadian Psychiatric Association Journal 20(3): 183-187, April 1975.
(37) DOMAGALA, J., DOMAGALA, L. Zachowanie sie wagi urodzeniowej oraz czestosc wystepowania wczesniactwa I wad wrodzonych u noworodkow kobiet palacych tyton (Birth weight and incidence of prematurity and congenital anomalies in newborns of mothers smoking tobacco). Pediatria Polska T.47(6): 735-738, 1972.
(38) DONOVAN, J.W. Effect on child of maternal smoking during pregnancy. Lancet 1: 376, February 17, 1973. (Letter)

(39) DOUGLAS, C.G., HALDANE, J.S., HALDANE, J.B.S. The laws of combination of haemoglobin with carbon monoxide and oxygen. Journal of Physiology (London). 44(4): 275-304, June 12, 1912.

(40) DOW, T.G.B., ROONEY, P.J., SPENCE, M. Does anaemia increase the risks to the fetus caused by smoking in pregnancy? British Medical Journal 4(5991): 253-254, November 1, 1975.

(41) DOWNING, G.C., CHAPMAN, W.E. Smoking and pregnancy. A statistical study of 5,659 patients. California Medicine 104(3): 187, March 1966.

(42) DUFFUS, G.M., MACGILLIVRAY, I. The incidence of pre-eclamptic toxaemia in smokers and non-smokers. Lancet 1(7550): 994-995, May 11, 1968.

(43) DUNN, H.G., MCBURNEY, A.K., INGRAM, S., HUNTER, C.M. Maternal cigarette smoking during pregnancy and the child's subsequent development: I. Physical growth to the age of 6 1/2 years. Canadian Journal of Public Health 67: 499-505, November/December 1976.

(44) DUNN, H.G., MCBURNEY, A.K., INGRAM, S., HUNTER, C.M. Maternal cigarette smoking during pregnancy and the child's subsequent development: II. Neurological and intellectual maturation to the age of 6 1/2 years. Canadian Journal of Public Health 68: 43-50, January/February 1977.

(45) EMANUEL, W. Ueber das vorkommen von nicotin in der frauenmilch nach zigarettengenuss (On the presence of nicotine in breast milk following the use of cigarettes). Zeitschrift fuer Kinderheilkunde 52: 41-46, 1931.

(46) ESSENBERG, J.M., SCHWIND, J.V., PATRAS, A.R. The effects of nicotine and cigarette smoke on pregnant female albino rats and their offsprings. Journal of Laboratory and Clinical Medicine 25: 708-717, 1940.

(47) FABIA, J. Cigarettes pendant la grossesse, poids de naissance et mortalite perinatale (Cigarette smoking during pregnancy, birth weight and perinatal mortality). Canadian Medical Association Journal 109: 1104-1109, December 1, 1973.

(48) FECHTER, L.D., ANNAU, Z. Toxicity of mild prenatal carbon monoxide exposure. Science 197(4304): 680-682, August 12, 1977.

(49) FEDRICK, J., ADELSTEIN, P. Factors associated with low birth weight of infants delivered at term. British Journal of Obstetrics and Gynaecology 85:(1): 1-7, January 1978.

(50) FERGUSON, B.B., WILSON, D.J., SCHAFFNER, W. Determination of nicotine concentrations in human milk. American Journal of Diseases of Children 130: 837-839, August 1976.

(51) FIELDING, J.E. Smoking and pregnancy. New England Journal of Medicine 298(6): 337-339, February 9, 1978.

(52) FISCHER, H. Kapillarschaden durch nikotin; eine experimentelle studie zur frage der pathologie des keimlings und der plazenta (Damage to the capillaries produced by nicotine; an experimental study on the pathology of the fetus and placenta). Zeitschrift fuer Geburtshilfe und Gynaekologie 149: 30-65, 1957.

(53) FORSTER, R.E. Carbon monoxide and the partial pressure of oxygen in tissue. Annals of the New York Academy of Sciences 174: 233-241, October 1970.

(54) FRAZIER, T.M., DAVIS, G.H., GOLDSTEIN, H., GOLDBERG, I.D. Cigarette smoking and prematurity: A prospective study. American Journal of Obstetrics and Gynecology 81(5): 988-996, May 1961.

(55) GARN, S.M., SHAW, H.A., MCCABE, K.D. Relative effect of smoking and other variables on size of newborn. Lancet 2(8039): 667, September 24, 1977. (Letter)

(56) GARVEY, D.J., LONGO, L.D. Chronic low level maternal carbon monoxide exposure and fetal growth and development. Biology of Reproduction 19: 8-14, 1978.

(57) GELLER, L.M. Failure of nicotine to affect development of offspring when administered to pregnant rats. Science 129: 212-214, January 23, 1959.

(58) GENNSER, G., MARSAL, K., BRANTMARK, B. Maternal smoking and fetal breathing movements. American Journal of Obstetrics and Gynecology 123(8): 861-867, December 15, 1975.

(59) GINSBERG, M.D., MYERS, R.E. Fetal brain damage following maternal carbon monoxide intoxication: An experimental study. Acta Obstetricia et Gynecologica Scandinavica. 53: 309-317, January 1974.

(60) GINSBERG, M.D., MYERS, R.E. Fetal brain injury after maternal carbon monoxide intoxication: Clinical and neuropathologic aspects. Neurology 26(1): 15-23, January 1976.

(61) GOLDSTEIN, H., GOLDBERG, I.D., FRAZIER, T.M., DAVIS, G.E. Cigarette smoking and prematurity. Public Health Reports 79(7): 553-560, July 1964.

(62) GOUJARD, J., ETIENNE, C., EVRARD, F. Caracteristiques maternelles et poids de naissance (Maternal characteristics and birth weight). Revue du Practicien 19(28, Supplement): 54, 59-62, 65, November 1, 1969.

(63) GOUJARD, J., RUMEAU, C., SCHWARTZ, D. Smoking during pregnancy, stillbirth and abruptio placentae. Biomedicine 23: 20-22, 1975.

(64) GREINER, I. Nikotinvergiftung, beobachtet bei einem saeugling (Nicotine poisoning observed in a breast feeding infant). Jahrbuch fuer Kinderheilkunde 96(146): 131-132, 1936.

(65) HADDON, W., JR., NESBITT, R.E.L., GARCIA, R. Smoking and pregnancy: Carbon monoxide in blood during gestation and at term. Obstetrics and Gynecology 18(3): 262-267, September 1961.

(66) HANSSON, E., SCHMITERLOW, C.G. Physiological disposition and fate of C^{14}-labelled nicotine in mice and rats. Journal of Pharmacology and Experimental Therapeutics 137: 91-102, July 1962.

(67) HARDY, J.B., MELLITS, E.D. Does maternal smoking during pregnancy have a long-term effect on the child? Lancet 2: 1332-1336, December 23, 1972.

(68) HATCHER, R.A., CROSBY, H. The elimination of nicotin in the milk. Journal of Pharmacology and Experimental Therapeutics 32(1): 1-6, November 1927.

(69) HAWORTH, J.C., FORD, J.D. Comparison of the effects of maternal undernutrition and exposure to cigarette smoke on the cellular growth of the rat fetus. American Journal of Obstetrics and Gynecology 112(5): 653-656, March 1, 1972.

(70) HELLMAN, L.M., JOHNSON, H.L., TOLLES, W.E., JONES, E.H. Some factors affecting the fetal heart rate. American Journal of Obstetrics and Gynecology 82(5): 1055-1063, November 1961.

(71) HERON, H.J. The effects of smoking during pregnancy: A review with a preview. New Zealand Medical Journal 61: 545-548, November 1962.

(72) HERRIOT, A., BILLEWICZ, W.Z., HYTTEN, F.E. Cigarette smoking in pregnancy. Lancet 1: 771-773, April 14, 1962.

(73) HILL, E.P., HILL, J.R., POWER, G.G., LONGO, L.D. Carbon monoxide exchanges between the human fetus and mother: A mathematical model. American Journal of Physiology 232(3): H311-H323, 1977.

(74) HOLLINGSWORTH, D.R., MOSER, R.J., CARLSON, J.W., THOMPSON, K.T. Abnormal adolescent primiparous pregnancy: Association of race, human chorionic somatomammotropin production, and smoking. American Journal of Obstetrics and Gynecology 126(2): 230-237, September 15, 1976.

(75) HOTOVY, R. Versuche zur frage des einflusses der chronischen nikotinschaedigung auf fruchtbarkeit und nachkommenschaft (Experiments to determine the effect of chronic exposure to nicotine upon fertility and subsequent progeny). Naunyn-Schmiedeberg's Archives of Pathology 205: 54-56, 1948.

(76) HOWREN, H.H., JR. A review of the literature concerning smoking during pregnancy. Virginia Medical Monthly 92: 274-279, June 1965.

(77) HUDSON, D.B., MEISAMI, E., TIMIRAS, P.S. Brain development in offspring of rats treated with nicotine during pregnancy, Experientia 29(3): 286-288, 1973.

(78) HUDSON, D.B., TIMIRAS, P.S. Effects of prenatal administration of nicotine on the biochemical development of the rat brain. Transactions of the American Society of Neurochemistry 2: 83, 1971. (Abstract)

(79) HUDSON, D.B., TIMIRAS, P.S. Nicotine injection during gestation: Impairment of reproduction, fetal viability, and development. Biology of Reproduction 7(2): 247-253, October 1972.

(80) JAEGER, J.J., MCGRATH, J.J. Effects of hypothermia on heart and respiratory responses of chicks to carbon monoxide. Journal of Applied Physiology 34(5): 564-567, May 1973.

(81) JARVINEN, P.A., OSTERLUND, K. Effect of smoking during pregnancy on the fetus, placenta and delivery. Annales Paediatriae Fenniae 9: 18-26, 1963.

(82) JOHNSON, D.E., RHOADES, J.W. N-nitrosamines in smoke condensate from several varieties of tobacco. Journal of the National Cancer Institute 48(6): 1845-1847, June 1972.

(83) KEITH, C.H., TESH, P.G. Measurement of the total smoke issuing from a burning cigarette. Tobacco Science 9: 61-64, July 1965.

(84) KING, J.E., BECKER, R.F. Studies on nicotine absorption during pregnancy. I. LD_{50} for pregnant and nonpregnant rats. American Journal of Obstetrics and Gynecology 95(4): 508-514, June 15, 1966.

(85) KIRSCHBAUM, T.H., DILTS, P.V. JR., BRINKMAN, C.R., III. Some acute effects of smoking in sheep and their fetuses. Obstetrics and Gynecology 35(4): 527-536, April 1970.

(86) KIZER, S. Influencia del habito de fumar sobre el embarazo, parto y recien nacido (Effect of the smoking habit on pregnancy, delivery, and the newborn). Revista de Obstetricia y Ginecologia de Venezuela 27(4): 595-643, 1967.

(87) KLINE, J., STEIN, Z.A., SUSSER, M., WARBURTON, D. Smoking: A risk factor for spontaneous abortion. New England Journal of Medicine 297(15): 793-796, October 13, 1977.

(88) KRUGER, H., ARIAS-STELLA, J. The placenta and the newborn infant at high altitudes. American Journal of Obstetrics and Gynecology 106(4): 586-591, February 15, 1970.

(89) KULLANDER, S., KAELLEN, B. A prospective study of smoking and pregnancy. Acta Obstetrica et Gynecologica Scandinavica 50(1): 83-94, 1971.

(90) KUMAR, D., ZOURLAS, P.A. Studies on human premature births. II. In vivo effect of smoking and in vitro effect of nicotine on human uterine contractility. American Journal of Obstetrics and Gynecology 87(3): 413-417, October 1, 1963.

(91) LANDAUER, W. Nicotine-induced malformations of chicken embryos and their bearing on the phenocopy problem. Journal of Experimental Zoology 143: 107-122, 1960.

(92) LOEHR, J., ARDELT, W., DEHNHARD, F. Nikotinarteriopathie der plazenta (Nicotine arteriopathy of the placenta). Geburtshilfe und Frauenheilkunde 32: 932-934, 1972.

(93) LONGO, L.D. The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. American Journal of Obstetrics and Gynecology 129(1): 69-103, September 1, 1977.

(94) LONGO, L.D. Carbon monoxide: Effects on oxygenation of the fetus in utero. Science 194: 523-525, October 29, 1976.

(95) LONGO, L.D. Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta. Annals of the New York Academy of Sciences 174(Article 1): 313-341, October 5, 1970.

(96) LONGO, L.D. Pollution and infant capabilities. In: Kretchmer, N., Hasselmeyer, E.G. (Editors). Horizons in Perinatal Research. Implications for Clinical Care. New York, John Wiley and Sons, 1974, pp. 62-79.

(97) LONGO, L.D., HILL, E.P. Carbon monoxide uptake and elimination in fetal and maternal sheep. American Journal of Physiology 232(3): H324-H330, 1977.

(98) LONGO, L.D., POWER, G.G., FORSTER, R.E., II. Placental diffusing capacity for carbon monoxide at varying partial pressures of oxygen. Journal of Applied Physiology 26(3): 360-370, March 1969.

(99) LONGO, L.D., POWER, G.G., FORSTER, R.E., II. Respiratory function of the placenta as determined with carbon monoxide in sheep and dogs. Journal of Clinical Investigation 46(5): 812-828, May 1967.

(100) LONGO, L.D., WYATT, J.F., HEWITT, C.W., GILBERT, R.D. A comparison of circulatory responses to hypoxic hypoxia and carbon monoxide hypoxia in fetal blood flow and oxygenation. In: Longo, L.D., Reneau, D.D. (Editors). Fetal and Newborn Cardiovascular Physiology: Fetal and Newborn Circulation. Volume 2. New York, Garland STPM Press, 1978, pp. 259-287.

(101) LOWE, C.R. Effect of mothers' smoking habits on birth weight of their children. British Medical Journal 2: 673-676, October 10, 1959.

(102) LUBS, M-L.E. Racial differences in maternal smoking effects on the newborn infant. American Journal of Obstetrics and Gynecology 115(1): 66-76, January 1, 1973.

(103) MACMAHON, B., ALPERT, M., SALBER, E.J. Infant weight and parental smoking habits. American Journal of Epidemiology 82(3): 247-261, November 1966.

(104) MANNING, F.A., FEYERABEND, C. Cigarette smoking and fetal breathing movements. British Journal of Obstetrics and Gynaecology 83(4): 262-270, April 1976.

(105) MANNING, F., WYN PUGH, E., BODDY, K. Effect of cigarette smoking on fetal breathing movements in normal pregnancies. British Medical Journal 1(5957): 552-553, March 8, 1975.

(106) MARTIN, J.C., BECKER, R.F. The effects of maternal nicotine absorption or hypoxic episodes upon appetitive behavior of rat offspring. Developmental Psychobiology 4(2): 133-147, 1971.

(107) MAU, G. Smoking and the fetus. Lancet 1(7966): 972, May 1, 1976. (Letter)

(108) MCCLUNG, J. Effects of High Altitude on Human Birth. Observations on Mothers, Placentas, and the Newborn in Two Peruvian Populations. Cambridge, Harvard University Press, 1969, 150 pp.

(109) MCDONALD, R.L., LANFORD, C.F. Effects of smoking on selected clinical obstetric factors. Obstetrics and Gynecology 26(4): 470-475, October 1965.

(110) MCGARRY, J.M., ANDREWS, J. Smoking in pregnancy and vitamin B_{12} metabolism. British Medical Journal 2: 74-77, April 8, 1972.

(111) MCGRATH, J.J., JAEGER, J. Effect of iodoacetate on the carbon monoxide tolerance of the chick. Respiration Physiology 12: 71-76, April 1971.

(112) MEYER, M.B. Effects of maternal smoking and altitude on birth weight and gestation. In: Reed, D.M., Stanley, F.J. (Editors). The Epidemiology of Prematurity. Baltimore, Urban and Schwarzenberg, 1977, pp. 81-101.

(113) MEYER, M.B. How does maternal smoking affect birth weight and maternal weight gain? Evidence from the Ontario Perinatal Mortality Study. American Journal of Obstetrics and Gynecology 131(8): 888-893, August 15, 1978.

(114) MEYER, M.B., COMSTOCK, G.W. Maternal cigarette smoking and perinatal mortality. American Journal of Epidemiology 96(1): 1-10, July 1972.

(115) MEYER, M.B., JONAS, B.S., TONASCIA, J.A. Perinatal events associated with maternal smoking during pregnancy. American Journal of Epidemiology 103(5): 464-476, 1976.

(116) MEYER, M.B., TONASCIA, J.A. Maternal smoking, pregnancy complications, and perinatal mortality. American Journal of Obstetrics and Gynecology 128(5): 494-502, July 1, 1977.

(117) MEYER, M.B., TONASCIA, J.A., BUCK, C. The interrelationship of maternal smoking and increased perinatal mortality with other risk factors. Further analysis of the Ontario perinatal mortality study, 1960-1961. American Journal of Epidemiology 100(6): 443-452, 1975.

(118) MILLER, H.C., HASSANEIN, K. Maternal smoking and fetal growth of full term infants. Pediatric Research 8: 960-963, 1964.

(119) MILLER, H.C., HASSANEIN, K., HENSLEIGH, P.A. Fetal growth retardation in relation to maternal smoking and weight gain in pregnancy. American Journal of Obstetrics and Gynecology 125(1): 55-60, May 1, 1976.

(120) MILLS, C.A. Tobacco smoking: Some hints of its biologic hazards. Ohio State Medical Journal 46(12): 1165-1170, December 1950.

(121) MOHR, U., ALTHOFF, J. Carcinogenic activity of aliphatic nitrosamines via the mother's milk in the offspring of Syrian Golden hamsters. Proceedings of the Society for Experimental Biology and Medicine 136(3): 1007-1009, March 1971.

(122) MOSIER, H.D., ARMSTRONG, M.K. Effects of maternal intake of nicotine on fetal and newborn rats. Proceedings of the Society of Experimental Biology and Medicine 116: 956-958, 1964.

(123) MUKHERJEE, S.M., MUKHERJEE, S.N. A study of premature births. Indian Journal of Pediatrics 38(285): 389-392, October 1971.

(124) MULCAHY, R., KNAGGS, J.F. Effect of age, parity, and cigarette smoking on outcome of pregnancy. American Journal of Obstetrics and Gynecology 101(6): 844-849, July 15, 1968.

(125) MULCAHY, R., MURPHY, J., MARTIN, F. Placental changes and maternal weight in smoking and nonsmoking mothers. American Journal of Obstetrics and Gynecology 106(5): 703-704, March 1, 1970.

(126) MURDOCH, D.E. Birth weight and smoking. Nebraska State Medical Journal 48(11): 604-606, November 1963.

(127) MURPHY, J.F., MULCAHY, R. The effect of age, parity, and cigarette smoking on baby weight. American Journal of Obstetrics and Gynecology 111(1): 22-25, September 1, 1971.

(128) MURPHY, J.F., MULCAHY, R. The effects of cigarette smoking, maternal age and parity on the outcome of pregnancy. Journal of the Irish Medical Association 67(11) 309-313, June 15, 1974.

(129) NAEYE, R.L. Causes of perinatal mortality in the U.S. Collaborative Perinatal Project. Journal of the American Medical Association 238(3): 228-229, July 18, 1977.

(130) NAEYE, R.L., LADIS, B., DRAGE, J.S. Sudden infant death syndrome. A prospective study. American Journal of Diseases of Children 130: 1207-1210, November 1976.

(131) NAEYE, R.L., HARKNESS, W.L., UTTS, J. Abruptio placentae and perinatal death: A prospective study. American Journal of Obstetrics and Gynecology 128(7): 740-746, August 1, 1977.

(132) NALL, J.F. Complexed cyanide in collected cigarette smoke. Abstracts of the 20th Tobacco Chemists' Research Conference. November 1-3, 1966, Winston-Salem, N.C., 1966, pp. 25,27.

(133) NEBERT, D.W., WINKER, J., GELBOIN, H.V. Aryl hydrocarbon hydroxylase activity in human placenta from cigarette smoking and nonsmoking women. Cancer Research 29: 1763-1769, October 1969.

(134) NEWSOME, J.R., NORMAN, V., KEITH, C.H. Vapor phase analysis of tobacco smoke. Tobacco Science 9: 102-110, July 23, 1965.

(135) NIKONOVA, T.V. Transplacental action of benzo(a)pyrene and pyrene. Bulletin of Experimental Biology and Medicine 84: 1025-1027, 1977.

(*136*) NISHIMURA, H., NAKAI, K. Developmental anomalies in offspring of pregnant mice treated with nicotine. Science 127: 877-878, April 1958.

(*137*) NISWANDER, J.R., GORDON, M. (Editors). Maternal characteristics. Section 1. Demographic characteristics. Cigarette smoking. In: The Women and Their Pregnancies. The Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. DHEW Publication No. (NIH) 73-379, 1972, pp. 72-80.

(*138*) NORMAN, V., NEWSOME, J.R., KEITH, C.H. Smoking machines for the analysis of the vapor phase of cigarette smoke. Tobacco Science 12: 216-221, 1968.

(*139*) NORTON, S., MULLENIX, P., CULVER, B. Comparison of the structure of hyperactive behavior in rats after brain damage from x-irradiation, carbon monoxide and pallidal lesions. Brain Research 116: 49-67, 1976.

(*140*) NYMAND, G. Maternal smoking and neonatal hyperbilirubinaemia. Lancet 2(7873): 173, July 20, 1974. (Letter)

(*141*) O'LANE, J.M. Some fetal effects of maternal cigaret smoking. Obstetrics and Gynecology 22(2): 181-184, August 1963.

(*142*) ONTARIO DEPARTMENT OF HEALTH. Second Report of the Perinatal Mortality Study in Ten University Teaching Hospitals. Toronto, Canada, Ontario Department of Health, Ontario Perinatal Mortality Study Committee, Volume I, 1967, 275 pp.

(*143*) ONTARIO DEPARTMENT OF HEALTH. Supplement to the Second Report of the Perinatal Mortality Study in Ten University Teaching Hospitals. Toronto, Canada, Ontario Department of Health, Ontario Perinatal Mortality Study Committee, Volume II, 1967, pp. 95-275.

(*144*) OSBORNE, J.S., ADAMEK, S., HOBBS, M.E. Some components of gas phase of cigarette smoke. Analytical Chemistry 28(2): 211-215, February 1956.

(*145*) OUNSTED, M. Maternal constraint of foetal growth in man. Developmental Medicine and Child Neurology 7: 479-491, October 1965.

(*146*) PALMGREN, B., WAHLEN, T., WALLANDER, B. Toxaemia and cigarette smoking during pregnancy: Prospective consecutive investigation of 3927 pregnancies. Acta Obstetrica et Gynecologica Scandinavica 52: 183-185, 1973.

(*147*) PALMGREN, B., WALLANDER, B. Cigarettrokning och abort. Konsekutiv prospektiv undersokning av 4312 graviditeter (Cigarette smoking and abortion. Consecutive prospective study of 4,312 pregnancies). Lakartidningen 68(22): 2611-2616, May 26, 1971.

(*148*) PELKONEN, O., JOUPPILA, P., KARKI, N.T. Effect of maternal cigarette smoking on 3,4-benzypyrene and n-methylaniline metabolism in human fetal liver and placenta. Toxicology and Applied Pharmacology 23: 399-407, 1972.

(*149*) PERLMAN, H.H., DANNENBERG, A.M., SOKOLOFF, N. The excretion of nicotine in breast milk and urine from cigaret smoking. Its effect on lactation and the nursling. Journal of the American Medical Association 120(13): 1003-1009, November 28, 1942.

(*150*) PERNOLL, M.L., METCALFE, J., SCHLENKER, T.L., WELCH, J.E., MATSUMOTO, J.A. Oxygen consumption at rest and during exercise in pregnancy. Respiration Physiology 25: 285-293, December 1975.

(*151*) PETERSON, W.F., MORESE, K.N., KALTREIDER, D.F. Smoking and prematurity. A preliminary report based on study of 7740 Caucasians. Obstetrics and Gynecology 26(6): 775-779, December 1965.

(*152*) PETTERSSON, F. Retrospective study of the influence of some factors on birth weight. Acta Socio-Medica Scandinavica 1(1): 13-18, 1969.

(*153*) PHILIPPE, R.J., HOBBS, M.E. Some components of the gas phase of cigarette smoke. Analytical Chemistry 28(12): 2002-2006, December 1956.

(*154*) POWER, G.G., LONGO, L.D. Fetal circulation times and their implications for tissue oxygenation. Gynecologic Investigation 6: 342-355, 1975.

(155) RANTAKALLIO, P. Groups at Risk in Low Birth Weight Infants and Perinatal Mortality. A prospective study of the biological characteristics and socioeconomic circumstances of mothers in 12,000 deliveries in North Finland 1966. A discriminant function analysis. Acta Paediatrica Scandinavica (Supplement 193): 1969, 71 pp.

(156) RAVENHOLT, R.T., LEVINSKI, M.J., NELLIST, D.J., TAKENAGA, M. Effects of smoking upon reproduction. American Journal of Obstetrics and Gynecology 96(2): 267-281, September 15, 1966.

(157) REINKE, W.A., HENDERSON, M. Smoking and prematurity in the presence of other variables. Archives of Environmental Health 12(5): 600-606, May 1966.

(158) RESNIK, R., BRINK, G.W., WILKES, M.M. Catecholamine mediated reduction in uterine blood flow following nicotine infusion in the pregnant ewe. Society for Gynecologic Investigation. Program and Abstracts, 25th Annual Meeting, March 15-18, 1978, p. 93.

(159) RHEAD, W.J. Smoking and SIDS. Pediatrics 59(5): 791-792, May 1977.

(160) RHOADES, J.W., JOHNSON, D.E. Method for the determination of N-nitrosamines in tobacco-smoke condensate. Journal of the National Cancer Institute 48(6): 1841-1843, June 1972.

(161) ROBINSON, P. Yishun nashim burmanyot bizman haheraiom vehashpaato al ha-em hauber vehaielot (Smoking of Burmese women during pregnancy and its influence on the mother, the fetus and the newborn). Harefuah 69(2): 37-39, 1965.

(162) RUSH, D. Examination of the relationship between birth weight, cigarette smoking during pregnancy and maternal weight gain. Journal of Obstetrics and Gynaecology of the British Commonwealth 81: 746-752, October 1974.

(163) RUSH, D., KASS, E.H. Maternal smoking: A reassessment of the association with perinatal mortality. American Journal of Epidemiology 96(3): 183-196, September 1972.

(164) RUSSELL, C.S., TAYLOR, R., LAW, C.E. Smoking in pregnancy, maternal blood pressure, pregnancy outcome, baby weight and growth, and other related factors. A prospective study. British Journal of Preventive and Social Medicine 22(3): 119-126, July 1968.

(165) RUSSELL, C.S., TAYLOR, R., MADDISON, R.N. Some effects of smoking in pregnancy. Journal of Obstetrics and Gynaecology of the British Commonwealth 73: 742-746, October 1966.

(166) SAVEL, L.E., ROTH, E. Effects of smoking in pregnancy: A continuing retrospective study. Obstetrics and Gynecology 20(3): 313-316, September 1962.

(167) SCHLEDE, E., MERKER, H.J. Effect of benzo(a)pyrene treatment on the benzo(a)pyrene hydroxylase activity in maternal liver, placenta, and fetus of the rat during day 13 to day 18 of gestation. Naunyn-Schmiedeberg's Archives of Pharmacology 272(1): 89-100, December 21, 1972.

(168) SCHOENECK, F.J. Cigarette smoking in pregnancy. New York State Journal of Medicine 41: 1945-1948, October 1, 1941.

(169) SCHWARTZ, D., GOUJARD, J., KAMINSKI, M., RUMEAU-ROUQUETTE, C. Smoking and pregnancy: Results of a prospective study of 6,989 women. Revue Europeene d'Etudes Cliniques et Biologiques 17(9): 867-879, 1972.

(170) SCHWETZ, B.A., LEONG, B.K.J., STAPLES, R.E. Teratology studies on inhaled carbon monoxide and imbibed ethanol in laboratory animals. Teratology 11: 33A, 1975. (Abstract)

(171) SILVERMAN, D.T. Maternal smoking and birth weight. American Journal of Epidemiology 105(6): 513-521, June 1977.

(172) SIMPSON, W.J. A preliminary report on cigarette smoking and the incidence of prematurity. American Journal of Obstetrics and Gynecology 73(4): 808-815, April 1957.

(173) SINGER, P.R., SCIBETTA, J.J., ROSEN, M.G. Simulated marihuana smoking in the maternal and fetal guinea pig. American Journal of Obstetrics and Gynecology 117: 331-340, October 1, 1973.

(174) SMITH, E., MCMILLAN, E., MACK, L. Factors influencing the lethal action of illuminating gas. Journal of Industrial Hygiene and Toxicology 17(1): 18-20, January 1935.

(175) SONTAG, L.W., WALLACE, R.F. The effect of cigaret smoking during pregnancy upon the fetal heart rate. American Journal of Obstetrics and Gynecology 29: 77-83, 1935.

(176) SPEARS, A.W., ROUTH, W.E. A combined approach to the quantitative analysis of the violatile components of cigarette smoke. Abstracts of the 18th Tobacco Chemists Research Conference, October 20-22, 1964, Raleigh, N.C., 1964, pp. 47,49.

(177) SPIRA, A., PHILLIPE, E., SPIRA, N., DREYFUS, J., SCHWARTZ, D. Smoking during pregnancy and placental pathology. Biomedicine 27: 266-270, 1977.

(178) STAINSBY, W.N., OTIS, A.B. Blood flow, blood oxygen tension, oxygen uptake, and oxygen transport in skeletal muscle. American Journal of Physiology 206(4): 858-866, April 1964.

(179) STALHANDSKE, T., SLANINA, P., TJALVE, H., HANSSON, E., SCHMITERLOW, C.G. Metabolism *in vitro* of ^{14}C-nicotine in livers of foetal, newborn and young mice. Acta Pharmacologica et Toxicologica 27: 363-380, 1969.

(180) STEELE, R., LANGWORTH, J.T. The relationship of antenatal and postnatal factors to sudden unexpected death in infancy. Canadian Medical Association Journal 94: 1165-1171, May 28, 1966.

(181) SUZUKI, K., HORIGUCHI, T., COMAS-URRUTIA, A.C., MUELLER-HEUBACH, E., MORISHIMA, H.O., ADAMSONS, K. Pharmacologic effects of nicotine upon the fetus and mother in the rhesus monkey. American Journal of Obstetrics and Gynecology 111(8): 1092-1101, December 15, 1971.

(182) SUZUKI, K., HORIGUCHI, T., COMAS-URRUTIA, A.C., MUELLER-HEUBACH, E., MORISHIMA, H.O., ADAMSONS, K. Placental transfer and distribution of nicotine in the pregnant rhesus monkey. American Journal of Obstetrics and Gynecology 119(2): 253-262, May 15, 1974.

(183) TANAKA, M. Studies on the etiological mechanism of fetal developmental disorders caused by maternal smoking during pregnancy. Nippon Sanka-Fujinka Gakkai Zasshi (Japanese edition) 17(1): 1107-1114, October 1, 1965.

(184) TERKEL, J., BLAKE, C.A., HOOVER, V., SAWYER, C.H. Pup survival and prolactin levels in nicotine-treated lactating rats. Proceedings of the Society for Experimental Biology and Medicine 143: 1131-1135, 1973.

(185) TERRIS, M., GOLD, E.M. An epidemiologic study of prematurity. I. Relation to smoking, heart volume, employment, and physique. American Journal of Obstetrics and Gynecology 103(3): 358-370, February 1, 1969.

(186) THOMPSON, W.B. Nicotine in breast milk. American Journal of Obstetrics and Gynecology 26: 662-667, 1933.

(187) TJALVE, H., HANSSON, E., SCHMITERLOW, C.G. Passage of ^{14}C-nicotine and its metabolites into mice foetuses and placentae. Acta Pharmacologica et Toxicologica 26: 539-555, 1968.

(188) UNDERWOOD, P., HESTER, L.L., LAFFITTE, T., JR., GREGG, K.V. The relationship of smoking to the outcome of pregnancy. American Journal of Obstetrics and Gynecology 91(2): 270-276, January 15, 1965.

(189) UNDERWOOD, P.B., KESLER, K.F., O'LANE, J.M., CALLAGAN, D.A. Parental smoking empirically related to pregnancy outcome. Obstetrics and Gynecology 29(1): 1-8, January 1967.

(190) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General. U.S. Department of Health, Education, and Welfare, DHEW Publication No. (HSM) 71-7513, 1971, pp. 387-418.

(191) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General. U.S. Department of Health, Education, and Welfare, DHEW Publication No. (HSM) 72-7516, 1972, pp. 81-91.

(192) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Report of the Surgeon General. U.S. Department of Health, Education, and Welfare, DHEW Publication No. (HSM) 73-8704, 1973, pp. 99-149.

(193) VAN DEN BERG, B.J. Epidemiologic observations of prematurity: Effects of tobacco, coffee, and alcohol. In: Reed, D.M., Stanley, F.J. (Editors). The Epidemiology of Prematurity. Baltimore, Urban and Schwarzenberg, 1977, pp. 157-176.

(194) VAN VUNAKIS, H., LANGONE, J.J., MILUNSKY, A. Nicotine and cotinine in the amniotic fluid of smokers in the second trimester of pregnancy. American Journal of Obstetrics and Gynecology 120(1): 64-66, September 1, 1974.

(195) VENULET, F. Nastepstwa niedoboru witaminy c u palaczy (Consequences of vitamin C deficiency in smokers). Polskie Archiwum Medycyny Wewnetrznej 26: 393-402, 1956.

(196) VENULET, F., DANYSZ, A. Wplyw palenia tytoniu na poziom witaminy c w mleku kobiecym (The influence of tobacco on the level of vitamin C in human milk). Pediatria Polska 30(9): 811-817, 1955.

(197) WAGNER, B., LAZAR, P., CHOUROULINKOV, I. The effects of cigarette smoke inhalation upon mice during pregnancy. Revue Europeene d'Etudes Clinques et Biologiques 17: 943-948, 1972.

(198) WEISBURGER, E.K. Mechanisms of chemical carcinogenesis. In: George, R., Okun, R., Cho, A.K. (Editors). Annual Review of Pharmacology and Toxicology 18: 395-415, 1978.

(199) WELCH, R.M., GOMMI, B., ALVARES, A.P., CONNEY, A.H. Effect of enzyme induction on the metabolism of benzo(a)pyrene and 3-methyl-4-monomethylaminoazobenzene in the pregnant and fetal rat. Cancer Research 32(5): 973-978, May 1972.

(200) WELLS, L.L. The prenatal effect of carbon monoxide on albino rats and the resulting neuropathology. Biologist 15: 80-81, 1933.

(201) WILLIAMS, I.R., SMITH, E. Blood picture, reproduction, and general condition during daily exposure to illuminating gas. American Journal of Physiology 110(3): 611-615, January 1935.

(202) WILSON, E.W. The effect of smoking in pregnancy on the placental coefficient. New Zealand Medical Journal 74(475): 384-385, 1972.

(203) WINGERD, J., CHRISTIANSON, R., LOVITT, W.V., SCHOEN, E.J. Placental ratio in white and black women: Relation to smoking and anemia. American Journal of Obstetrics and Gynecology 124(7): 671-675, April 1, 1976.

(204) WINGERD, J., SCHOEN, E.J. Factors influencing length at birth and height at five years. Pediatrics 53(5): 737-741, May 1974.

(205) YERUSHALMY, J. Congenital heart disease and maternal smoking habits. Nature 242(5395): 262-264, March 23, 1973.

(206) YERUSHALMY, J. Mother's cigarette smoking and survival of infant. American Journal of Obstetrics and Gynecology 88(4): 505-518, February 15, 1964.

(207) YERUSHALMY, J. The relationship of parents' cigarette smoking to outcome of pregnancy—implications as to the problem of inferring causation from observed associations. American Journal of Epidemiology 93(6): 443-456, June 1971.

(*208*) YERUSHALMY, J. Statistical considerations and evaluation of epidemiological evidence. In: James, G., Rosenthal, T. (Editors). Tobacco and Health. Springfield, Charles C. Thomas, 1962, pp. 208-230.

(*209*) YOUNG, I.M., PUGH, L.G.C.E. The carbon monoxide content of foetal and maternal blood. Journal of Obstetrics and Gynaecology of the British Commonwealth. 70: 681-684, 1963.

(*210*) YOUNOSZAI, M.K., KACIC, A., HAWORTH, J.C. Cigarette smoking during pregnancy: The effect upon the hematocrit and acid-base balance of the newborn infant. Canadian Medical Association Journal 99(5): 197-200, August 3, 1968.

(*211*) YOUNOSZAI, M.K., PELOSO, J., HAWORTH, J.C. Fetal growth retardation in rats exposed to cigarette smoke during pregnancy. American Journal of Obstetrics and Gynecology 104(8): 1207-1213, August 15, 1969.

(*212*) ZABRISKIE, J.R. Effect of cigaret smoking during pregnancy. Study of 2000 cases. Obstetrics and Gynecology 21(4): 405-411, April 1963.

9. PEPTIC ULCER DISEASE.

National Institute of Arthritis, Metabolism, and
Digestive Diseases

CONTENTS

LIST OF TABLES

Epidemiology

For over half a century the medical literature has carried reports of an association between peptic ulcer disease (PUD), including gastric ulcer and duodenal ulcer, and cigarette smoking. Barnett (*2*) in 1927 was the first to examine the epidemiological evidence for this suspected relationship. Although he found that patients with duodenal and gastric ulcer smoked more than controls, the difference was not significant, and he concluded that the purported relationship between smoking and PUD did not exist. However, the majority of subsequent reports have found a significant association between smoking and PUD. Some recent reviews of the older studies (*3, 59, 60*) present support for the conclusions that (1) the prevalence of smoking is increased in persons with PUD, and (2) both gastric and duodenal ulcers are more prevalent in smokers than in nonsmokers. During the past decade several studies have been published which support these conclusions. These will now be considered.

Prevalence of Smoking in Persons with Peptic Ulcer Disease

Kasanen and Forsstroem (*33*) studied the stresses and habits of 100 patients with gastric or duodenal ulcer and found that 90 percent of ulcer patients smoked compared to 60 percent of controls and that 61 percent of ulcer patients smoked one or more packs per day as opposed to 36 percent of controls ($p < .01$). Smoking was the only variable significantly related to ulcer in this study, as no relation to stress (financial, work, or family) was found.

Monson (*38*) studied 10,000 Massachusetts physicians and found that those with gastric or duodenal ulcers smoked significantly more than comparable control subjects. About 1.3 times as many duodenal ulcer patients as control subjects smoked. He did not find a difference between PUD patients and controls in years of smoking or in number of packs per day smoked.

In a Danish study (*32*), 78 percent of PUD patients smoked compared to 71 percent among controls, a difference which was not statistically significant. Bock (*6*), in a South African study, found that 89 percent of men and 45 percent of women with gastric ulcer smoked, but he did not study a control group.

Doll (*18*), who has written extensively on the subject of smoking and ulcer disease (*17, 19*), found a significantly increased frequency of smoking in both duodenal and gastric ulcer patients as compared to controls: gastric ulcer—91 percent smokers, control—79 percent smokers; duodenal ulcer—85 percent smokers, control—81 percent smokers ($p < 0.01$).

Although there is some problem in determining the adequacy of controls in these studies, all five in which controls as well as ulcer

patients were studied (*6, 19, 32, 33, 38*) show a higher proportion of smokers among ulcer patients than among controls.

Prevalence of Peptic Ulcer Disease in Smokers

We turn now to studies of the prevalence of PUD among smokers and nonsmokers, which are described below and summarized in Table 1.

Edwards and coworkers (*22*) examined 1,753 men over age 59 in regard to smoking and health. A history of peptic ulcer was present in 6.0 percent of nonsmokers and in 10.0 percent of cigarette smokers ($p < .01$). Also, the prevalence of peptic ulcer increased with increasing number of cigarettes smoked daily.

Higgins and Kjelsberg (*28*), in a large community health study in Tecumseh, Michigan, discovered a greater frequency of peptic ulcer in male and female smokers and ex-smokers than among nonsmokers (the increased frequency reached statistical significance only in women).

The interrelationships among coffee, alcohol, and smoking were examined by Friedman, et al. (*23*). They studied 36,656 men and women, aged 30 to 59, 2,597 of them with a history of peptic ulcer disease. They found that men who smoked had a 2.1-fold greater frequency of ulcer disease than those who did not smoke, and women had a 1.6-fold greater frequency. The degree of smoking was evaluated by looking at three variables: quantity, years of smoking, and inhalation; all showed positive relationships with the frequency of PUD. On the other hand, since neither coffee drinking nor alcohol consumption was related to an increased occurrence of peptic disease, they concluded that the association of cigarette smoking with PUD is independent of any possible association between smoking and alcohol or coffee consumption.

Similar results were found in a study of 4,000 Polish men and women (*31*) in which the prevalence of PUD was evaluated. Among men, ulcers were found with greater frequency in smokers and ex-smokers than among nonsmokers; and, among smokers, the prevalence of ulcers was greater in those persons who had smoked for more than 5 years and in those smoking more than 14 cigarettes per day. Women smokers did not show an increased frequency of PUD, but only 7 percent of those studied were current smokers. Among women smokers, however, PUD prevalence was higher for those with a longer smoking history and for heavier smokers. On the other hand, in a study of 402 Czechoslovakian men with PUD (*43*), smoking did not make a strong contribution to a stepwise regression predicting the presence of PUD (the data were not provided in the paper and therefore could not be included in Table 1).

In the only truly prospective study (*41*), a 16- to 50-year follow-up study using smoking history in college, PUD was found in 2.2 percent of those who smoked in college as opposed to 1.5 percent of

TABLE 1.—Peptic ulcer prevalence in smokers and nonsmokers (no. per 100)

Reference	How diagnosed	No. with ulcers	Rates: age-adjusted	Sex	Current cigarette smokers	Non-smokers	Ratio	Dose-response
Edwards, F. (1959) (*22*)	Doctor	143	no	M	10.1	6.0	1.7[a]	yes
Higgins, M.W. (1966) (*28*)	Doctor	140	yes	M	7.1	5.2	1.4	—
		47	yes	F	2.8	1.4	2.0	—
Friedman, G.D. (1974) (*23*)	History	1520[b]	yes	M	12.2	5.8	2.1[c]	yes
		1092[b]	yes	F	6.3	3.9	1.6	yes
Jedrychowski, W. (1974) (*31*)	Doctor	106[b]	no	M	6.4	1.9	3.4	yes
		26[b]	no	F	.8	1.3	.6	yes
Paffenbarger, R.S. (1974) (*41*)	History	389	yes	M	2.2[d]	1.5[d]	1.5[d]	yes
Goldbourt, U. (1975) (*25*)	X-ray	895	no	M	10.2	6.2	1.6	no

[a]Also, ratio > 1 within age and social class.
[b]Not given - estimated, using total population and reported rates.
[c]Also, ratio > 1 within occupational groups.
[d]Smoking categories in college, ulcers developed in 16 to 50 year follow-up.