(34) HARRIS, T.R., MERCHANT, J.A., KILBURN, K.H., HAMILTON, J.D. Byssinosis and respiratory diseases of cotton mill workers. Journal of Occupational Medicine 14(3): 199-206, March 1972.

(35) HENDRY, N.W. The geology, occurrences, and major uses of asbestos. Annals of The New York Academy of Sciences, 132(1): 12-22, December 31, 1965.

(36) HORVAT, M., YOSHIDA, S., PRAKASH, R., MARCUS, H.S., SWAN, H.J.C., GANZ, W. Effect of oxygen breathing on pacing-induced angina pectoris and other manifestations of coronary insufficiency. Circulation 45(4): 837-844, April 1972.

(37) HOSEY, A.D. Priorities in developing criteria for "breathing air" standards. Journal of Occupational Medicine 12(2): 43-46, February 1970.

(38) JOHNS-MANVILLE. President's Bulletin No. 640-1. Denver, Johns-Manville Corporation, January 1, 1978, 20 pp.

(39) JONES, J.G., WALTERS, D.H. A study of carboxyhaemoglobin levels in employees at an integrated steelworks. Annals of Occupational Hygiene 5: 221-230, 1962.

(40) JUDD, H.J. Levels of carbon monoxide recorded on aircraft flight decks. Aerospace Medicine 42(3): 344-348, March 1971.

(41) KIBELSTIS, J.A., MORGAN, E.J., REGER, R., LAPP, N.L., SEATON, A., MORGAN, W.K.C. Prevalence of bronchitis and airway obstruction in American bituminous coal miners. American Review of Respiratory Disease 108(4): 886-893, 1973.

(42) KJELLSTROM, T., EVRIN, P.-E., RAHNSTER, B. Dose-response analysis of cadmium-induced tubular proteinuria. A study of urinary β_2-microglobulin excretion among workers in a battery factory. Environmental Research 13(2): 303-317, April 1977.

(43) KRAIN, L.S. The rising incidence of carcinoma of the pancreas—Real or apparent? Journal of Surgical Oncology 2(2): 115-124, 1970.

(44) KUNTZ, W.D., MCCORD, C.P. Polymer-fume fever. Journal of Occupational Medicine 16(7): 480-482, July 1974.

(45) LAUWERYS, R. BUCHET, J.P., ROELS, H. Une etude de la fonction pulmonaire et renale de travailleurs exposes au cadmium (A study of pulmonary and renal function in workers exposed to cadmium). The 18th International Congress on Occupational Health, Brighton, England, September 14-19, 1975, pp. 279-280. (Abstract)

(46) LAUWERYS, R.R., BUCHET, J.P., ROELS, H.A., BROUWERS, J., STANESCU, D. Epidemiological survey of workers exposed to cadmium. Effect on lung, kidney, and several biological indices. Archives of Environmental Health 28(3): 145-148, March 1974.

(47) LEDNAR, W.M., TYROLER, H.A., MCMICHAEL, A.J., SHY, C.M. The occupational determinants of chronic disabling pulmonary disease in rubber workers. Journal of Occupational Medicine 19(4): 263-268, April 1977.

(48) LUNDIN, F.E., JR., WAGONER, J.K., ARCHER, V.E. Radon Daughter Exposure and Respiratory Cancer. Quantitative and Temporal Aspects. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health. National Institute of Environmental Health Science. Joint Monograph No. 1, June 1971, 175 pp.

(49) LYNCH, K.M., SMITH, W.A. Pulmonary asbestosis III: Carcinoma of lung in asbesto-silicosis. American Journal of Cancer 24(1): 56-64, May 1935.

(50) MARTISCHNIG, K.M., NEWELL, D.J., BARNSLEY, W.C., COWAN, W.K., FEINMANN, E.L., OLIVER, E. Unsuspected exposure to asbestos and bronchogenic carcinoma. British Medical Journal 1(6063): 746-749, March 19, 1977.

(51) MATERNE, D., LAUWERYS, R., BUCHET, J.P., ROELS, H., BROUWERS, J., STANESCU, D. Investigations sur les risques resultant de l'exposition au cadmium dans deux entreprises de production et deux entreprises d'utilisation du cadmium (Investigations on the risk resulting from exposure to cadmium in two production plants and two plants using cadmium). Cahiers de Medecine du Travail 12(1 and 2): 5-76, March-June 1975.

(52) MERCHANT, J.A., HALPRIN, G.M., HUDSON, A.R., KILBURN, K.H., MCKENZIE, W.N., JR., HURST, D.J., BERMAZOHN, P. Responses to cotton dust. Archives of Environmental Health 30(5): 222-229, May 1975.

(53) MERCHANT, J.A., KILBURN, K.H., O'FALLON, W.M., HAMILTON, J.D., LUMSDEN, J.C. Byssinosis and chronic bronchitis among cotton textile workers. Annals of Internal Medicine 76(3): 423-433, March 1972.

(54) MERCHANT, J.A., LUMSDEN, J.C., KILBURN, K.H., O'FALLON W.M., UJDA, J.R., GERMINO, V.H., JR., HAMILTON, J.D. Dose response studies in cotton textile workers. Journal of Occupational Medicine 15(3): 222-230, March 1973.

(55) MERCHANT, J.A., LUMSDEN, J.C., KILBURN, K.H., O'FALLON, W.M., UJDA, J.R., GERMINO, V.H., JR., HAMILTON, J.D. An industrial study of the biological effects of cotton dust and cigarette smoke exposure. Journal of Occupational Medicine 15(3): 212-221, March 1973.

(56) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH. Adult Use of Tobacco, 1970. U.S. Department of Health, Education, and Welfare, Public Health Service, June 1973, 137 pp.

(57) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard ...Occupational Exposure to Boron Trifluoride. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-122, December 1976, 83 pp.

(58) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Carbaryl. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-107, September 1976, 192 pp.

(59) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Decomposition Products of Fluorocarbon Polymers. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-193, September 1976, 112 pp.

(60) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Dinitro-Ortho-Cresol. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 78-131, February 1978, 147 pp.

(61) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Formaldehyde. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-126, December 1976, 165 pp.

(62) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Hydrogen Cyanide and Cyanide Salts (NzCN, KCN, and $Ca(CN)_2$). U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-108, October 1976, 191 pp.

(63) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Inorganic Fluorides. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, HEW Publication No. (NIOSH) 76-103, 1975, 191 pp.

(64) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Inorganic Mercury. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health, HSM 73-11024, 1973, 129 pp.

(65) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Methyl Parathion. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-106, September 1976, 177 pp.

(66) NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH. Criteria for a Recommended Standard....Occupational Exposure to Organotin Compounds. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77-115, November 1976, 187 pp.

(67) NAUS, A., ENGLER, V., HETYCHOVA, M., VAVRECKOVA, O. Work injuries and smoking. Industrial Medicine and Surgery 35(10): 880-881, October 1966.

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

(69) PETTIGREW, A.R., FELL, G.S. Simplified colorimetric determination of thiocyanate in biological fluids, and its application to investigation of the toxic amblyopias. Clinical Chemistry, 18(9): 996-1000, September 1972.

(70) PISCATOR, M., ADAMSON, E., ELINDER, C.-G., PETTERSSON, B., STENINGER, P. Studies on cadmium exposed women. Eighteenth International Congress on Occupational Health, Brighton, England, September 14-19, 1975, pp. 281-282. (Abstract)

(71) RADOJICIC, B. Odredivanje rodanida u mokraci u radnika izlozenih cijanidima (Determination of thiocyanates in urine of workers occupationally exposed to cyanides). Arhiv za Higijenu Rada i Toksikologiju 24: 227-232, 1973.

(72) RENTCHNICK, P. (Editor). Recent results in cancer research 3. In: Hueper, W.C. Occupational and Environmental Cancers of the Respiratory System. Berlin, Springer-Verlap, 1966, pp. 38-56, 166-170.

(73) ROBBINS, J.J., WARE, R.L. Pulmonary edema from teflon fumes. Report of a case. New England Journal of Medicine 271(7): 360-361, August 13, 1964.

(74) SELIKOFF, I.J. Cancer risk of asbestos exposure. In: Hiatt, H.H., Watson, J.D., Winston, J.A. (Editors). Origins of Human Cancer. New York, Cold Spring Harbor Laboratory, 1977, pp. 1765-1783.

(75) SELIKOFF, I.J., HAMMOND, E.C., CHURG, J. Asbestos exposure, smoking, and neoplasia. Journal of the American Medical Association 204(2): 106-112, April 8, 1968.

(76) SHERWOOD, R.J. The hazards of fluon. Transactions of the Association of Industrial Medical Officers 5: 10-12, 1955.

(77) SIDOR, R., PETERS, J.M. Prevalence rates of chronic non-specific respiratory disease in fire fighters. American Review of Respiratory Disease 109(2): 255-261, February 1974.

(78) SLUIS-CREMER, G.K., WALTERS, L.G., SICHEL, H.S. Chronic bronchitis in miners and non-miners: An epidemiological survey of a community in the gold-mining area in the Transvaal. British Journal of Industrial Medicine 24(1): 1-12, January 1967.

(79) STELL, P.M., MCGILL, T. Exposure to asbestos and laryngeal carcinoma. Journal of Larynogology and Otology 89(5): 513-517, May 1975.

(80) STEWART, R.D., HAKE, C.L. Paint-remover hazard. Journal of the American Medical Association 235(4): 398-401, January 26, 1976.

(81) TOLA, S., NORDMAN, C.H. Smoking and blood lead concentrations in lead-exposed workers and an unexposed population. Environmental Research 13: 250-255, 1977.

(82) TOUEY, G.P., MUMPOWER, R.C., II. Measurement of the combustion-zone temperature of cigarettes. Tobacco 144(8): 18-22, February 22, 1957.

(83) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, PHS Publication No. 1103, 1964, 387 pp.

(84) WAGNER, J.C., GILSON, J.C., BERRY, G., TIMBRELL, V. Epidemiology of asbestos cancers. British Medical Bulletin 27(1): 71-76, 1971.

(85) WEGMAN, D.H., PETERS, J.M. Polymer fume fever and cigarette smoking. Annals of Internal Medicine 81(1): 55-57, July 1974.

(86) WEISS, W. Chloromethyl ethers, cigarettes, cough and cancer. Journal of Occupational Medicine 18(3): 194-199, March 1976.

(87) WEISS, W. Cigarette smoking, asbestos, and pulmonary fibrosis. American Review of Respiratory Disease 104(2): 223-227, August 1971.

(88) WEISS, W., THEODOS, P.A. Pleuropulmonary disease among asbestos workers in relation to smoking and type of exposure. Journal of Occupational Medicine 20(5): 341-345, May 1978.

(89) WILLIAMS, N., ATKINSON, G.W., PATCHEFSKY, A.S. Polymer-fume fever: Not so benign. Journal of Occupational Medicine 16(8): 519-522, August 1974.

(90) WILLIAMS, N., SMITH, F.K. Polymer-fume fever. An elusive diagnosis. Journal of the American Medical Association 219(12): 1587-1589, March 20, 1972.

(91) WOOD, J.L. Biochemistry. In: Wood, J.L. (Editor). Chemistry and Biochemistry of Thiocyanic Acid and its Derivatives. New York, Academic Press Inc., 1975, pp. 156-221.

(92) WYNDER, E.L., GOLDSMITH, R. The epidemiology of bladder cancer. A second look. Cancer 40(3): 1246-1268, September 1977.

(93) YUSTE, P.C., DE GUEVARA, M.L. Influencia del fumar en los accidentes laborales. Encuesta estadistica (The influence of smoking on industrial accidents. A statistical study). Medicina y Seguridad del Trabajo 21(84): 38-46, October/December 1973.

(94) ZIELHUIS, R.L., STUIK, E.J., HERBER, R.F.M., SALLE, H.J.A., VERBERK, M.M., POSMA, F.D., JAGER, J.H. Smoking habits and levels of lead and cadmium in blood in urban women. International Archives of Occupational and Environmental Health 39: 53-58, 1977.

8. PREGNANCY AND INFANT HEALTH.

National Institute of Child Health and Human Development

CONTENTS

LIST OF FIGURES

LIST OF TABLES

Introduction

Biomedical Aspects of Smoking

Data accumulating in the scientific literature during the past decade strongly corroborate findings reported in the 1960's that cigarette smoking during pregnancy has a significant and adverse effect upon the well-being of the fetus, the health of the newborn baby, and the future development of the infant and child. Adverse effects on pregnancy range from increased risk for reproductive loss, fetal mortality, preterm birth, and neonatal death, to retardation in fetal growth as reflected in birth measurements of lower mean body weight, shortened body length, and smaller head circumference, as well as to a number of problems of adaptation in the neonatal period. In addition, there is suggestive evidence of long-term impairments in physical growth, diminished intellectual function, and deficiencies in behavioral development for those babies who survive the first 4 weeks of life. It appears that children of smoking mothers do not catch up with the offspring of nonsmoking mothers in various phases of development.

The present chapter highlights previously reported and recent studies on the relationships between cigarette smoking and pregnancy outcome, including sections on historical considerations, birth weight and fetal growth, fetal and infant mortality, lactation and breast feeding, and physiologic-experimental studies. The concluding section of this chapter, entitled Research Issues, identifies questions and areas of concern that need clarification and further investigation.

Historical Considerations

In 1957, Simpson (*172*) reported that infants born to women who smoked during their pregnancies were of significantly lower birth weight relative to babies born to nonsmokers. During the intervening 20 years, there has been increasing concern, coupled with the conduct of a large number of related studies, about the effect of smoking during pregnancy upon the well-being of the developing fetus and infant.

Concern about the effects of exposure to tobacco and cigarette smoking during pregnancy upon reproductive loss, maternal health, pregnancy outcome, and infant well-being dates back a century. In 1902, Ballantyne (*9*) questioned what might be the effect of tobacco poisoning upon antenatal life. While he did not specifically mention maternal smoking during pregnancy, he summarized the opinions of a number of authors writing during the latter part of the 19th century about the risks of spontaneous abortion for women who worked in tobacco factories. He referred specifically to an 1879 paper by Decaisne from France and to an 1868 report by Kostial from Austria about female tobacco workers. Ballantyne wrote that both of these authors "were quite convinced that abortion was very frequent in women workers in tobacco [factories]...." Ballantyne concluded by stating, "While there is much doubt, therefore, regarding the evil effect of nicotism in cutting short antenatal life, there seems to be no shadow of doubt that there is a very large infantile mortality in postnatal life among the offspring of women workers in tobacco. Possibly this may be due in part to the influence of the milk, but it is more probable that it is on account of congenital debility."

Discussion of the problem of smoking during pregnancy at the turn of the century appears to have been based on empirical evidence and anecdotal reports. Until the end of the 1920's, there was a sparsity of reports on this topic in the scientific literature. Thereafter, several articles were published reporting the results of animal studies and clinical investigations pertinent to the effects of nicotine and smoking during pregnancy upon reproductive loss, maternal health, and pregnancy outcome.

In 1935, Sontag and Wallace (*175*) investigated the effects of cigarette smoking during pregnancy upon fetal heart rate. Their observations were made during the last 2 months of pregnancy on eight mothers and their fetuses. Their data revealed that the smoking of one cigarette by the pregnant woman generally produced an increase in the rate of the fetal heart beat, and sometimes a decrease. They concluded that there was "a definite and real" increase in the fetal heart rate after the mother began to smoke a cigarette and that this was probably due to transplacental transfer of nicotine into the fetal circulation.

In 1935 and again in 1936, Campbell (*23*, *24*) reported that heavy cigarette smoking was prejudicial to efficient childbearing as a result of chronic nicotine poisoning. Campbell warned that excessive smoking in certain cases was detrimental to maternal health. He noted that, in general, a woman who smoked during pregnancy was likely to have more difficulty during the course of pregnancy, parturition, and lactation than a woman who did not smoke.

In 1940, Essenberg and associates (*46*), in a well-designed study, investigated the effects of nicotine and cigarette smoke on pregnant female albino rats and their offspring. The three groups of subjects included a group of animals that received intraperitoneal or subcutaneous injections of solutions of chemically pure nicotine, a second group of animals that were exposed to tobacco smoke that approximated human smoking of one pack of cigarettes a day, and a third group of animals that were untreated.

The immediate effects on the animals in the two treated groups were similar, although more severe in the injected group. It was reported that:

1. Two-thirds of all the young of treated mothers were underweight; the young from nicotine-injected mothers were more underweight than those from mothers exposed to tobacco smoke.

2. The underweight group remained underweight during the entire period of observation; many of the young of this group were undersized and died early.
3. Of the females injected, 63.0 percent lost one or more young before weaning, and 33.3 percent lost all of their young.
4. Of the mothers exposed to tobacco smoke, 28 percent lost one or more of their young before weaning, and 25 percent were underweight.
5. Of the mothers exposed to smoke prior to mating, 23.3 percent lost one or more of their young before weaning, and 25 percent were underweight.
6. In both groups of treated mothers, temporary sterility, resorption of young *in utero*, and abortions were noted.
7. Alteration of maternal behavior was observed, consisting of cannibalism and neglect of the young as to care and feeding.

The findings of Essenberg, et al. (*46*), reported in 1940, raised important questions regarding the effects of smoking on pregnancy outcome that were not investigated in depth until some 20 years later when Simpson reported her findings (*172*).

Results of epidemiological surveys and experimental studies appearing in the literature over the past two decades owe much to improvements in research technology which contributed to more accurate and reproducible measurements in the laboratory. For example, nicotine concentrations in minute amounts can be determined with gas chromatography, and the degree of carbon monoxide displacement of oxygen from hemoglobin can be assessed with considerable precision by biophysical methodology. Use of new technology has often permitted scientists to confirm earlier impressions obtained with the use of crude but ingenious bioassays. Such confirmation is a tribute to the perception and the dedication of these pioneering investigators and astute clinicians.

Smoking, Birth Weight, and Fetal Growth

Birth Weight

Babies born to women who smoke during pregnancy are, on the average, 200 grams lighter than babies born to comparable women who do not smoke. Since 1957, when Simpson reported this finding from her original study (*172*), it has been confirmed by over 45 studies of more than half a million births (*1, 2, 7, 20, 22, 29-31, 37, 41, 47, 54, 61, 62, 71, 72, 86, 89, 90, 101-103, 115, 118, 119, 123-127, 137, 141-143, 145, 147, 151, 155-157, 161, 163-166, 168, 169, 185, 188, 189, 190-192, 208, 212*). Results of these studies are expressed as mean birth weights of smokers' and nonsmokers' babies, or alternatively, as the percentage of babies who weigh less than a specified amount, usually 2,500 grams. The methods and results of 28 studies carried out between 1957 and 1970 were summarized in the chapter on smoking and pregnancy in *The Health Consequences of Smoking. A Report of the Surgeon General: 1971*, which concluded: "Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birth weight and an increased incidence of prematurity, defined by weight alone" (*190*). The same conclusion has been drawn from subsequent studies.

In the chapter on pregnancy in *The Health Consequences of Smoking* in 1973, a detailed, critical review is given of studies published to that date. The chapter summary of the evidence that the association between maternal smoking and reduced birth weight is one of cause and effect includes the following (*192*):

1. Results are consistent in all studies, retrospective and prospective, from many different countries, races, cultures, and geographic settings (*2, 7, 20, 22, 30, 31, 41, 47, 54, 62, 72, 81, 86, 89, 109, 115, 118, 119, 125–127, 137, 141–143, 147, 151, 152, 157, 161, 163, 164, 166, 169, 172, 185, 189, 192, 193, 206, 212*).

2. The relationship between smoking and reduced birth weight is independent of all other factors that influence birth weight, such as race, parity, maternal size, socioeconomic status, sex of child, and other factors that have been studied (*1, 2, 7, 20, 22, 31, 47, 54, 71, 101, 102, 115, 118, 119, 142, 143, 152, 157, 164, 169, 192, 193*). It is also independent of gestational age (*2, 19, 20, 22, 54, 72, 115, 141, 157, 163, 166, 169, 192, 206*).

3. The more the woman smokes during pregnancy, the greater the reduction in birth weight; this is a dose-response relationship (*2, 22, 31, 47, 54, 89, 101, 102, 103, 115, 118, 119, 137, 142, 143, 169, 189, 192, 193, 206*).

4. If a woman gives up smoking during pregnancy, her risk of delivering a low-birth-weight baby is similar to that of a nonsmoker (*22, 54, 101, 103, 206*).

To illustrate typical results of studies showing the association between maternal smoking and an increased proportion of low-birth-weight infants, five published studies with an aggregated total of almost 113,000 births in Wales, the United States, and Canada are summarized in Table 1. In these populations, 34 to 54 percent of the mothers smoked during pregnancy and on the average had twice as many low-birth-weight babies as the nonsmokers. Under these conditions, from 21 to 39 percent of the low-birth-weight incidence in the total population could be attributed to maternal smoking (*2, 20, 47, 115, 137, 142, 143*).

An outstanding feature of the relationship between maternal smoking and birth weight is its dependence on the level of maternal smoking and its independence of the large variety of other factors that influence birth weight, such as maternal size, maternal weight gain, age, parity, socioeconomic status, and sex of child (*1, 2, 20, 22, 31, 47,*

TABLE 1.—Birth weight under 2,500 grams by maternal smoking habit, relative and attributable risks derived from published studies

Study	Nonsmokers (No.)	Smokers		Births <2,500 gm(%)		Relative risk smoker: nonsmoker	Attributable risk* (%)
		No.	Proportion	Nonsmoker	Smoker		
Cardiff	7,176	6,238	.465	4.1	8.1	1.98	31
US Collaborative							
White	8,466	9,781	.536	4.3	9.5	2.21	39
Black	11,252	7,777	.409	10.7	17.5	1.64	21
California, Kaiser Permanente							
White	3,189	2,145	.402	3.5	6.4	1.83	25
Black	934	479	.338	6.4	13.4	2.09	27
Montreal	3,954	3,004	.432	5.2	11.4	2.19	34
Ontario	27,316	21,062	.435	4.5	9.1	2.02	31

*Percentage of total birth weights <2,500 gm attributable to maternal smoking. Attributable risk in population = b(r-1) divided by b(r-1) + 1 where b = proportion of mothers who smoke and r = relative risk of low birth-weight = smoker rate/nonsmoker rate

SOURCE: Meyer, M.B. (*115*).

71, 101, 102, 115, 118, 119, 137, 152, 157, 163, 164, 169, 192, 193). This feature is illustrated in Tables 2 and 3. Table 2 shows mean birth weights for babies of smokers and nonsmokers in selected subdivisions by biologic and socioeconomic factors, using data from the approximately 10,000 white births studied from 1960 to 1967 by the Berkeley Child Health and Development Studies whose subjects were members of the Kaiser Foundation Health Plan. Mean birth weights vary with maternal age, parity, height, weight, and socioeconomic status, from a low of 2,912 grams for babies of smoking mothers who had given birth to previous low-birth-weight infants, to a high of 3,573 grams for babies of nonsmoking mothers of high parity. Nevertheless, within each subgroup the effect of maternal smoking on mean birth weight is clearly seen, with smokers' infants weighing from 193 to 286 grams less than nonsmokers' infants in the subgroups shown (*193*). Table 3, using data from the 50,097 births of the Ontario Perinatal Mortality Study, shows the incidence of low birth weight (percent under 2,500 grams) for three levels of maternal smoking and for subcategories of hospital pay status, mother's height and weight, and the sex of the child. Despite percentages of births under 2,500 grams that vary from 2.7 percent for nonsmokers who were 68 inches or taller to 15.8 percent for smokers of more than a pack per day who weighed less than 120 pounds before pregnancy, the increased risk of having a baby weighing less than 2,500 grams is remarkably stable—about 70 percent for women who smoke less than a pack of cigarettes per day and about 160 percent for smokers of a pack or more per day—compared with the risk for nonsmokers (*119*).

The picture that emerges from these findings is that birth weight is affected by maternal smoking independently and to a uniform extent, regardless of other determinants of birth weight. Comparisons of the percentage distributions of birth weights for smokers' and nonsmokers' babies show a downward shift of the whole set of weights of smokers' babies by about 200 grams, as illustrated in Figure 1 (*103*). In other words, the data displayed in Figure 1 corroborate the impression that all births are affected similarly by maternal smoking and negate the possibility that changes in mean birth weight are due to extreme effects in a few cases with other cases unchanged.

Placental Ratios

Authors of a few earlier studies in which placental weights were analyzed by maternal smoking habits noted that these weights were either not affected or were less affected by maternal smoking than were birth weights (*81, 89, 125, 141, 202*). As a result, because of the dose-related reduction in birth weights with increasing number of cigarettes smoked, the ratio of placental weight to birth weight, or placental ratio, tended to be larger for smokers than for nonsmokers.

TABLE 2.—Mean birth weight of infants of smoking and nonsmoking mothers, by other biologic and socioeconomic factors

Prepregnancy factors	Mean birth weight (gm)	Mean difference Nonsmokers-Smokers(gm)
Gravida's age <20 years		
Smokers	3,219	193
Nonsmokers	3,412	
Parity > 4 previous pregnancies		
Smokers	3,287	286
Nonsmokers	3,573	
Previous birth <2,500 grams		
Smokers	2,912	208
Nonsmokers	3,120	
Gravida's height <60 inches		
Smokers	3,058	201
Nonsmokers	3,259	
Gravida's prepregnancy weight <100 lbs.		
Smokers	2,918	246
Nonsmokers	3,164	
Gravida's education: less than high school graduate		
Smokers	3,196	253
Nonsmokers	3,446	
Husband's education: less than high school graduate		
Smokers	3,196	256
Nonsmokers	3,452	
Husband's occupation: unskilled laborer, service worker		
Smokers	3,224	247
Nonsmokers	3,471	

SOURCE: van den Berg, B.J. (*193*).

Kullander and Kaellen reported placental ratios of 0.171, 0.175, 0.178, and 0.188, respectively, for nonsmokers, smokers of less than 10 cigarettes a day, those smoking 10 to 20 a day, and those smoking more than 20 cigarettes per day, based on a prospective study of 6,376 pregnancies in Malmo, Sweden (*89*). Wilson compared the ratios of untrimmed, fresh placenta weights to birth weights for 1,895 deliveries in Sheffield, England, finding a significantly higher ratio for babies born to smokers than to nonsmokers. He suggested that the increase might signify a response by the placenta to chronic hypoxia in the fetus (*202*).

Wingerd, et al. have now published a definitive study of this relationship, using data from a prospective study of 7,000 pregnancies among members of the Kaiser Foundation Health Plan in Oakland,

TABLE 3.—Birth weight under 2,500 grams by maternal smoking and other factors (Ontario data)

Factor and class	Births under 2,500 grams (per hundred total births) Maternal smoking: packs per day			Smoker: nonsmoker Relative risk Packs per day	
	0	<1	1+	<1	1+
Hospital status					
Private	4.4	7.1	10.6	1.6	2.4
Public	5.8	10.3	16.5	1.8	2.8
Mother's height					
< 62 inches	5.9	10.8	15.1	1.8	2.6
62–64 inches	4.7	7.9	12.8	1.7	2.7
65–67 inches	3.9	6.2	10.1	1.6	2.6
68+ inches	2.7	6.0	9.3	2.2	3.5
Prepregnant weight					
< 120 pounds	6.1	10.2	15.8	1.7	2.6
120–134 pounds	4.2	6.3	9.5	1.5	2.2
135+ pounds	3.3	5.1	8.7	1.5	2.6
Sex of child					
Male	4.2	7.3	11.5	1.7	2.7
Female	5.2	8.3	12.7	1.6	2.4

SOURCE: Meyer, M.B. (*115*).

California (*203*). At an interview early in pregnancy, information was obtained about numerous factors related to the pregnancy, including the woman's smoking habits. Placentas were weighed by specially trained personnel after the cord and attached membranes had been trimmed off according to Benirschke's protocol, an extremely important procedure to reduce variability of measurement. The study was confined to black or white women who delivered single, live infants without severe anomalies between 37 and 43 weeks' gestation and for whom at least one hemoglobin value during gestation had been reported. Because placental ratios change with gestational age, it is important to compare values specific for weeks of gestation at the time of delivery. Results of this study are shown in Figure 2. At each gestational age from 37 through 43 weeks, the more the mother smoked during pregnancy the higher is the placental ratio. Comparison of the observed mean weights by smoking level showed that, as expected, birth weights decreased as smoking level increased. Furthermore, mean placental weights were the same or slightly lower for light smokers and slightly higher for heavy smokers (over 20 cigarettes per day) than for nonsmokers. Ratios were higher for black than for white women and tended to increase as maternal hemoglobin level decreased. This trend was most marked in black women who smoked (*203*).

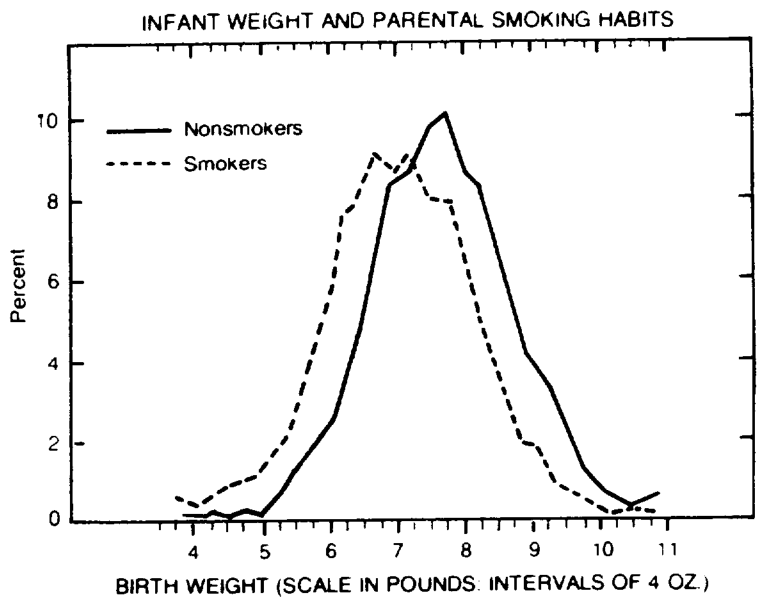

FIGURE 1.—Percentage distribution by birth weight of infants of mothers who did not smoke during pregnancy and of those who smoked one pack or more of cigarettes per day
SOURCE: MacMahon, B. (*103*).

As described in another section of this chapter, the carbon monoxide present in cigarette smoke combines with maternal and fetal hemoglobin and results in a reduced carrying capacity of the blood for oxygen and also a reduction of the pressure at which oxygen is delivered to the fetal tissues. Somewhat similar reductions of oxygen availability for the fetus occur at high altitude and in cases of maternal anemia. Under these conditions, increases in placental ratios have also been observed that are in proportion to the elevation or to the degree of anemia (*14*, *88*, *108*). The possibility that these changes may represent physiological responses to relative fetal hypoxia, with increased oxygen delivery by a larger placenta and decreased oxygen demand by a smaller fetus, has been considered (*14*, *88*, *108*, *202*, *203*). If this is the case, it is important to know whether a mechanism that might increase the possibility of survival at a lower birth weight is accompanied by any long-term costs in later growth and development.

Gestation

The consistent finding that mean birth weights were lower and the frequency of low-weight babies higher for women who smoked during pregnancy than for similar nonsmokers raised the obvious question of

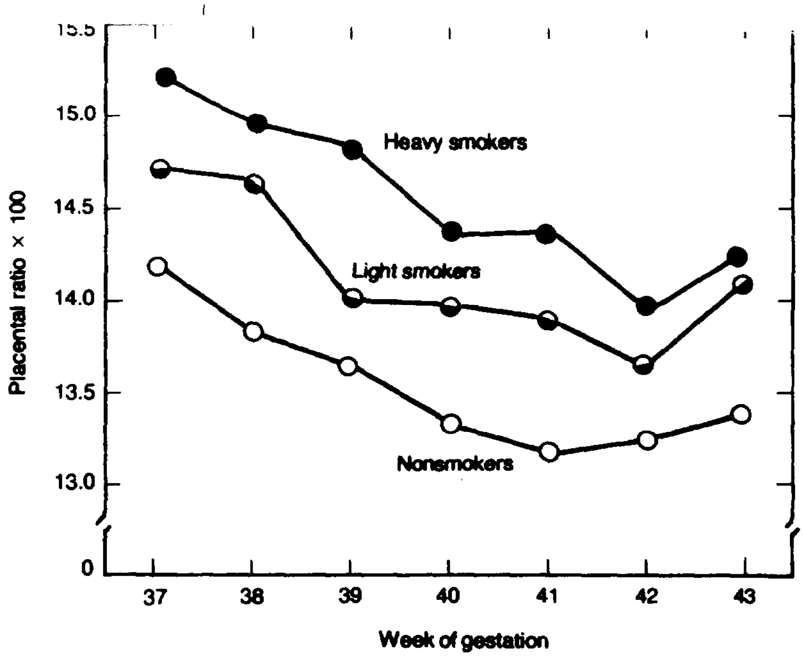

FIGURE 2.—Ratio of placental weight to birth weight by length of gestation and maternal smoking category
SOURCE: Wingerd, J. (*205*).

whether this might be due to a corresponding reduction in the duration of gestation if the mother smoked. In his study of 2,042 women in Birmingham, England, published in 1959, Lowe noted that the infants of smoking mothers were delivered only 1.4 days earlier on the average than those of nonsmokers, not enough to account for the mean birth weight reduction of 170 grams (*101*). Subsequent studies of mean gestation have shown similarly small differences between mean durations of pregnancy for smokers and nonsmokers (*2, 19, 20, 67, 72, 141, 157, 166, 206*). For example, Buncher, in an analysis of the 49,897 births to U.S. Navy wives studied by Underwood, et al. (*189*), found that the mean duration of pregnancy was only 0.25 weeks shorter for male babies and 0.18 weeks shorter for female babies if the mother smoked during pregnancy (*19*).

The finding that maternal smoking does not cause an overall downward shift in the distribution of gestational ages, such as was shown for birth weights, leads to the conclusion that the lower birth weight of smokers' infants must be due to a direct retardation of fetal growth. In other words, these infants are small-for-dates rather than preterm. The truth of this conclusion has been demonstrated by studies in which mean birth weights or percentages of low-birth-weight babies

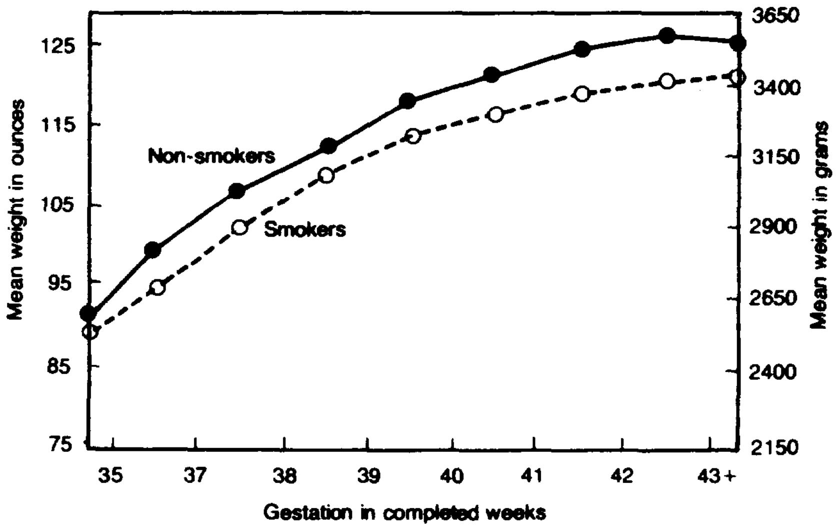

FIGURE 3.—Mean birth weight for week of gestation according to maternal smoking habit: control week singletons
SOURCE: Butler, N.R. (*20*).

were compared within units of gestational age. Butler and Alberman, in an analysis of data from the British Perinatal Mortality Study of 17,000 births in Great Britain in March, 1958, found lower mean birth weights for smokers' than for nonsmokers' babies at each week of gestation from 36 through 43, as shown in Figure 3 (*20*). Evidence of the same birth weight relationship is presented in Figure 4 (*113*), taken from Meyer's analysis of data from the Ontario Perinatal Mortality Study (*142*, *143*). This Figure shows that, as one would expect, the proportion of births under 2,500 grams decreases as gestation increases. It also shows, within each gestational age group, the effect of maternal smoking on birth weight, as the frequency of low-weight births increases directly with smoking level for term births of early, average, and late time of delivery.

Fetal Growth

As the low birth weight associated with maternal smoking is independent of gestational age and is not due to a significant reduction in mean gestation, it must therefore be due to a reduction in the rate of fetal growth. In several studies the relationship between maternal smoking and other body measurements besides birth weight has been examined. Kullander and Kaellen, in a prospective study of 6,376 births in Malmo, Sweden, found that, as the level of maternal smoking increased, the body length, head circumference, and shoulder circumference decreased consistently for both male and female babies (*89*).

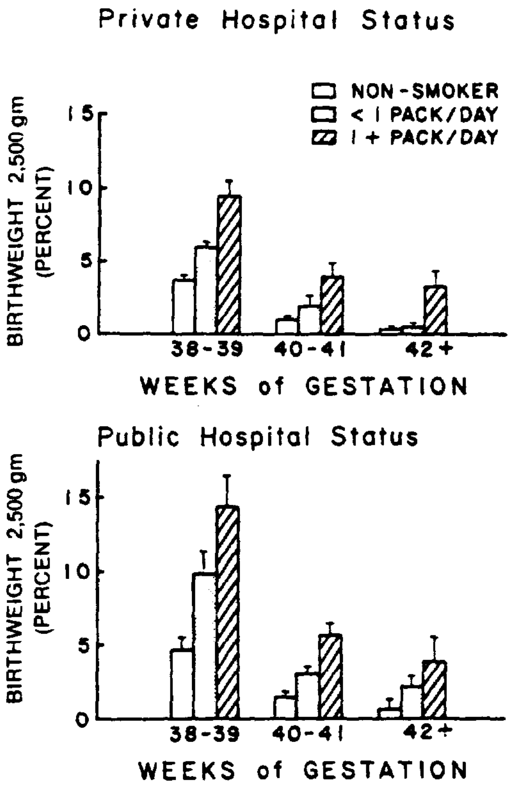

FIGURE 4.—Percentage of birth weights under 2,500 grams by maternal smoking level for early, average, and late-term births. Private hospital status and public hospital status (Bars show 95 percent confidence intervals)

SOURCE: Meyer, M.B. (*113*).

Other studies have corroborated these findings (*34*, *67*, *81*, *141*). Hardy and Mellits compared the birth measurements and subsequent growth of 88 pairs of neonates from the population of the Collaborative Perinatal Study of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (*137*). Women who reported smoking 10 or more cigarettes a day and whose children had survived and been examined at age 7 were matched by race, age, educational background, sex of child, and delivery date with women who did not smoke any cigarettes during pregnancy and whose children were examined at age 7. At birth, the smokers' babies weighed an average of 250 grams less ($p \leq 0.001$), were 1.34 centimeters shorter ($p < 0.001$), and had head circumferences 0.32 centimeters smaller than babies of nonsmoking mothers (*67*). In a study of 1,159 infants whose mothers' smoking habits were ascertained early in pregnancy, Davies and coworkers found the familiar gradient of decreasing mean birth weights with increasing smoking level. When these infants were measured at 7 to 14 days of age, a similar gradient was found for body length and head circumference of both male and female babies (*34*). These and other studies (*33, 67, 204*) indicate that maternal smoking leads to an overall retardation of fetal growth.

Miller, Hassanein, and coworkers have described two types of fetal growth retardation in term babies. One is characterized by an abnormally low ratio of birth weight to crown-heel length, the thin baby with a low ponderal index but with normal length. The other is characterized by abnormally short crown-heel length for fetal age, the baby who is generally smaller than expected in all measurements (*118*). A study of 1,112 uncomplicated term pregnancies indicated that mothers who smoked cigarettes during pregnancy were more likely to have infants with short body lengths for dates, whereas mothers who had abnormally low weight gain in the last two trimesters were more likely to have babies with low ponderal indices (*119*).

Long-Term Growth and Development

Whether or not there are long-term consequences of the fetal growth retardation associated with maternal smoking during pregnancy is of much greater concern than are measurements at the time of birth. There is evidence that children of smoking mothers have measurable deficiencies in physical growth, intellectual development, and emotional development that are independent of other known predisposing factors.

The matched-pair study of Hardy and Mellits compared physical measurements and intellectual function in children of smokers and nonsmokers through age 7. Among 88 pairs, although the babies of smokers were 250 grams lighter and 1 to 2 cm shorter at birth and still shorter than their counterparts at one year, the authors reported that there was no significant difference in either physical measurements or intellectual function at 4 and 7 years (*67*). It should be noted, however, that to achieve statistical significance from such numbers of cases, the difference between them must be very strong. In Hardy and Mellits' study of the 88 pairs of children matched for race, date of delivery, maternal age and education, and sex of child, mean values for the children of nonsmokers were larger than those of smokers at all ages for all measurements through age 7, including body weight, body length, and head circumference. At age 1 year, 96 percent of nonsmokers' babies and 90 percent of smokers' babies had normal neurological status. At age 4, nonsmokers' babies had slightly higher scores on the Stanford-Binet intelligence test, and at age 7 they tested higher on all of the tests reported except for the Wide Range Achievement Test subtest for arithmetic. An additional set of 55 pairs of children of smokers and nonsmokers who were matched on birth weight as well as on the other factors listed also showed fewer smokers' children with normal neurological status and lower scores for smokers' children on 6 out of 8 tests of intellectual function. The fact that few of these differences reached "statistical significance" does not rule out the possibility that harmful long-term effects may exist (*38*, *43*).

In the California study by Wingerd and Schoen (*204*), the net effect of various factors on length at birth and height at 5 years was determined in 3,707 single-born, white, California children. Children of smoking mothers were found to be shorter ($p<0.001$) at birth and at 5 years than children of nonsmoking mothers. (Intellectual development was not measured in this study.)

In a prospective study of children of low birth weight, Dunn and coworkers analyzed growth with respect to maternal smoking habits of 81 who were "small-for-dates," 99 "truly premature," and 146 controls of full birth weight. At 6½ years of age, the children of nonsmoking mothers had a slightly greater mean height and weight in all three categories. The mean social class of the smoking mothers was lower than that of the nonsmokers, but within the two lowest social classes, IV and V (77 percent of all subjects), the nonsmokers' children had a greater mean height and weight than their counterparts whose mothers smoked. Statistically significant differences in favor of nonsmokers' children were demonstrable with regard to weight gain and growth in length/weight at 1 to 4 years and with regard to actual height at 4 and 6½ years and weight at 6½ years in the full birth weight controls (*43*). There was no evidence that the children of smoking women "caught up" in growth with the nonsmokers' children, a concept postulated by Russell, et al. (*164*) but not corroborated by other studies.

Dunn also evaluated the neurological, intellectual, and behavioral status of these children at age 7 and analyzed the results according to the mothers' smoking habits during pregnancy. Neurological abnormalities, including minimal cerebral dysfunction and abnormal or borderline encephalograms, were slightly more common among children of smoking women, although this difference was not quite statistically significant. In a battery of psychological tests, the mean scores of children of nonsmoking mothers were better than those of smokers' children in 45 out of 48 correlations, and the difference was significant in 14 of these. Factorial analysis of variance suggested that these differences could be only partially attributed to the slightly lower social status of smokers' children. Some significant differences in favor of nonsmokers' children were also demonstrated with respect to behavior ratings and school placement (*44*). These results are very similar to those of Hardy and Mellits in that the direction of the differences is almost always in favor of the nonsmokers' child. Perhaps more attention should be paid to these patterns and less to the question of "statistical significance," which is difficult to achieve with such small numbers. Dunn concludes that "some slight direct damaging effect on foetal brain development and subsequent intelligence and behaviour cannot be excluded" (*44*).

Small numbers and population selection factors are not a problem in the longitudinal follow-up of the population originally included in the British Perinatal Mortality Study, comprising approximately 17,000 births, an estimated 98 percent of all births in England, Scotland, and Wales during the week of March 3 to 9, 1958. These children have been traced and studied again at age 7 and at age 11, to describe their behavior, their health, their physical development, their educational standards, and their home environment. At ages 7 and 11 years, physical and mental retardation due to smoking in pregnancy were found, and this deficit increased with the number of cigarettes smoked during pregnancy. Children whose mothers smoked 10 or more cigarettes a day during pregnancy were on average 1.0 centimeters shorter and between 3 to 5 months retarded in reading, mathematics, and general ability, as compared with the offspring of nonsmokers. After allowing for associated social and biological factors, all of these differences are highly significant ($p<0.001$)(*33, 38, 43, 204*).

Recently an association has been reported between maternal smoking and hyperkinesis in children. Denson and colleagues matched each of 20 consecutive methyl-phenidate-sensitive cases with a nonhyperkinetic dyslexic child and also with a normal control by sex, age within six months, and social class. Mean birth weights were similar for the three groups. Mothers of hyperkinetic children tended to be younger, and significantly more of their children were first-born. Outstanding and highly significant differences were found in maternal cigarette consumption. Mothers of hyperkinetic children consumed more cigarettes during the study pregnancy ($p<0.05$), had higher maximum consumption during that pregnancy ($p<0.01$), and consumed more at the time of questioning ($p<0.001$). The present mean consumption by mothers of hyperkinetic children was 23.3 cigarettes per day, more than three times the average for the two control groups. Only four mothers of hyperkinetic children had not smoked during pregnancy, and all of these reported complicated deliveries. Of smokers, 11 with complicated pregnancies had a mean consumption of 13.4 cigarettes daily, and 5 with various complications smoked an average of 28 cigarettes daily throughout pregnancy. The role of anoxia as a possible cause of hyperkinetic disease and the hypoxic effects of carbon monoxide and of smoking-related complications of pregnancy and labor are discussed in the study. The authors conclude: "These findings are consistent with the hypothesis that smoking during pregnancy is an important cause of the hyperkinetic syndrome" (*36*).