current smokers had a penile cancer risk 1.6 times that of never smokers, but the risk among former smokers was similar to that among current smokers (Table 8).

Primary hepatocellular cancer has been associated with smoking in a number of recent studies (Trichopoulous et al. 1980; Lam et al. 1982; Yu et al. 1983; Oshima et al. 1984; Trichopoulos et al. 1987; Hirayama 1989). This association is of potentially great public health importance because of the high incidence of primary liver cancer and the epidemic of cigarette smoking worldwide, which is increasingly involving countries in which liver cancer is the leading cause of cancer mortality. The mechanism whereby smoking might affect liver cancer risk is unknown. Although potential confounding by alcohol consumption is of concern in interpreting this association, the association of smoking with hepatocellular cancer has remained significant in several studies after controlling for alcohol intake (Trichopoulos et al. 1980; Yu et al. 1983; Oshima et al. 1984; Trichopoulos et al. 1987). One case–control study (Yu et al. 1983) and two cohort studies (Cederlof et al. 1975; Carstensen, Pershagen, Eklund 1987; Rogot and Murray 1980) have examined the effects of smoking cessation on liver cancer risk. In all three studies, current smokers were found to have higher risks than either never smokers or former smokers. In the case–control study, potential confounding by different alcohol consumption of current and former smokers was controlled (Yu et al. 1983). Many of the earlier studies (including the prospective studies reviewed in this Chapter) did not exclude the possibility that cancer of the liver may have been primary in another (smoking-related) organ. The possible role of hepatitis B as a modifier of the effect of smoking on the risk of liver cancer is not clear (IARC 1986).

Tobacco has been associated with stomach cancer, but whether this association is causal remains unclear (IARC 1986; US DHHS 1982, 1989). Few studies have considered the effect of cessation on the risk of stomach cancer. The U.S. Veterans Study (Kahn 1966; Rogot and Murray 1980) and the Swedish study (Cederlof et al. 1975) indicate a reduction in stomach cancer risk after cessation, although the relative risks among current smokers were small in these studies (Table 8).

Leukemia has recently been implicated as a smoking-related disease (Austin and Cole 1986; Severson 1987; Kinlen and Rogot 1988), but this observation has not been consistent (for review, see Kinlen and Rogot 1988). The U.S. Veterans Study showed only a slight dose–response relationship for myelogenous leukemias, but there was little difference in risk between current and former smokers (Kahn 1966; Rogot and Murray 1980; Kinlen and Rogot 1988). In the earlier presentation of these data, there was no difference in risk among ex-smokers, compared with current smokers, at any of four levels of prior cigarette smoking (Kahn 1966). The most recent analysis of these data indicated there was little difference in risk among former smokers compared with current smokers for any of the subtypes of leukemia. One study demonstrated a poorer prognosis for patients with myelogenous leukemia who were cigarette smokers (Archimbaud et al. 1989).

MULTIPLE PRIMARY CANCERS

The occurrence of multiple primary cancers may reflect the effects of the same risk factors in the pathogenesis of the multiple cancers, the effects of agents used in treating

the initial malignancy, or simply the consequence of chance (Schottenfeld 1982). Thus, multiple primary cancers have been investigated with the goals of examining environmental and host factors increasing cancer risk and of identifying adverse consequences of cancer treatment. Tobacco use, including cigarette smoking, has been examined as a risk factor for the development of a second primary cancer, after diagnosis of a first malignancy at cigarette-associated and non-cigarette-associated sites; the effect of smoking cessation on the occurrence of second cancers has also been addressed in several investigations.

Descriptive studies have shown that an initial malignancy at a smoking-associated site is followed by an increased risk for cancer at the same or another cigarette-associated site (Wynder et al. 1969; Schottenfeld 1982). In an early study of multiple primary cancers, Berg, Schottenfeld, and Ritter (1970) examined the risks of second primary cancers in persons evaluated at Memorial Hospital for squamous cell cancers of the respiratory or upper digestive tract or other histologic types of lung cancer. In comparison with expected numbers of cases based on incidence rates for New York State, significant excesses were observed for cancers of the lip, oral cavity or pharynx, esophagus, larynx, and lung.

Only limited evidence is available on the effects of smoking cessation on the occurrence of multiple primary cancers. Moore reported two studies (1965, 1971) of second primary cancers in persons with an index malignancy of the mouth, pharynx, or larynx; both showed reduced risk for a second primary cancer in persons who stopped smoking after diagnosis of the first cancer. For 1 to 15 years, Silverman, Gorsky, and Greenspan (1983) observed 117 smokers who had a primary cancer of the head and neck region. Thirty percent of continuing smokers developed a second oral primary cancer compared with 15 percent of those reducing smoking and 13 percent of those completely stopping.

In contrast, an effect of cessation was not found in two other studies (Castigliano 1968; Schottenfeld, Gantt, Wynder 1974). Castigliano's 1968 study included 88 subjects with mouth or throat cancer who survived for at least 3 years without evidence of recurrence. During a minimum followup period of 3 years, the occurrence of a second primary cancer was not related to smoking status. Schottenfeld, Gantt, and Wynder (1974) examined multiple primary cancers in 733 patients admitted to Memorial Sloan-Kettering Cancer Center with a primary epidermoid carcinoma of the oral cavity, pharynx, or larynx. During the 5-year followup period, the smoking status of those developing and not developing a second primary did not differ significantly.

Interpretation of these studies is limited by the small numbers of subjects and the limited duration of followup. Furthermore, the interactions of tobacco smoking with other risk factors of cancers of the head and neck, particularly alcohol consumption, complicate interpretation of these data.

SUMMARY

This review of the relationship between cigarette smoking cessation and the risk of nonrespiratory cancers has shown that former smokers tend to have lower risk than current smokers for cancers of the oral cavity, esophagus, pancreas, bladder, and uterine

cervix. This lower risk appears to be neither an artifact of a lower exposure to cigarettes in former smokers prior to quitting nor a result of confounding by other known risk factors for these cancers. This observation of a diminution in risk further supports the hypothesis that cigarette smoking is a causal factor for cancers of many sites other than the respiratory system. Although smoking is not as strong a risk factor for non-respiratory cancers as it is for cancers of the lung and larynx, substantial numbers of cases of many nonrespiratory cancers can be attributed to tobacco use (US DHHS 1989). The patterns of diminution in risk with increasing duration of abstinence indicate that smoking cessation provides a substantial reduction in the risk of nonrespiratory cancer.

CONCLUSIONS

1. Smoking cessation halves the risks for cancers of the oral cavity and esophagus, compared with continued smoking, as soon as 5 years after cessation, with further reduction over a longer period of abstinence.

2. Smoking cessation reduces the risk of pancreatic cancer, compared with continued smoking, although this reduction in risk may only be measurable after 10 years of abstinence.

3. Smoking is a cause of bladder cancer; cessation reduces risk by about 50 percent after only a few years, in comparison with continued smoking.

4. The risk of cervical cancer is substantially lower among former smokers in comparison with continuing smokers, even in the first few years after cessation. This finding supports the hypothesis that cigarette smoking is a contributing cause of cervical cancer.

5. Neither smoking nor smoking cessation are associated with the risk of cancer of the breast.

References

ADAMI, H.O., LUND, E., BERGSTROM, R., MEIRIK, O. Cigarette smoking, alcohol consumption and risk of breast cancer in young women. *British Journal of Cancer* 58(6):832–837, December 1988.

AMERICAN CANCER SOCIETY. Unpublished tabulations provided by L. Garfinkel from the Cancer Prevention Study II. August 1989.

ARCHIMBAUD, E., MAUPAS, J., LECLUZE-PALAZZOLO, C., FIERE, D., VIALA, J.J. Influence of cigarette smoking on the presentation and course of chronic myelogenous leukemia. *Cancer* 63(10):2060–2065, May 15, 1989.

AUGUSTINE, A., HEBERT, J.R., KABAT, G.C., WYNDER, E.L. Bladder cancer in relation to cigarette smoking. *Cancer Research* 48:4405–4408, August 1, 1988.

AUSTIN, H., COLE, P. Cigarette smoking and leukemia. *Journal of Chronic Diseases* 39(6):417–421, 1986.

BARON, J.A. Smoking and estrogen-related disease. *American Journal of Epidemiology* 119(1):9–22, January 1984.

BARON, J.A., BYERS, T., GREENBERG, E.R., CUMMINGS, K.M., SWANSON, M. Cigarette smoking in women with cancers of the breast and reproductive organs. *Journal of the National Cancer Institute* 77(3):677–680, September 1986.

BARTON, S.E., MADDOX, P.H., JENKINS, D., EDWARDS, R., CUZICK, J., SINGER, A. Effect of cigarette smoking on cervical epithelial immunity: A mechanism for neoplastic change? *Lancet* 2(8612):652–654, September 17, 1988.

BERG, J.W., SCHOTTENFELD, D., RITTER, F. Incidence of multiple primary cancers. III. Cancers of the respiratory and upper digestive system as multiple primary cancers. *Journal of the National Cancer Institute* 44:263–274, 1970.

BERGGREN, G., SJOSTEDT, S. Preinvasive carcinoma of the cervix uteri and smoking. *Acta Obstetricia et Gynecologica Scandinavica* 62(6):593–598, 1983.

BLOT, W.J., MCLAUGHLIN, J.K., WINN, D.M., AUSTIN, D.F., GREENBERG, R.S., PRESTON-MARTIN, S., BERNSTEIN, L., SCHOENBERG, J.B., STEMHAGEN, A., FRAUMENI, J.F. JR. Smoking and drinking in relation to oral pharyngeal cancer. *Cancer Research* 48:3282–3287, June 1, 1988.

BRINTON, L.A., SCHAIRER, C., HAENSZEL, W., STOLLEY, P., LEHMAN, H.F., LEVINE, R., SAVITZ, D.A. Cigarette smoking and invasive cervical cancer. *Journal of the American Medical Association* 255(23):3265–3269, 1986.

BRINTON, L.A., SCHAIRER, C., STANFORD, J.L., HOOVER, R.N. Cigarette smoking and breast cancer. *American Journal of Epidemiology* 123(4):614–622, April 1986.

BRISSON, J., ROY, M., FORTIER, M., BOUCHARD, C., MEISELS, A. Condyloma and intraepithelial neoplasia of the uterine cervix: A case–control study. *American Journal of Epidemiology* 128(2):337–342, August 1988.

BROCK, K.E., BERRY, G., MOCK, P.A., MACLENNAN, R., TRUSWELL, A.S., BRINTON, L.A. Nutrients in diet and plasma and risk of in situ cervical cancer. *Journal of the National Cancer Institute* 80(8):580–585, June 15, 1988.

BROWNSON, R.C., BLACKWELL, C.W., PEARSON, D.K., REYNOLDS, R.D., RICHENS, J.W., PAPERMASTER, B.W. Risk of breast cancer in relation to cigarette smoking. *Archives of Internal Medicine* 148(1):140–144, January 1988.

BROWNSON, R.C., CHANG, J.C., DAVIS, J.R. Occupation, smoking, and alcohol in the epidemiology of bladder cancer. *American Journal of Public Health* 77(10):1298–1300, October 1987.

BURCH, J.D., ROHAN, T.E., HOWE, G.R., RISCH, H.A., HILL, G.B., STEELE, R., MILLER, A.B. Risk of bladder cancer by source and type of tobacco exposure: A case–control study. *International Journal of Cancer* 44:622–628, 1989.

BYERS, T., MARSHALL, J., GRAHAM, S., METTLIN, C., SWANSON, M. A case–control study of dietary and nondietary factors in ovarian cancer. *Journal of the National Cancer Institute* 71(4):681–686, October 1983.

CARNEY, R.M., GOLDBERG, A.P. Weight gain after cessation of cigarette smoking. A possible role for adipose-tissue lipoprotein lipase. *New England Journal of Medicine* 310(10):614–616, March 8, 1984.

CARSTENSEN, J.M., PERSHAGEN, G., EKLUND, G. Mortality in relation to cigarette and pipe smoking: 16 years' observation of 25,000 Swedish men. *Journal of Epidemiology and Community Health* 41:166–172, 1987.

CARTWRIGHT, R.A., ADIB, R., APPLEYARD, I., GLASHAN, R.W., GRAY, B., HAMILTON-STEWART, P.A., ROBINSON, M., BARHAM-HALL, D. Cigarette smoking and bladder cancer: An epidemiologic inquiry in West Yorkshire. *Journal of Epidemiology and Community Health* 37(4):256–263, December 1983.

CASTIGLIANO, S.G. Influence of continued smoking on the incidence of second primary cancers involving mouth, pharynx, and larynx. *Journal of the American Dental Association* 77:580–585, 1968.

CEDERLOF, R., FRIBERG, L., HRUBEC, Z., LORICH, U. *The Relationship of Smoking and Some Social Covariables to Mortality and Cancer Morbidity. A Ten Year Follow-up in a Probability Sample of 55,000 Swedish Subjects Age 18–69. Part 1 2.* Stockholm, Sweden: Karolinska Institute, Department of Environmental Hygiene, 1975.

CLARKE, E.A., MORGAN, R.W., NEWMAN, A.M. Smoking as a risk factor in cancer of the cervix: Additional evidence from a case–control study. *American Journal of Epidemiology* 115(1):59–66, January 1982.

CLAUDE, J.C., FRENTZEL-BEYME, R.R., KUNZE, E. Occupation and risk of cancer of the lower urinary tract among men. A case–control study. *International Journal of Cancer* 41(3):371–379, March 15, 1988.

CLAVEL, F., BENHAMOU, E., AUQUIER, A., TARAYRE, M., FLAMANT, R. Coffee, alcohol, smoking and cancer of the pancreas: A case–control study. *International Journal of Cancer* 43(1):17–21, January 15, 1989.

CUBILLA, A.L., FITZGERALD, P.J. Classification of pancreatic cancers (nonendocrine). *Mayo Clinic Proceedings* 54:449–458, 1979.

CUZICK, J., BABIKER, A.G. Pancreatic cancer, alcohol, diabetes mellitus, and gall-bladder disease. *International Journal of Cancer* 43(3):415–421, March 15, 1989.

DALING, J.R., WEISS, N.S., HISLOP, T.G., MADEN, C., COATES, R.J., SHERMAN, K.J., ASHLEY, R.L., BEAGRIE, M., RYAN, J.A., COREY, L. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *New England Journal of Medicine* 317(16):973–977, October 15, 1987.

DANIELL, H.W. Re: Causes of anal carcinoma. (Letter.) *Journal of the American Medical Association* 254(3):358, July 19, 1985.

DANIELL, H.W. Increased lymph node metatastases at mastectomy for breast cancer associated with host obesity, cigarette smoking, age, and large tumor size. *Cancer* 62(2):429–435, July 15, 1988.

FALK, R.T., PICKLE, L.W., FONTHAM, E.T., CORREA, P., FRAUMENI, J.F. JR. Life-style risk factors for pancreatic cancer in Louisiana: A case–control study. *American Journal of Epidemiology* 128(2):324–336, August 1988.

FARROW, D.C., DAVIS, S. Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. *International Journal of Cancer*, in press.

FRANCO, E.L., KOWALSKI, L.P., OLIVEIRA, B.V., CURADO, M.P., PEREIRA, R.N., SILVA, M.E., FAVA, A.S., TORLONI, H. Risk factors for oral cancer in Brazil: A case–control study. *International Journal of Cancer* 43(6):992–1000, June 15, 1989.

FRANKS, A.L., LEE, N.C., KENDRICK, J.S., RUBIN, G.L., LAYDE, P.M., THE CANCER AND STEROID HORMONE STUDY GROUP. Cigarette smoking and the risk of epithelial ovarian cancer. *American Journal of Epidemiology* 126(1):112–117, 1987.

GOLD, E.B., GORDIS, L., DIENER, M.D., SELTSER, R., BOITNOTT, J.K., BYNUM, T.E., HUTCHEON, D.F. Diet and other risk factors for cancer of the pancreas. *Cancer* 55(2):460–467, January 15, 1985.

GREENBERG, E.R., VESSEY, M., MCPHERSON, K., YEATES, D. Cigarette smoking and cancer of the uterine cervix. *British Journal of Cancer* 51:139–141, January 1985.

GUPTA, P.C., PINDBORG, J.J., BHONSLE, R.B., MURTI, P.R., MEHTA, F.S., AGHI, M.B., DAFTARY, D.K., SHAH, H.T., SINOR, P.N. Intervention study for primary prevention of oral cancer among 36,000 Indian tobacco users. *Lancet* 1(8492):1235–1239, May 31, 1986.

HARRIS, R.W., FORMAN, D., DOLL, R., VESSEY, M.P., WALD, N.J. Cancer of the cervix uteri and vitamin A. *British Journal of Cancer* 53(5):653–659, May 1986.

HARTGE, P., SILVERMAN, D., HOOVER, R., SCHAIRER, C., ALTMAN, R., AUSTIN, D., CANTOR, K., CHILD, M., KEY, C., MARRETT, L.D., MASON, T.J., MEIGS, J.W., MYERS, M.H., NARAYANA, A., SULLIVAN, J.W., SWANSON, G.M., THOMAS, D., WEST, D. Changing cigarette habits and bladder cancer risk: A case–control study. *Journal of the National Cancer Institute* 78(6):1119–1125, June 1987.

HELLBERG, D., NILSSON, S. Smoking and cancer of the ovary. (Letter.) *New England Journal of Medicine* 318(12):782–783, March 24, 1988.

HELLBERG, D., VALENTIN, J., EKLUND, T., STAFFAN, N. Penile cancer: Is there an epidemiological role for smoking and sexual behaviour? *British Medical Journal* 295(6609):1306–1308, November 21, 1987.

HELLBERG, D., VALENTIN, J., NILSSON, S. Smoking as a risk factor for cervical neoplasia. (Letter.) *Lancet* 2(8365/8366):1497, December 24–31, 1983.

HERRERO, R., BRINTON, L.A., REEVES, W.C., BRENES, M.M., TENORIO, F., DEBRITTON, R.C., GAITAN, E., GARCIA, M., RAWLS, W.E. Invasive cervical cancer and smoking in Latin America. *Journal of the National Cancer Institute* 81(3):205–211, February 1, 1989.

HIATT, R.A., FIREMAN, B.H. Smoking, menopause, and breast cancer. *Journal of the National Cancer Institute* 76:833–838, 1986.

HIRAYAMA, T. A large-scale cohort study on risk factors for primary liver cancer, with special reference to the role of cigarette smoking. *Cancer Chemotherapy and Pharmacology* 23(Supplement):S114–S117, 1989.

HOFSTETTER, A., SCHUTZ, Y., JEQUIER, E., WAHREN, J. Increased 24-hour energy expenditure in cigarette smokers. (Letter.) *New England Journal of Medicine* 314(25):1641, June 19, 1986.

HOLLY, E.A., PETRAKIS, N.L., FRIEND, N.F., SARLES, D.L., LEE, R.E., FLANDER, L.B. Mutagenic mucus in the cervix of smokers. *Journal of the National Cancer Institute* 76(6):983–986, June 1986.

HOLMES, F., BOREK, D., OWEN-KUMMER, M., HASSANEIN, R., FISHBACK, J., BEHBEHANI, A., BAKER, A., HOLMES, G. Anal cancer in women. *Gastroenterology* 95(1):107–111, July 1988.

HOWE, G.R., BURCH, J.D., MILLER, A.B., COOK, G.M., ESTEVE, J., MORRISON, B., GORDON, P., CHAMBERS, L.W., FODOR, G., WINSOR, G.M. Tobacco use, occupation, coffee, various nutrients, and bladder cancer. *Journal of the National Cancer Institute* 64(4):701–713, April 1980.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. *Tobacco Smoking*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 38. Lyon: International Agency for Research on Cancer, 1986.

ISCOVICH, J., CASTELLETTO, R., ESTEVE, J., MUNOZ, N., COLANZI, R., CORONEL, A., DEAMEZOLA, I., TASSI, V., ARSLAN, A. Tobacco smoking, occupational exposure and bladder cancer in Argentina. *International Journal of Cancer* 40(6):734–740, December 15, 1987.

JENSEN, J., CHRISTIANSEN, C., RODBRØ, P. Cigarette smoking, serum estrogens, and bone loss during hormone-replacement therapy early after menopause. *New England Journal of Medicine* 313:973–975, 1985.

JENSEN, O.M., KNUDSEN, J.B., MCLAUGHLIN, J.K., SORENSON, B.L. The Copenhagen case–control study of renal pelvis and ureter cancer: Role of smoking and occupational exposures. *International Journal of Cancer* 41(4):557–561, April 15, 1988.

JENSEN, O.M., WAHRENDORF, J., BLETTNER, M., KNUDSEN, J.B., SORENSEN, B.L. The Copenhagen case–control study of bladder cancer: Role of smoking in invasive and non-invasive bladder tumours. *Journal of Epidemiology and Community Health* 41(1):30–36, March 1987.

JOHNSTON, W.D., BALLANTYNE, A.J. Prognostic effect of tobacco and alcohol use in patients with oral tongue cancer. *American Journal of Surgery* 134:444–447, 1977.

KABAT, G.C., HEBERT, J.R., WYNDER, E.L. Risk factors for oral cancer in women. *Cancer Research* 49(10):2803–2806, May 15, 1989.

KABAT, G.C., WYNDER, E.L. Type of alcoholic beverage and oral cancer. *International Journal of Cancer* 43(2):190–194, February 15, 1989.

KAHN, H.A. The Dorn study of smoking and mortality among US veterans: Report on eight and one-half years of observation. In: Haenzel, W. (ed.) *Epidemiological Approaches to the Study of Cancer and Other Chronic Diseases*. NCI Monograph 19. U.S. Department of Health, Education, and Welfare, U.S. Public Health Service, National Cancer Institute, January 1966, pp. 1–125.

KINLEN, L.J., ROGOT, E. Leukemia and smoking habits among United States veterans. *British Medical Journal* 297(6649):657–659, September 10, 1988.

KOUMANTAKI, Y., TZONOU, A., KOUMANTAKIS, E., KAKLAMANI, E., ARAVANTINOS, D., TRICHOPOULOS, D. A case–control study of cancer of the endometrium in Athens. *International Journal of Cancer* 43(5):795–799, May 15, 1989.

KUCERA, H., ENZELSBERGER, H., EPPEL, W., WEGHAUPT, K. The influence of nicotine abuse and diabetes mellitus on the results of primary irradiation in the treatment of carcinoma of the cervix. *Cancer* 60(1):1–4, July 1, 1987.

LA VECCHIA, C., FRANCESCHI, S., DECARLI, A., FASOLI, M., GENTILE, A., TOGNONI, G. Cigarette smoking and the risk of cervical neoplasia. *American Journal of Epidemiology* 123(1):22–29, January 1986.

LA VECCHIA, C., LIATI, P., DECARLI, A., NEGRELLO, I., FRANCESCHI, S. Tar yields of cigarettes and the risk of oesophageal cancer. *International Journal of Cancer* 38:381–385, 1986.

LA VECCHIA, C., LIATI, P., DECARLI, A., NEGRI, E., FRANCESCHI, S. Coffee consumption and risk of pancreatic cancer. *International Journal of Cancer* 40:309–313, September 15, 1987.

LA VECCHIA, C., NEGRI, E. The role of alcohol in oesophageal cancer in non-smokers, and the role of tobacco in non-drinkers. *International Journal of Cancer* 43(5):784–785, May 15, 1989.

LAM, K.C., YU, M.C., LEUNG, J.W.C., HENDERSON, B.E. Hepatitis B virus and cigarette smoking: Risk factors for hepatocellular carcinoma in Hong Kong. *Cancer Research* 42(12):5246–5248, December 1982.

LESKO, S.M., ROSENBERG, L., KAUFMAN, D.W., HELMRICH, S.P., MILLER, D.R., STROM, B., SCHOTTENFELD, D., ROSENSHEIN, N.B., KNAPP, R.C., LEWIS, J., SHAPIRO, S. Cigarette smoking and the risk of endometrial cancer. *New England Journal of Medicine* 313(10):593–596, 1985.

LONDON, S.J., COLDITZ, G.A., STAMPFER, M.J., WILLETT, W.C., ROSNER, B.A., SPEIZER, F.E. Prospective study of smoking and the risk of breast cancer. *Journal of the National Cancer Institute* 81(21):1625–1631, November 1, 1989.

LYON, J.L., GARDNER, J.W., WEST, D.W., STANISH, W.M., HEBERTSON, R.M. Smoking and carcinoma in situ of the uterine cervix. *American Journal of Public Health* 73(5):558–562, May 1983.

MACDONALD, P.C., EDMAN, C.D., HEMSELL, D.L., PORTER, J.C., SIITERI, P.K. Effect of obesity on conversion of plasma androstenedione to estrone in postmenopausal women with and without endometrial cancer. *American Journal of Obstetrics and Gynecology* 130:448–455, 1978.

MACK, T.M., YU, M.C., HANISCH, R., HENDERSON, B.E. Pancreas cancer and smoking, beverage consumption, and past medical history. *Journal of the National Cancer Institute* 76(1):49–60, January 1986.

MACMAHON, B., YEN, S., TRICHOPOULOS, D., WARREN, K., NARDI, G. Coffee and cancer of the pancreas. *New England Journal of Medicine* 304(11):630–633, March 12, 1981.

MARSHALL, J.R., GRAHAM, S., BYERS, T., SWANSON, M., BRASURE, J. Diet and smoking in the epidemiology of cancer of the cervix. *Journal of the National Cancer Institute* 70(5):847–851, May 1983.

MICHNOVICZ, J.J., HERSHCOPF, R.J., NAGANUMA, H., BRADLOW, H.L., FISHMAN, J. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. *New England Journal of Medicine* 315(21):1305–1309, November 1986.

MILLS, P.K., BEESON, W.L., ABBEY, D.E., FRASER, G.E., PHILLIPS, R.L. Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer* 61(12):2578–2585, June 15, 1988.

MOORE, C. Smoking and cancer of the mouth, pharynx, and larynx. *Journal of the American Medical Association* 191(4):107–110, January 25, 1965.

MOORE, C. Cigarette smoking and cancer of the mouth, pharynx, and larynx. A continuing study. *Journal of the American Medical Association* 218(4):553–558, October 25, 1971.

MORI, M., HARABUCHI, I., MIYAKE, H., CASAGRANDE, J.T., HENDERSON, B.E., ROSS, R.K. Reproductive, genetic, and dietary risk factors for ovarian cancer. *American Journal of Epidemiology* 128(4):771–777, October 1988.

MORRISON, A.S., BURING, J.E., VERHOEK, W.G., AOKI, K., LECK, I., OHNO, Y., OBATA, K. An international study of smoking and bladder cancer. *Journal of Urology* 131(4):650–654, April 1984.

NISCHAN, P., EBELING, K., SCHINDLER, C. Smoking and invasive cervical cancer risk. Results from a case–control study. *American Journal of Epidemiology* 128(1):74–77, July 1988.

NOMURA, A., GROVE, J.S., STEMMERMANN, G.N., SEVERSON, R.K. A prospective study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption. *Cancer Research* 50:627–631, February 1, 1990.

NORELL, S.E., AHLBOM, A., ERWALD, R., JACOBSON, G., LINDBERG-NAVIER, I., OLIN, R., TORNBERG, B., WIECHEL, K.L. Diet and pancreatic cancer: A case–control study. *American Journal of Epidemiology* 124(6):894–902, December 1986.

OLSEN, G.W., MANDEL, J.S., GIBSON, R.W., WATTENBERG, L.W., SCHUMAN, L.M. A case–control study of pancreatic cancer and cigarettes, alcohol, coffee, and diet. *American Journal of Public Health* 79(8):1016–1019, 1989.

OSHIMA, A., TSUKUMA, H., HIYAMA, T., FUJIMOTO, I., YAMANO, H., TANAKA, M. Follow-up study of HBs Ag-positive blood donors with special reference to effect of drinking and smoking on development of liver cancer. *International Journal of Cancer* 34:775–779, 1984.

PETERS, R.K., THOMAS, D., HAGAN, D.G., MACK, T.M., HENDERSON, B.E. Risk factors for invasive cervical cancer among Latinas and non-Latinas in Los Angeles County. *Journal of the National Cancer Institute* 77(5):1063–1077, November 1986.

ROGOT, E., MURRAY, J.L. Smoking and causes of death among U.S. veterans: 16 years' of observation. *Public Health Reports* 95(3):213–222, May/June 1980.

ROHAN, T.E., BARON, J.A. Cigarette smoking and breast cancer. *American Journal of Epidemiology* 129(1):36–42, January 1989.

ROSENBERG, L., SCHWINGL, P.J., KAUFMAN, D.W., MILLER, D.R., HELMRICH, S.P., STOLLEY, P.D., SCHOTTENFELD, D., SHAPIRO, S. Breast cancer and cigarette smoking. *New England Journal of Medicine* 310(2):92–94, January 12, 1984.

SASSON, I.M., HALEY, N.J., HOFFMANN, D., WYNDER, E.L., HELLBERG, D., NILSSON, S. Cigarette smoking and neoplasia of the uterine cervix: Smoke constituents in cervical mucus. *New England Journal of Medicine* 312(5):315–316, January 31, 1985.

SCHECHTER, M.T., MILLER, A.B., HOWE, G.R. Cigarette smoking and breast cancer: A case-control study of screening participants. *American Journal of Epidemiology* 121(4):479–487, April 1985.

SCHIFFMAN, M.H., HALEY, N.J., FELTON, J.S., ANDREWS, A.W., KASLOW, R.A., LANCASTER, W.D., KURMAN, R.J., BRINTON, L.A., LANNOM, L.B., HOFFMANN, D. Biochemical epidemiology of cervical neoplasia: Measuring cigarette smoke constituents in the cervix. *Cancer Research* 47(14):3886–3888, July 15, 1987.

SCHOTTENFELD, D. Multiple primary cancers. In: Schottenfeld, D., Fraumeni, J.F. Jr. (eds.) *Cancer Epidemiology and Prevention*. Philadelphia: W.B. Saunders, Co., 1982, p. 1025.

SCHOTTENFELD, D., GANTT, R.C., WYNDER, E.L. The role of alcohol and tobacco in multiple primary cancers of the upper digestive system, larynx and lung: A prospective study. *Preventive Medicine* 3(2):277–293, June 1974.

SEVERSON, R.K. Cigarette smoking and leukemia. *Cancer* 60(2):141–144, July 15, 1987.

SILVERMAN, S. JR., GORSKY, M., GREENSPAN, D. Tobacco usage in patients with head and neck carcinomas: A follow-up study on habit changes and second primary oral/oropharyngeal cancers. *Journal of the American Dental Association* 106(1):33–35, January 1983.

SLATTERY, M.L., ROBISON, L.M., SCHUMAN, K.L., FRENCH, T.K., ABBOTT, T.M., OVERALL, J.C. JR., GARDNER, J.W. Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. *Journal of the American Medical Association* 261(11):1593–1598, March 17, 1989.

SLATTERY, M.L., SCHUMACHER, M.C., WEST, D.W., ROBISON, L.M. Smoking and bladder cancer. The modifying effect of cigarettes on other factors. *Cancer* 61(2):402–408, January 15, 1988.

SMITH, E.M., SOWERS, M.F., BURNS, T.L. Effects of smoking on the development of female reproductive cancers. *Journal of the National Cancer Institute* 73(2):371–376, August 1984.

SPITZ, M.R., FUEGER, J.J., GOEPFERT, H., HONG, W.K., NEWELL, G.R. Squamous cell carcinoma of the upper aerodigestive tract. A case comparison analysis. *Cancer* 61:203–208, 1988.

STELLMAN, S.D., AUSTIN, H., WYNDER, E.L. Cervix cancer and cigarette smoking: A case–control study. *American Journal of Epidemiology* 111(4):383–388, April 1980.

STEVENS, M.H., GARDNER, J.W., PARKIN, J.L., JOHNSON, L.P. Head and neck cancer survival and life-style change. *Archives of Otolaryngology* 109(11):746–749, November 1983.

STOCKWELL, H.G., LYMAN, G.H. Cigarette smoking and the risk of female reproductive cancer. *American Journal of Obstetrics and Gynecology* 157(1):35–40, July 1987.

STRYKER, W.S., KAPLAN, L.A., STEIN, E.A., STAMPFER, M.J., SOBER, A., WILLETT, W.C. The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. *American Journal of Epidemiology* 127(2):283–296, 1988.

TREVATHAN, E., LAYDE, P., WEBSTER, L.A., ADAMS, J.B., BENIGNO, B.B., ORY, H. Cigarette smoking and dysplasia and carcinoma in situ of the uterine cervix. *Journal of the American Medical Association* 250(4):499–502, July 22–29, 1983.

TRICHOPOULOS, D., DAY, N.E., KAKLAMANI, E., TZONOU, A., MUÑOZ, N., ZAVITSANOS, X., KOUMANTAKI, Y., TRICHOPOULOU, A. Hepatitis B virus, tobacco smoking and ethanol consumption in the etiology of hepatocellular carcinoma. *International Journal of Cancer* 39(1):45–49, January 1987.

TRICHOPOULOS, D., MACMAHON, B., SPARROS, L., MERIKAS, G. Smoking and hepatitis B-negative primary hepatocellular carcinoma. *Journal of the National Cancer Institute* 65(1):111–114, July 1980.

TUYNS, A.J. Oesophageal cancer in non-smoking drinkers and non-drinking smokers. *International Journal of Cancer* 32(4):443–444, October 15, 1983.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health. DHHS Publication No. (PHS) 82-50179, 1982.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *The Health Consequences of Using Smokeless Tobacco. A Report of the Advisory Committee to the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NIH Publication No. 86-2874, April 1986.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. *Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General.* U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. DHHS Publication No. (CDC) 89-8411, 1989.

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.

VINEIS, P., CICCONE, G., GHISETTI, V., TERRACINI, B. Cigarette smoking and bladder cancer in females. *Cancer Letters* 26(1):61–66, February 1985.

VINEIS, P., ESTEVE, J., TERRACINI, B. Bladder cancer and smoking in males: Types of cigarettes, age at start, effect of stopping and interaction with occupation. *International Journal of Cancer* 34(2):165–170, August 15, 1984.

VINEIS, P., FREA, B., UBERTI, E., GHISETTI, V., TERRACINI, B. Bladder cancer and cigarette smoking in males: A case–control study. *Tumori* 69(1):17–22, February 28, 1983.

WHITTEMORE, A.S., WU, M.L., PAFFENBARGER, R.S. JR., SARLES, D.L., KAMPERT, J.B., GROSSER, S., JUNG, D.L., BALLON, S., HENDRICKSON, M. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *American Journal of Epidemiology* 128(6):1228–1240, December 1988.

WIGLE, D.T., MAO, Y., GRACE, M. Relative importance of smoking as a risk factor for selected cancers. *Canadian Journal of Public Health* 71(4):269–275, July–August 1980.

WILLETT, W.C., BROWNE, M.L., BAIN, C., LIPNICK, R.J., STAMPFER, M.J., ROSNER, B., COLDITZ, G.A., HENNEKENS, C.H., SPEIZER, F.E. Relative weight and risk of breast cancer among premenopausal women. *American Journal of Epidemiology* 122:731–740, 1985.

WILLIAMS, R.R., HORM, J.W. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the Third National Cancer Survey. *Journal of the National Cancer Institute* 58(3):525–547, March 1977.

WINKELSTEIN, W. JR. Smoking and cervical cancer—Current status: A review. *American Journal of Epidemiology* 131(6): 945–957, June 1990.

WINKELSTEIN, W. JR., SHILLITOE, E.J., BRAND, R., JOHNSON, K.K. Further comments on cancer of the uterine cervix, smoking, and herpesvirus infection. *American Journal of Epidemiology* 119(1):1–8, January 1984.

WINN, D.M., BLOT, W.J., SHY, C.M., PICKLE, L.W., TOLEDO, A., FRAUMENI, J.F. Snuff dipping and oral cancer among women in the southern United States. *New England Journal of Medicine* 304(13):745–749, March 26, 1981.

WYNDER, E.L., DODO, H., BLOCH, D.A., GANTT, R.C., MOORE, O.S. Epidemiologic investigation of multiple primary cancer of the upper alimentary and respiratory tracts. I. A retrospective study. *Cancer* 24:730–739, 1969.

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

WYNDER, E.L., HALL, N.E.L, POLANSKY, M. Epidemiology of coffee and pancreatic cancer. *Cancer Research* 43(8):3900–3906, August 1983.

WYNDER, E.L., STELLMAN, S.D. Comparative epidemiology of tobacco related cancers. *Cancer Research* 37(12):4608–4622, December 1977.

YU, M.C., MACK, T., HANISCH, R., PETERS, R.L., HENDERSON, B.E., PIKE, M.C. Hepatitis, alcohol consumption, cigarette smoking, and hepatocellular carcinoma in Los Angeles. *Cancer Research* 43(12, Part 1):6077–6079, December 1983.

CHAPTER 6
SMOKING CESSATION AND CARDIOVASCULAR DISEASE

CONTENTS

INTRODUCTION

Cigarette smoking is firmly established as an important cause of coronary heart disease (CHD), arteriosclerotic peripheral vascular disease, and stroke (US DHHS 1983, 1989). Eliminating smoking presents an opportunity for bringing about a major reduction in the occurrence of CHD, the leading cause of death in the United States. Before examining the epidemiologic evidence relating smoking cessation and risk of CHD and other forms of cardiovascular disease (CVD), the mechanisms by which smoking leads to these diseases are briefly reviewed. The objectives in considering these mechanisms are to address the plausibility that smoking cessation reduces risk of CVD, to estimate the expected magnitude in risk reduction, and to assess the rapidity with which any risk reduction might occur. Whether these mechanisms are immediately reversible, irreversible, or slowly reversible is of particular relevance to the rapidity with which smoking cessation will reduce risk. The role of smoking in the pathogenesis of CHD is discussed at length. The etiologies of peripheral vascular disease and stroke share several common features with CHD; thus, discussion focuses on distinguishing features.

PATHOPHYSIOLOGIC FRAMEWORK

Smoking and Development of CHD

Pathogenesis of CHD, which includes the clinical manifestations of myocardial infarction (MI), angina pectoris, and sudden death, is extremely complex and mediated by multiple mechanisms and etiologic factors (Munro and Cotran 1988). At least five interrelated processes are likely to contribute to the clinical manifestations of MI—atherosclerosis, thrombosis, coronary artery spasm, cardiac arrhythmia, and reduced capacity of the blood to deliver oxygen. Smoking appears to influence many steps in the development of CHD. Although not all of these effects are proven fully, the evidence for an influence on several mechanisms is convincing. The exact components of cigarette smoke that are responsible are not known in each instance, but experimental data have implicated nicotine and carbon monoxide (CO) in several processes. Other products of cigarette smoking, such as cadmium, nitric oxide, hydrogen cyanide, and carbon disulfide, have been hypothesized to play a role, but their quantitative contributions remain unknown (US DHHS 1983).

Atherosclerosis

Atherosclerosis is the mechanical narrowing of medium-sized arteries by the proliferation of smooth muscle cells, lipid accumulation, and ultimately, plaque formation and calcification (Munro and Cotran 1988). These lesions develop over decades and are not immediately reversible; whether they are substantially reversible at all in humans is a matter of current interest. Reversibility has been demonstrated in nonhuman primates (Clarkson et al. 1984; Malinow and Blaton 1984) and suggested in studies of humans using repeated arteriography (Blankenhorn et al. 1987). Smoking is

clearly associated with the presence of atherosclerosis of the coronary arteries, small arteries of the myocardium, the aorta, and other vessels as demonstrated in many autopsy and angiographic studies (US DHHS 1983). The development of atherosclerosis is complex, and several processes are likely to be important.

Endothelial damage is thought to play a primary role in the development of atherosclerosis by exposing the arterial intima to blood lipids and white cells and by stimulating platelet adhesion. The endothelial damage can be an actual physical denudation, but toxic functional damage may have similar consequences. In animal studies, serum nicotine at levels similar to those of human smokers caused endothelial damage (Krupski et al. 1987; Zimmerman and McGeachie 1987). Evidence that smoking has a direct toxic effect on human endothelium is provided by the observation that smoking 2 tobacco cigarettes approximately doubled the number of nuclear-damaged endothelial cells in circulating blood (Davis et al. 1985, 1986); smoking non-tobacco cigarettes had little effect. In addition, Asmussen and Kjeldsen (1975) found pronounced degenerative changes of the umbilical artery endothelium at the time of delivery among mothers who smoked; these changes were not present in the arteries of nonsmoking mothers.

Smooth muscle cell proliferation is a primary feature of atherosclerotic lesions and may result from several stimuli; the most clearly demonstrated is platelet-derived growth factor from adherent platelets. Smoking appears to increase the adherence of platelets to arterial endothelium: blood drawn from persons after smoking 2 cigarettes results in a more-than-hundredfold adhesion of platelets to rabbit endothelium than does blood drawn from persons before smoking or from never smokers (Pittilo et al. 1984). Platelets from chronic smokers have a greater tendency to aggregate on an artificial surface than do those from nonsmokers (Rival, Riddle, Stein 1987). In minipigs, both cigarette smoke and CO increase the adhesion of platelets to arterial endothelium (Marshall 1986). The influence of smoking on platelet activity is discussed further in the following section.

Lipid infiltration of the arterial intima, largely cholesterol, is another primary feature of atherosclerosis and is directly related to higher blood levels of low-density lipoprotein cholesterol (LDL-C) and reduced blood levels of high-density lipoprotein cholesterol (HDL-C). Smoking reduces the level of HDL-C. A strong inverse association between daily cigarette consumption and HDL-C has been observed in many cross-sectional studies in the United States (Freedman et al. 1987; Gordon and Doyle 1986; Reichley, Mueller, Hanis et al. 1987; Willett et al. 1983) and in other countries (Assmann, Schulte, Schriewer 1984; Goldbourt et al. 1986; Gomo 1986; Jacobsen and Thelle 1987; Pelletier and Baker 1987; Robinson et al. 1987; Tuomilehto et al. 1986). In a longitudinal, community-based study, HDL-C decreased among persons starting to smoke and increased among those who stopped smoking (Fortmann, Haskell, Williams 1986). In other prospective studies, smoking abstinence has been associated with substantial increases in HDL-C levels in both men and women (Hulley, Cohen, Widdowson 1977; Hubert et al. 1987; Rabkin 1984). In a study among young adults in Louisiana, those who began smoking experienced substantial reductions in HDL-C compared with those who did not start (Freedman et al. 1986). HDL-C increased among 13 adult women who successfully stopped smoking for 48 days, but decreased to its

previous levels among those who returned to smoking (Stamford et al. 1986). Thus, data indicate that smoking reduces the level of HDL-C, a potent protective factor against CHD.

In a number of studies, smokers have been found to have higher levels of triglycerides (Freedman et al. 1986; Jacobsen and Thelle 1987; Gomo 1986; Willett et al. 1983); however, the independent relation of triglyceride level with risk of CHD is not clear. Smoking appears to have little, if any, relation with LDL-C level. However, smokers have approximately twice the level of serum malondialdehyde of nonsmokers (Nadiger, Mathew, Sadasivudu 1987); malondialdehyde can alter LDL-C and may promote its incorporation into arterial wall macrophages (Steinberg et al. 1989). In a metabolic study among young men, smokers had a decreased cholesterol net transport from cell membranes into plasma, which could partially explain the accumulation of cholesterol in arterial walls (de Parscau and Fielding 1986).

Thrombosis

Coronary artery thrombosis, resulting from platelet-fibrin thrombi, is a key element in most cases of MI. Thrombi are visualized in a high percentage of coronary arteries studied angiographically within hours of the onset of infarction (DeWood et al. 1980), and agents that lyse thrombi are effective treatments for MI (Stampfer et al. 1982; Loscalzo and Braunwald 1988). The efficacy of aspirin, an antiplatelet agent, in preventing MI further supports the role of thrombus formation (Steering Committee of the Physicians' Health Study Research Group 1989). The finding that smoking is associated with history of MI even after controlling for atherosclerosis (Hartz et al. 1981) emphasizes the importance of mechanisms in addition to those that promote atherosclerosis.

Platelets play a central role in thrombus formation in addition to releasing growth factors that stimulate the proliferation of smooth muscle cells in arterial intima (Packham and Mustard 1986). Platelets can form microthrombi that become incorporated into the arterial wall, thus contributing to plaque formation and participating in generation of larger platelet-fibrin thrombi that may acutely occlude a coronary artery. Smoking cigarettes acutely increases spontaneous platelet aggregation in humans (Davis et al. 1985) and in dogs with coronary artery stenosis (Folts and Bonebrake 1982). Madsen and Dyerberg (1984) observed that smoking 2 high-nicotine cigarettes substantially reduced bleeding time among healthy young men, although ex vivo tests of platelet aggregability were only minimally inhibited. In this study, smoking low-nicotine cigarettes and inhalation of CO had little effect on bleeding time. Shortened platelet survival, an indirect indicator of activation, was observed in smokers and reverted to normal after 4 weeks of smoking abstinence (Fuster et al. 1981).

Studies of smoking and platelet aggregation ex vivo in response to the typical stimuli used in the laboratory, such as adenosine diphosphate (ADP) or thrombin, are inconsistent. Increased aggregation has been seen with platelets from chronic smokers (Belch et al. 1984) and in blood drawn 10 minutes after smoking 1 cigarette (Renaud et al. 1985; Renaud et al. 1984); in the latter study, aggregation was associated with blood nicotine levels but not with carboxyhemoglobin (COHb) levels. However, in

other studies, ex vivo platelet aggregation was not related to cigarette smoking (Pittilo et al. 1984; Dotevall et al. 1987; de Lorgeril et al. 1985; Madsen and Dyerberg 1984). In one large study, aggregation in response to ADP stimulation was actually somewhat greater in nonsmokers (Meade et al. 1985). Studies of the effect of smoking on platelet production of thromboxane, which mediates the aggregatory effect, have also been inconsistent. In some studies, smoking was found to acutely increase thromboxane blood levels, which reflect the capacity to produce thromboxane in response to stimulation, and urinary metabolites, which reflect the normal steady-state production (Toivanen, Ylikorkala, Viinikka 1986; Marasini et al. 1986; Fischer et al. 1986). However, serum thromboxane B_2 levels were found to be similar among chronic smokers compared with nonsmokers in another study (Dotevall et al. 1987). The serious limitations of ex vivo aggregability measurements in the evaluation of in vivo platelet activity have been noted (Fitzgerald, Oates, Nowak 1988). These researchers measured urinary excretion of a thromboxane metabolite and found elevated levels in chronic smokers that were reduced to the level of nonsmokers after aspirin administration, suggesting a platelet origin of the excess excretion (Nowak et al. 1987).

The lack of a consistent relation between smoking and ex vivo tests of platelet aggregability despite the demonstration that platelets of smokers adhere more readily to endothelium has led to the suggestion that smoking inhibits the production in arterial walls of prostacyclin, an inhibitor of platelet aggregation (Madsen and Dyerberg 1984). Reinders and coworkers (1986) demonstrated that the production of prostacyclin by cultured human endothelial cells is impaired by incubation with cigarette smoke condensate. Pittilo and colleagues (1982) also found that smoking reduces endothelial cell synthesis of prostacyclin in rats. Thus, in vivo smoking-related effects on platelet function may be mediated in part by an interaction with endothelium.

Fibrinogen levels have been found to be elevated among smokers in numerous cross-sectional studies (Meade et al. 1986; Kannel, D'Agostino, Belanger 1987; Wilhelmsen et al. 1984; Dotevall et al. 1987; Belch et al. 1984; Balleisen et al. 1985). Fibrinogen levels, in turn, are strongly related to risk of CHD and stroke (Meade et al. 1986; Kannel, D'Agostino, Belanger 1987; Wilhelmsen et al. 1984). Smoking cessation resulted in a decrease in fibrinogen levels after 4 weeks among 9 female smokers (Harenberg et al. 1985) and after 8 weeks among 14 male smokers (Ernst and Matrai 1987). In the latter study, the levels after 8 weeks were similar to those among never smokers. When fibrinogen was remeasured after 5 years, values had decreased to the levels of never smokers among men who had stopped smoking and had increased among those who started or resumed smoking (Meade, Imeson, Stirling 1987). In multivariate analyses of data from the Framingham Study (Kannel, D'Agostino, Belanger 1987) and Northwick Park Study (Meade et al. 1986) that both included cigarette smoking as well as fibrinogen levels, fibrinogen retained a clear independent association with risk of CHD, whereas the effect of smoking was substantially reduced after the inclusion of fibrinogen in the model. This analysis suggests that elevated fibrinogen levels may mediate a quantitatively important part of the effect of smoking on CHD risk.

Other clotting abnormalities, such as increased plasma viscosity and reduced red cell deformability, that tend to promote thrombus formation have also been observed in smokers (Belch et al. 1984). In addition, levels of plasminogen, which promotes lysis

of thrombi, are lower in smokers (Wilhelmsen et al. 1984; Belch et al. 1984), but the levels increase after smoking cessation (Harenberg et al. 1985).

Spasm

Coronary artery spasm can cause acute ischemia manifested as angina pectoris and may promote thrombus formation at the site of repeated arterial constriction (Folts and Bonebrake 1982). Both chronic and acute cigarette smoking have a demonstrable vasoconstrictor effect on the coronary vasculature (Klein 1984). Compared with never smokers, current smokers have an approximately twentyfold risk of vasospastic angina pectoris (Scholl et al. 1986). Coronary artery spasm has also been identified by angiography after smoking a single cigarette (Maouad et al. 1984). Smoking-induced vasoconstriction has been demonstrated in patients with atherosclerotic coronary artery disease (Martin et al. 1984) that is mediated by an α-adrenergic increase in coronary artery tone (Winniford et al. 1986). In addition, smoking acutely increases platelet and plasma vasopressin (Nussey et al. 1986) as well as the carrier protein of vasopressin and oxytocin (de Lorgeril et al. 1985). In addition to causing acute arterial spasm, cigarette smoking appears to be associated with a reduction in long-term coronary artery diameter independent of atherosclerotic plaque (Fried, Moore, Pearson 1986), although the mechanism for this relationship is unclear.

Arrhythmias

In some instances, arrhythmias can precipitate MI by reducing cardiac output or increasing myocardial demand. More importantly, arrhythmias are a major complication of infarction. Thus, reducing the threshold for serious arrhythmias tends to increase the case-fatality rate of MI. Cigarette smoking was found to lower the threshold for ventricular fibrillation in a study of animals (Downey et al. 1977) and was found to be associated with a 21-percent increased prevalence of ventricular premature beats on two-minute electrocardiographic rhythm strips obtained from 10,119 men (Hennekens et al. 1980). Smoking-related ventricular arrhythmias may contribute to the occurrence of sudden death and to increased case-fatality ratios during the course of MI.

Reduced Blood Oxygen Delivery

Cigarette smoking acutely increases myocardial oxygen demand by raising peripheral resistance, blood pressure, and heart rate (Martin et al. 1984; Klein 1984). Concurrently, the capacity of the blood to deliver oxygen is reduced by increased COHb, greater viscosity (Galea and Davidson 1985), and higher coronary vascular resistance. Imbalance between oxygen requirement and delivery as a result of these factors is not likely to be a cause of MI but may contribute to infarction in the presence of significant atherosclerotic narrowing of vessels. Consistent with these mechanisms, low levels of COHb exacerbate myocardial ischemia during graded exercise (Allred et al. 1989), and smoking is associated with more frequent and longer ischemic episodes detected by ambulatory electrocardiographic monitoring among patients with chronic

stable CHD (Barry et al. 1989). Blood and plasma viscosities among former smokers are lower than those among current smokers and similar to those among never smokers (Ernst and Matrai 1987). In the same study, both blood and plasma viscosity decreased after smoking cessation and were similar to levels of never smokers after 8 weeks. Reduced oxygen delivery to the myocardium may play a role in lowering the threshold for ventricular arrhythmias.

In addition to influencing the development of CHD, smoking has been hypothesized to have direct toxic effects on the myocardium. Hartz and coworkers (1984) found a nearly threefold increased prevalence of diffuse ventricular hypokinesis among heavy smokers compared with never smokers within a population of patients undergoing diagnostic coronary angiography and ventriculography.

Smoking and Development of Peripheral Arterial Disease

The extremely strong association between smoking and peripheral artery disease is likely to be mediated largely through the mechanisms that promote atherosclerosis (Criqui et al. 1989). The peripheral vasoconstrictive effects of smoking, mediated by nicotine-stimulated release of catecholamines (US DHHS 1983), are likely to play a further important role (Lusby et al. 1981).

Smoking and Development of Cerebrovascular Disease

Cerebrovascular disease represents a heterogeneous group of pathologic processes that include infarction due to stenosis and thrombosis (referred to here as ischemic stroke), embolism from the heart, and hemorrhage from medium-sized vessels in the subarachnoid space (subarachnoid hemorrhage) and from microaneurysms of small penetrating vessels (intracerebral hemorrhage). The association of smoking with ischemic stroke is likely to be mediated largely through the mechanisms that promote atherosclerosis and thrombus formation. Associations between smoking and extent of cerebral artery atherosclerosis have been observed at autopsy among persons who have died of causes unrelated to CVD (Reed et al. 1988) and among volunteers in a cross-sectional study evaluated by a noninvasive method (Rogers et al. 1983). Smoking was also a strong predictor of the extent and severity of cerebral vessel atherosclerosis in an Italian multicenter study of reversible cerebral ischemic attacks (Passero et al. 1987) and in an investigation of 28 pairs of Finnish twins (Haapanen et al. 1989).

The mechanistic basis is unknown for the strong relation between smoking and subarachnoid hemorrhage (US DHHS 1989; Shinton and Beevers 1989), which is thought to result most commonly from the rupture of a saccular aneurysm. Although hypertension is associated with this occurrence, chronic smoking is unrelated to sustained elevation in blood pressure. A weak and clinically unimportant inverse relation with hypertension has been seen in several studies (Schoenenberger 1982; US DHHS 1983), although the association between cigarette smoking and risk of hypertension was observed in a large prospective investigation (Witteman et al. 1990).

Anticipated Effects of Smoking Cessation on Risk of Cardiovascular Diseases Based on Knowledge of Mechanisms

The possible effects of smoking cessation on the risk of CHD are illustrated in Figure 1. The incidence of CHD increases sharply with age among both smokers and never smokers; similar patterns are seen with other smoking-related cardiovascular diseases. At each age, the rates are higher for smokers, and the increase with age is more rapid among smokers (US DHHS 1983; ACS, unpublished tabulations), probably because of the ongoing, cumulative damage caused by smoking. Thus, the absolute excess incidence or mortality (attributable risk) of CHD due to smoking, represented by the vertical difference between the lines for smokers and never smokers in Figure 1, increases with age. However, the relative risk, represented by the ratio of incidence or mortality rates, tends to decrease with age.

Theoretically possible outcomes of smoking cessation are depicted by lines A, B, and C (Figure 1). Line A represents an immediate and complete reversal of the effect of smoking, so that the quitter almost instantly assumes the rate of the never smoker. Line B represents the worst-case scenario; although the stimulus for progressive damage is removed, no reversibility exists so that the former smoker assumes a constant absolute excess risk above that of the never smoker. In this case, it is apparent that quitting would still provide a substantial benefit compared with not quitting and that the relative risk for a former smoker compared with a never smoker would decline over time. An intermediate effect of smoking cessation is depicted by line C; the effects of smoking are slowly reversed, and the rate for the quitter gradually approaches that of the never smoker.

The effects of smoking on CHD are probably mediated by multiple mechanisms, several of which are well established. Some of the effects of smoking appear to be reversible within days or weeks, including the increase in platelet activation, clotting factors, COHb, coronary artery spasm, and increased susceptibility to ventricular arrhythmias. Other effects may be irreversible or only slowly reversible, such as the development of atherosclerosis as a result of smooth muscle proliferation and lipid deposition in the arterial intima resulting from lower HDL-C levels. Thus, persons who stop smoking are likely to experience a component of rapid decline in risk compared with those who continue to smoke and another component that more slowly approaches the risk of never smokers. Because the effects of smoking are multiple and complex, the rapidity and magnitude of risk reduction achieved by smoking cessation can best be estimated by empirical data based on epidemiologic studies in humans. Available data are examined in detail in the remaining sections of this Chapter.

SMOKING CESSATION AND CHD

Epidemiologic evidence on smoking and CHD has been reviewed in detail in previous reports of the U.S. Surgeon General (US PHS 1964; US DHEW 1971, 1979; US DHHS 1983, 1989). After an exhaustive review of the data, the 1983 Report of the Surgeon General concluded that "cigarette smoking is a major cause of CHD in the United States for both men and women" and "should be considered the most important of the known

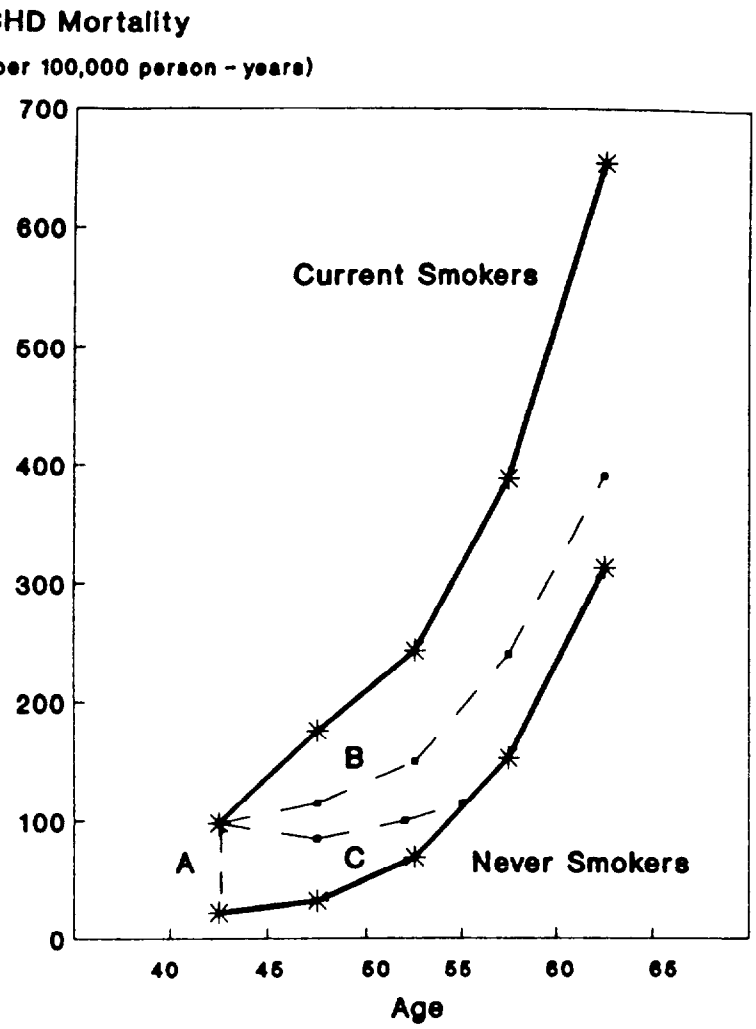

FIGURE 1.—Hypothetical effects of smoking cessation on risk of CHD if mechanisms are predominantly rapidly reversible (A), irreversible (B), or slowly reversible (C). (CHD mortality rates shown in solid lines are for men in ACS CPS-II, 1982–86.)

NOTE: CHD=coronary heart disease; ACS CPS-II=American Cancer Society Cancer Prevention Study II.

SOURCE: Unpublished tabulations, American Cancer Society.

modifiable risk factors for CHD" (US DHHS 1983, p.6). Overall, the Report noted that smokers have about a 70-percent excess death rate from CHD, and heavier smokers have an even greater excess risk.

Since 1983, additional evidence has accumulated to further support these conclusions. Some of these data were presented or summarized in the 1989 Report of the Surgeon General (US DHHS 1989). For 1985, cigarette smoking was estimated to be responsible for 21 percent of all CHD deaths in the United States among men aged 65 years or older and for 45 percent of CHD deaths among younger men. Twelve percent of the CHD deaths among women aged 65 or older and 41 percent of those in younger women were attributed to cigarette smoking. In 1985, 115,000 deaths from CHD were attributed to cigarette smoking.

A large amount of data supports the view that active cigarette smoking substantially increases risk of CHD. Data also indicate that former smokers have a lower risk of CHD than do current smokers. Despite methodologic and geographic differences, the studies are remarkably consistent in demonstrating a reduced risk of CHD among former smokers. Much of this literature has been reviewed in earlier reports of the Surgeon General (US DHEW 1979; US DHHS 1983) as well as by Kuller and colleagues (1982).

This Section reviews the epidemiologic evidence of the effects of cigarette smoking cessation on CHD risk, specifically MI and CHD death. The relevant studies may be divided into those that examine the effect among apparently healthy individuals (primary prevention) and the effect among individuals already diagnosed with CHD for risk of recurrence or CHD death (secondary prevention). Cross-sectional studies of the extent of coronary atherosclerosis also provide relevant information.

Cross-Sectional Studies

In a detailed study of coronary atherosclerosis, Auerbach and coworkers (1976) examined 1,056 autopsied hearts from patients at the East Orange Veterans Administration Hospital and found that smokers had more severe disease than never smokers, with past smokers having intermediate levels. Those who died from CHD or diabetes or those who had hearts weighing more than 500 g were excluded. After adjustment for age, current cigarette smokers had a prevalence of advanced CHD that ranged from 11.7 to 23.4 percent, depending on the number of cigarettes smoked per day. The prevalence among never smokers was 5.3 percent compared with 11.0 percent among former smokers. The prevalence odds ratio of advanced versus no disease or minimal disease was 2.4, when former smokers were compared with never smokers. In contrast, among current smokers of 1 to 2 packs per day, the ratio was 6.7. A similar pattern was observed for different pathologic manifestations of CHD. The effect of duration of abstinence among former smokers was not analyzed.

Ramsdale and coworkers (1985) used arteriography to assess the extent of coronary atherosclerosis before surgery for valve replacement among 387 patients. All patients provided a smoking history, including age at initiation of smoking and cessation of smoking and average number of cigarettes smoked per week. Among never smokers, 87 percent had no stenosis greater than 50 percent; only 60 percent of past smokers and 60 percent of current smokers were without this degree of stenosis. Of never smokers, only 2.6 percent had three or more arteries affected compared with 10.6 percent of former smokers and 12.2 percent of current smokers. Both current and past smokers

had more severe coronary artery disease. The median score among never smokers and current smokers was 0.2 and 2.8, respectively. For past smokers, the data were presented by duration since quitting. There was no evidence for a trend of decreased effect by increasing time since cessation. The median score for those quitting within the previous 5 years was 5.0; for 5 to 10 years, 5.0; and for 10 years or more, 7.5. Coronary atherosclerosis was positively correlated with lifetime number of cigarettes smoked among both current or past smokers. In this study, past smokers had a slightly worse coronary risk profile than other groups. No information was provided about past or concurrent illness that may have motivated the former smokers to quit. Nonetheless, this study supports the view that cigarette smoking is a risk factor for atherosclerosis and that a substantial duration of abstinence may be necessary to appreciably reduce its extent.

Weintraub and coworkers (1985) evaluated smoking history in 1,349 coronary arteriography patients. Of these patients, 984 had significant coronary disease (75 percent or more obstruction). Amount of current smoking was not a significant predictor of serious obstruction after total pack-years were considered. On average, the risk for such obstruction increased by about 1 percent per pack-year.

Cross-sectional studies of arteriographic findings can be difficult to interpret because patients undergoing angiography are clearly not representative of the general population. Nonetheless, these studies support the view that smoking causes an increase in atherosclerosis and that very recent quitting has little impact on coronary stenosis.

Fried, Moore, and Pearson (1986) studied the effects of smoking by assessing the coronary diameter in 31 men who had normal coronary arteriograms. Men with any detectable stenosis in the main coronary arteries or more than 25 percent in any coronary branch were excluded to assess the effects of smoking on the caliber of coronary arteries in the absence of atherosclerosis. These researchers found that after adjustment for alcohol intake (which is associated with wider arteries), current and former smokers had 40 to 50 percent narrower arteries than did never smokers. The past smokers had somewhat narrower arteries than current smokers although this was not statistically significant. Of the 11 ex-smokers, 6 had quit in the previous year. This study suggests the possibility of another persisting effect of smoking, apart from promoting atherosclerosis, not rapidly reversed by cessation.

Studies of Smoking Cessation and Risk of MI Among Healthy Persons

Case–Control Studies

Table 1 summarizes data from case–control studies (Willett et al. 1981; Rosenberg, Kaufman, Helmrich, Miller et al. 1985; LaVecchia et al. 1987; Rosenberg, Palmer, Shapiro 1990), of men and women from the United States and abroad. Prospective studies of CHD are generally considered less prone to bias than case–control studies, although case–control studies are probably less susceptible to misclassification resulting from resumption of smoking among former smokers. For example, an individual diagnosed with a recent MI can probably recall his or her smoking status just before the infarction with considerable accuracy (Chapter 2). Thus, case–control studies may