

tious in the upper and lower airways. Such alterations could be expected to interfere with the cleansing mechanisms of the lung.

Pathological changes in pulmonary parenchyma, such as rupture of alveolar septa and fibrosis, have a remarkably close association with past history of cigarette smoking. These changes cannot be related with certainty to emphysema or other recognized diseases at the present time.

Chronic bronchitis and pulmonary emphysema are the chronic bronchopulmonary diseases of greatest health significance. Epidemiological evidence provides the most important information relating cigarette smoking to chronic bronchitis and emphysema. All seven of the major prospective studies show a higher mortality rate for chronic bronchitis and emphysema among cigarette smokers than among non-smokers. In the few studies that have examined mortality rates separately for the two conditions, chronic bronchitis or emphysema, both rates are higher among cigarette smokers than among non-smokers. In one of the studies, the risk of mortality from chronic bronchitis was four times greater among cigarette smokers than among non-smokers. Emphysema was listed as a cause of death 13 times more frequently among smokers in one study, and  $7\frac{1}{2}$  times more frequently among smokers in another study.

Extensive prevalence studies, based largely on prevalence of specific symptoms and signs rather than imprecise diagnostic labels, show a consistently more frequent occurrence of cough, sputum, or the two symptoms combined, in cigarette smokers than in non-smokers. These manifestations are the clinical expressions found in chronic bronchitis. The results of the prevalence surveys, however, offer less direct evidence relating cigarette smoking to pulmonary emphysema, as clinical diagnosis of this disease is less exact. Breathlessness, which may result from emphysema or airway obstruction in chronic bronchitis, is associated with cigarette smoking in males, particularly in the older age groups, but not females. Similarly, a consistent association of cigarette smoking and chest illness is more evident for males. In the prevalence surveys in which various combinations of respiratory manifestations have been studied, a greater prevalence of these conditions is found consistently among cigarette smokers.

The majority of clinical studies have noted a relationship between cigarette smoking and chronic bronchitis and emphysema. Cigarette smoking is a more common habit in the United States among patients with chronic bronchitis or emphysema than in the control groups studied. The clinical studies also show a decrease in clinical manifestations of chronic bronchopulmonary disease after cessation of smoking.

Examination of experimental evidence shows that the lung may be damaged by noxious agents found in either tobacco smoke or atmospheric pollution. In the United States, the noxious agents from cigarette smoking are much more important in the causation of chronic bronchopulmonary disease than are those present as community air pollutants. In the United Kingdom, persons who smoke cigarettes and are exposed frequently to atmospheric pollutants are at greater risk of developing disabling respiratory disease and death than those exposed to either alone.

The relative importance of cigarette smoking also appears to be much greater than occupational exposure as an etiologic factor for the chronic bronchopulmonary diseases.

Cigarette smoking does not appear to cause asthma; in rare instances, allergy to tobacco products has been ascribed a causative role in asthma-like syndromes.

Evidence does not support a direct association between smoking and infectious diseases of the respiratory system. The category, influenza and pneumonia, contributes moderately to the excess mortality of cigarette smokers but other data are not available to extend this observation. The association of cigarette smoking and tuberculosis does not appear to be a direct one, but both are associated with the use of alcohol.

Only for "stomatitis nicotina" and the epithelial changes in the larynx is there sufficient documentation to substantiate the clinical opinion that non-malignant alterations in the mouth, nose, or throat are induced by smoking. The changes in the mouth are more often associated with pipe smoking but disappear after cessation of smoking.

## CONCLUSIONS

1. Cigarette smoking is the most important of the causes of chronic bronchitis in the United States, and increases the risk of dying from chronic bronchitis.

2. A relationship exists between pulmonary emphysema and cigarette smoking but it has not been established that the relationship is causal. The smoking of cigarettes is associated with an increased risk of dying from pulmonary emphysema.

3. For the bulk of the population of the United States, the importance of cigarette smoking as a cause of chronic bronchopulmonary disease is much greater than that of atmospheric pollution or occupational exposures.

4. Cough, sputum production, or the two combined are consistently more frequent among cigarette smokers than among non-smokers.

5. Cigarette smoking is associated with a reduction in ventilatory function. Among males, cigarette smokers have a greater prevalence of breathlessness than non-smokers.

6. Cigarette smoking does not appear to cause asthma.

7. Although death certification shows that cigarette smokers have a moderately increased risk of death from influenza and pneumonia, an association of cigarette smoking and infectious diseases is not otherwise substantiated.

## REFERENCES

1. Abbott, C. A., Hopkins, W. A., Van Fleit, W. E., Robinson, J. S. A new approach to pulmonary emphysema. *Thorax* 8: 116-32, 1953.
2. Albert, R. E., Nelson, N. Special report to the Surgeon General's Advisory Committee on Smoking and Health.

3. Altschuler, B. L. Personal communication to the Surgeon General's Advisory Committee on Smoking and Health.
4. American Thoracic Society. Definitions and classification of chronic bronchitis, asthma and pulmonary emphysema. *Amer Rev Resp Dis* 85: 762, 1962.
5. Amdur, M. O. The effect of aerosols on the response to irritant gases. In: Davies, C. N. ed. *Proceedings of International Symposium on Inhaled Particles and Vapors*. Oxford, England, April 1960. London. Pergamon Press, 1961. p. 281-92.
6. Anderson, D. O., Ferris, B. G., Jr. Role of tobacco smoking in the causation of chronic respiratory disease. *New Eng J Med* 267: 787-94, 1962.
7. Ashford, J. R., Brown, S., Duffield, D. P., Smith, C. S., Fay, J. W. J. The relation between smoking habits and physique, respiratory symptoms, ventilatory function, and radiological pneumoconiosis, amongst coal workers at three Scottish collieries. *Brit J Prev Soc Med* 15: 106-17, 1961.
8. Attinger, E. O., Goldstein, M. M., Segal, M. S. Effects of smoking upon the mechanics of breathing: I. In normal subjects. II. In patients with cardiopulmonary disease. *Amer Rev Tuberc* 77: 1-16, 1958.
9. Auerbach, O., Stout, A. P., Hammond, E. C., Garfinkel, L. Bronchial epithelium in former smokers. *N Eng J Med* 267: 119-25, 1962.
10. Auerbach, O., Stout, A. P., Hammond, E. C., Garfinkel, L. Changes in the bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. *New Eng J Med* 265: 253-67, 1961.
11. Auerbach, O., Stout, A. P., Hammond, E. C., Garfinkel, L. Changes in bronchial epithelium in relation to sex, age, residence, smoking and pneumonia. *New Eng J Med* 267: 111-9, 1962.
12. Auerbach, O., Stout, A. P., Hammond, E. C., Garfinkel, L. Smoking habits and age in relation to pulmonary changes: rupture of the alveolar septums, fibrosis and thickening of walls of small arteries and arterioles. *New Eng J Med* 269: 1045-53, 1963.
13. Badham, C. Observations on the inflammatory affections of the mucous membranes of the bronchia. London, Callow, 1808.
14. Badham, C. Practical observations on the pneumonic diseases of the poor. *Edinburgh Med Surg J* 1: 166-70, 1805.
15. Balchum, C. J., Dybicki, J., Meneely, G. R. The dynamics of sulphur dioxide inhalation. *AMA Arch Industr Health*. (Chicago) 21: 564, 1960.
16. Balchum, O. J., Felton, J. S., Jamison, J. N., Gaines, R. S., Clarke, D. R., Owan, T. A survey for chronic respiratory disease in an industrial city. *Amer Rev Resp Dis* 86: 675-85, 1962.
17. Ballenger, J. J. Experimental effect of cigarette smoke on human respiratory cilia. *New Eng J Med* 263: 832-5, 1960.
18. Baumberger, J. P. The amount of smoke produced from tobacco and its absorption in smoking as determined by electrical precipitation. *J Pharmacol Exp Ther* 21: 47-57, 1927.

19. Becklake, M. R., Goldman, H. I., Bosman, A. R., Freed, C. C. Long-term effects of exposure to nitrous fumes. *Amer Rev Tuberc and Pul Dis* 76: 398-409, 1957.
20. Bickerman, H. A., Barach, A. L. The effect of cigarette smoking on ventilatory function in patients with bronchial asthma and obstructive pulmonary emphysema. *J Lab Clin Med* 43: 455-62, 1954.
21. Boake, W. C. A study of illness in a group of Cleveland families. *New Eng J Med* 259: 1245-9, 1958.
22. Boche, R. D., Quilligan, J. J. The effects of air pollutants on tissue cultures. *Fed Proc Bull* 18: 559, 1959.
23. Bokhaven, C., Niessen, H. J. Amounts of oxides of nitrogen and carbon monoxide in cigarette smoke, with and without inhalation. *Nature (London)* 192: 458-9, 1961.
24. Boren, H. Carbon as a carrier mechanism for irritant gases. Presented at California State Department of Public Health Sixth Air Pollution Medical Research Conference. San Francisco, 1963.
25. Boucot, K. R., Cooper, D. A., Weiss, W. Smoking and health of older men. 1. Smoking and chronic cough. *Arch Environ Health (Chicago)* 4: 59-78, 1962.
26. Bower, G. Respiratory symptoms and ventilatory function in 172 adults employed in a bank. *Amer Rev Resp Dis* 83: 684-9, 1961.
27. Brinkman, G. L., Coates, E. O., Jr. The prevalence of chronic bronchitis in an industrial population. *Amer Rev Resp Dis* 86: 47-55, 1962.
28. Bronchitis. Report of a Sub-Committee of the Standing Medical Advisory Committee, Scottish Home and Health Department. Edinburgh, H M Stationery Off, 1963. 59 p.
29. Brown, K. E., Campbell, A. H. Tobacco, alcohol, and tuberculosis. *Brit J Dis Chest* 55: 150-8, 1961.
30. Butler, W. T., Alling, D. W., Knight, V. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
31. Chang, S. C. Microscopic properties of whole mounts and sections of human bronchial epithelium of smokers and non-smokers. *Cancer* 10: 1246-61, 1957.
32. Chang, S. C. Studies of bronchial epithelium from smokers and non-smokers. [Abstract] *Proc Amer Ass Cancer Res* 2: 99-100, 1956.
33. Chang, C. S. Studies of subepithelial tissue of bronchi from smokers and non-smokers. [Abstract] *Proc Amer Ass Cancer Res* 2: 286-7, 1958.
34. Chapman, I., Redish, C. H. Tobacco-induced epithelial proliferation in human subject. Long-term effects of pipe smoking on epithelium of hard palate. *AMA Arch Path* 70: 133-40, 1960.
35. Chatgidakis, C. B. A study of bronchial mucous glands in white South African gold miners. *AMA Arch Environ Health* 1: 335-42, 1960.
36. Chivers, C. P. Respiratory function and disease among workers in alkaline dusts. *Brit J Industr Med* 16: 51-60, 1959.
37. College of General Practitioners: Chronic bronchitis in Great Britain: A national survey. *Brit Med J* 2: 973-9, 1961.

38. Cross, K. R., Walz, D. V., Palmer, G. K., Warner, E. D. A study of the tracheobronchial epithelium and changes related to smoking. *J Iowa Med Soc* 51: 137-40, 1961.
39. Dalhamn, T. The effect of cigarette smoke on ciliary activity in the upper respiratory tract. *AMA Arch Otolaryng* 70: 166-8, 1959.
40. Dalhamn, T., Rhodin, J. Mucous flow and ciliary activity in the trachea of rats exposed to pulmonary irritant gas. *Brit J Industr Med* 13: 110-3, 1956.
41. Davies, C. M. The handling of particles by the human lung. *Brit. Med Bull* 19: 49, 1963.
42. Deichmann, W. B., Kitzmiller, M. D., Witherup, S. The effects upon experimental animals of the inhalation of phenol vapor. *Amer J Clin Path* 14: 273, 1944.
43. Deichmann, W. B., Witherup, S., Dierker, M. Phenol studies 12. *J Pharmacol Exp Ther* 105: 265, 1952.
44. Densen, P. M., Breuer, J., Bass, H. E., Jones, E. W. New York City Health Department Chronic Respiratory Disease Survey, Interim Report. May 1963.
45. Devine, K. D. Pathologic effects of smoking on the larynx and oral cavity. *Proc Mayo Clin* 35: 349-52, 1960.
46. Djuric, D., Raicevic, P., Konstantinovic, I. Excretion of thiocyanate in the urine of smokers. *Arch Environ Health* 5: 12-5, 1962.
47. Dorn, H. F. Personal communication to the Surgeon General's Advisory Committee on Smoking and Health.
48. Dorn, H. F. The increasing mortality from chronic respiratory diseases. *Amer Stat Ass Proc Soc Stat Sec* p. 148-53, 1961.
49. Dorn, H. F. The mortality of smokers and non-smokers. *Amer Stat Ass Proc Soc Stat Sec* p. 34-71, 1958.
50. Dowling, H. F., Jackson, G. G., Inouye, T. Transmission of the experimental common cold in volunteers. 2. The effect of certain host factors upon susceptibility. *J Lab Clin Med* 50: 516-25, 1957.
51. Dysinger, P. W., Lemon, F. R. Pulmonary emphysema in a non-smoking population. *Dis Chest* 43: 17-25, 1963.
52. Ebert, R. V., Filley, G., Miller, W. F. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
53. Ebert, R. V., Pierce, J. A. Pathogenesis of pulmonary emphysema. *Arch Intern Med* 111: 34, 1963.
54. Edwards, F., McKeown, T., Whitfield, A. G. W. Association between smoking and disease in men over sixty. *Lancet* 1: 196, 1959.
55. Edwards, J. H. Contribution of cigarette smoking to respiratory disease. *Brit J Prev Soc Med* 11: 10-21, 1957.
56. Eich, R. H., Gilbert, R., Auchincloss, J. H., Jr. The acute effect of smoking on the mechanics of respiration in chronic obstructive pulmonary emphysema. *Amer Rev Tuberc* 76: 22, 1957.
57. Ermala, P., Holsti, L. R. Distribution and absorption of tobacco tars in organs of the respiratory tract. *Cancer* 8: 673, 1955.
58. Fairbairn, A. S., Fletcher, C. M., Tinker, C. M., Wood, C. H. A comparison of spirometric and peak expiratory flow measurements in men with and without chronic bronchitis. *Thorax* 17: 168-71, 1962.

59. Falk, H. L., Tremen, H. M., Kotin, P. Effects of cigarette smoke and its constituents on ciliated mucus-secreting epithelium. *J Nat Cancer Inst* 23: 999-1012, 1959.
60. Fassett, D. W. Cyanides and nitrites. In: Patty, F. A. ed. *Industrial hygiene and toxicology*; Fassett, D. W. and Irish, D. D. eds. *Toxicology*. 2 rev ed. New York. Interscience Pub., 1962. Chapter 44, p. 1991-2036.
61. Ferris, B. G., Jr., Anderson, D. O. The prevalence of chronic respiratory disease in a New Hampshire town. *Amer Rev Resp Dis* 86: 165-77, 1962.
62. Ferris, B. G., Jr., Anderson, D. O., Burgess, W. A. Prevalence of respiratory disease in a flax mill in the United States. *Brit J Industr Med* 19: 180-5, 1962.
63. Fletcher, C. M. Chronic bronchitis in Great Britain and America. An account of chronic bronchitis in Great Britain with a comparison between British and American experience of the disease. *Dis Chest* 44: 1-10, 1963.
64. Fletcher, C. M. Chronic bronchitis: Its prevalence, nature and pathogenesis. *Amer Rev Resp Dis* 80: 483-94, 1959.
65. Fletcher, C. M. Chronic Bronchitis, Smoking and Air Pollution. *Tobacco and Health*. Charles C. Thomas, Springfield, Illinois, 1962. p. 380-401.
66. Fletcher, C. M., Hugh-Jones, P., McNicol, N. W., Pride, N. B. The diagnosis of pulmonary emphysema in the presence of chronic bronchitis. *Quart J Med* 32-51, 1963.
67. Fletcher, C. M., Tinker, C. M. Chronic bronchitis; a further study of simple diagnostic methods in a working population. *Brit Med J* 1: 1491-8, 1961.
68. Flick, A. L., Paton, R. R. Obstructive emphysema in cigarette smokers. *AMA Arch Intern Med* 104: 518-26, 1959.
69. Florey, H., Carleton, H. M., Wells, A. Q. Mucous secretion in the trachea. *Brit J Exp Path* 13: 269, 1932.
70. Forsey, R. R., Sullivan, T. J. Stomatitis nicotine. *Arch Derm (Chicago)* 83: 945-50, 1961.
71. Foster, D., Gassney, H. An investigation of the retention of smoke particulate matter by inhaling and non-inhaling type of cigarette smoker. Presented at the Tobacco Chemists Conference. Hoboken, N.J., Oct. 1958.
72. Frank, N. R., Amdur, M. O., Worcester, J., Whittenberger, J. L. Effects of acute controlled exposure to SO<sub>2</sub> on respiratory mechanics in healthy adult males. *J Appl Physiol* 17: 252-8, 1962.
73. Franklin, W., Lowell, F. C. Unrecognized airway obstruction associated with smoking: A probable forerunner of obstructive pulmonary emphysema. *Ann Intern Med* 54: 379-86, 1961.
74. Freeman, G., Haydon, G. Effects of continuous low-level exposure to nitrogen dioxide. Presented at California State Department of Public Health Sixth Annual Air Pollution Medical Research Conference. San Francisco, 1963.

75. Fry, J. Chronic bronchitis in general practice. *Brit Med J* 1: 190-4, 1954.
76. Goldsmith, J. R. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
77. Goldsmith, J. R., Hechter, H. H., Perkins, N. M., Borhani, N. O. Pulmonary function and respiratory findings among longshoremen. *Amer Rev Resp Dis* 86: 867-74, 1962.
78. Gray, E. LeB. Oxides of nitrogen: Their occurrence toxicity, hazard. *AMA Arch Industr Health (Chicago)* 19: 479-86, 1959.
79. Gross, P., Hatch, T. Pulmonary clearance: Its mechanism and relation to pulmonary disease. *J Occup Med* 5: 191-4, 1963.
80. Guillermin, R., Badre, R., Vignon, B. Inhibitory effects of tobacco smoke on the ciliary activity of the respiratory epithelium and nature of the responsible constituents. *Bull Acad Nat Med (Paris)* 145: 416-23, 1961.
81. Haagen-Smit, A. J., Brunelle, M. F., Hara, J. Nitrogen oxide content of smokes from different types of tobacco. *AMA Arch Industr Health (Chicago)* 20: 399-400, 1959.
82. Hammond, E. C. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
83. Hatch, T. Respiratory dust retention and elimination. *Proc Pneumoconiosis Conf Johannesburg*, 1959. p. 133.
84. Hausknecht, R. Experiences of a respiratory disease panel selected from a representative sample of the adult population. *Amer Rev Resp Dis* 86: 858-66, 1962.
85. Heath, C. W. Differences between smokers and nonsmokers. *AMA Arch Intern Med* 101: 377-88, 1958.
86. Heimann, H. Effects of air pollution on human health. *WHO Monogr Ser No 46*: 159-220, 1961.
87. Higgins, I. T. T. An approach to the problem of bronchitis in industry: Studies in agricultural, mining and foundry communities. In: King, E. J., Fletcher, C. M., eds. *Symposium on Industrial Pulmonary Diseases*. London, Churchill, 1960. p. 195-207.
88. Higgins, I. T. T. Respiratory symptoms, bronchitis, and ventilatory capacity in random sample of an agricultural population. *Brit Med J* 2: 1198-1203, 1957.
89. Higgins, I. T. T. The role of irritation in chronic bronchitis. In: Orie, N. G. M., Sluiter, H. J. eds. *Bronchitis*. Springfield, Ill., Thomas, 1961. p. 31-42.
90. Higgins, I. T. T. Tobacco smoking, respiratory symptoms, and ventilatory capacity. Studies in random samples of the population. *Brit Med J* 1: 325-9, 1959.
91. Higgins, I. T. T., Cochrane, A. L. Chronic respiratory diseases in a random sample of men and women in the Rhondda Fach in 1958. *Brit J Industr Med* 18: 93-102, 1961.
92. Higgins, I. T. T., Cochrane, A. L., Gilson, J. C., Wood, C. H. Population studies of chronic respiratory disease: A comparison of miners, foundry workers and others in Staveley, Derbyshire. *Brit J Industr Med* 16: 255-68, 1959.

93. Higgins, I. T. T., Cochran, J. B. Respiratory symptoms, bronchitis and disability in a random sample of an agricultural community in Dumfriesshire. *Tubercle* 39: 296-301, 1958.
94. Higgins, I. T. T., Oldham, P. D. Ventilatory capacity in miners. A five year follow-up study. *Brit J Industr Med* 19: 65-76, 1962.
95. Higgins, I. T. T., Oldham, P. D., Cochrane, A. L., Gilson, J. C. Respiratory symptoms and pulmonary disability in an industrial town. Survey of a random sample of the population. *Brit Med J* 2: 904-9, 1956.
96. Hilding, A. C. On cigarette smoking, bronchial carcinoma and ciliary action. 2. Experimental study on the filtering action of cow's lung, the deposition of tar in the bronchial tree and removal by ciliary action. *New Eng J Med* 254: 1154-60, 1956.
97. Hilding, A. C. On cigarette smoking, bronchial carcinoma and ciliary action. 3. Accumulation of cigarette tar upon artificially produced deciliated islands in the respiratory epithelium. *Ann Otol* 65: 116-30, 1956.
98. Hill, L. The ciliary movement of the trachea studied in vitro. *Lancet* 2: 802-5, 1928.
99. Hogner, R. Tobacco poisoning without using tobacco. *Amer Med* 26: 111-2, 1920.
100. Holland, R. H., Wilson, R. H., Morris, D., McCall, M. S., Lanz, H. The effect of cigarette smoke on the respiratory system of the rabbit. *Cancer* 11: 709-12, 1958.
101. Holland, W. W. A respiratory disease study of industrial groups. *Arch Environ Health (Chicago)* 6: 15-22, 1963.
102. Horton, A. W., Tye, R., Stemmer, K. L. Experimental carcinogenesis of the lung. Inhalation of gaseous formaldehyde or an aerosol of coal tar by C3H mice. *J Nat Cancer Inst* 30: 31-43, 1963.
103. Hyatt, R. E., Kistin, A. D., Mahaw, T. K. Respiratory disease in southern West Virginia coal workers. *Amer Rev Resp Dis* (In Press).
104. Ide, G., Suntzeff, V., Cowdry, E. V. A comparison of the histopathology of the tracheal and bronchial epithelium of smokers and non-smokers. *Cancer* 12: 473-84, 1959.
105. Jimenez-Diaz, C., Sanchez Cuenca, B. Asthma produced by susceptibility to unusual allergies. Linseed, insects, tobacco, and chicory. *J Allerg* 6: 397-403, 1935.
106. Joules, H. A preventive approach to common diseases of the lung. *Brit Med J* 2: 1259-63, 1954.
107. Keith, C. H., Newsome, J. R. Quantitative studies on cigarette smoke. 1. An automatic smoking machine. *Tobacco* 144: (13) 26-32, Mar 29, 1957.
108. Kensler, C. J., Battista, S. P. Components of cigarette smoke with ciliary-depressant activity. Their selective removal by filters containing activated charcoal granules. *New Eng J Med* 269: 1161-66, 1963.



109. Kleinerman, J., Wright, G. W. The reparative capacity of animal lungs after exposure to various single and multiple doses of nitrite. *Amer Rev Resp Dis* 83: 423-24, 1961.
110. Kler, J. H. An analysis of colds in industry. *Tr Amer Acad Ophthal Otol* 49: 201-7, 1945.
111. Kordik, P., Bülbring, E., Bum, J. H. Ciliary movement and acetylcholine. *Brit J Pharmacol* 7: 67-79, 1952.
112. Krueger, A. P., Smith, R. F. Effects of gaseous ions on tracheal ciliary rate. *Proc Soc Exp Biol Med* 98: 412-4, 1958.
113. LaBelle, C. W., Long, J. E., Christofano, E. E. Synergistic effects of aerosols. Particulates as carriers of toxic vapors. *Arch Industr Health (Chicago)* 11: 297-304, 1955.
114. Laennec, R. T. H. A treatise on the disease of the chest. Translated by J. Forbes. Published under the auspices of the Library of the New York Academy of Medicine by Hafner, NY 81-97, 1962.
115. Landau, E., Morton, J. An epidemiologic view of chronic pulmonary insufficiency in the United States. *Amer Rev Resp Dis* 83: 405-7, 1961.
116. Langer, G., Fisher, M. A. Concentration and particle size of cigarette-smoke particles. *AMA Arch Industr Health (Chicago)* 13: 372-8, 1956.
117. Leese, W. L. B. An investigation into bronchitis. *Lancet* 2: 762-5, 1956.
118. Leuchtenberger, C., Leuchtenberger, R., Doolin, P. F. A correlated histological, cytological and cytochemical study of the tracheobronchial tree and lungs of mice exposed to cigarette smoke. *Cancer* 11: 490-506, 1958.
119. Leuchtenberger, C., Leuchtenberger, R., Zebrun, W., Shaffer, P. A correlated histological, cytological, and cytochemical study of the tracheobronchial tree and lungs of mice exposed to cigarette smoke. 2. Varying responses of major bronchi. *Cancer* 13: 721-32, 1960.
120. Liebeschuetz, H. J. Respiratory signs and symptoms in young soldiers and their relationship to smoking. *J Roy Army Med Corps* 105: 76-81, 1959.
121. Liggett & Myers Tobacco Co., Arthur D. Little, Inc. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
122. Lindsey, A. J. Some observations on the chemistry of tobacco smoke. In: James, G., Rosenthal, T., eds. *Tobacco and Health*. Springfield, Ill., Thomas, 1962. p. 21.
123. Loudon, R. G. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
124. Lowe, C. R. An association between smoking and respiratory tuberculosis. *Brit Med J* 2: 1081-6, 1956.
125. Lowell, F. C., Franklin, W., Michelson, A. L., Schiller, I. W. Chronic obstructive pulmonary emphysema: A disease of smokers. *Ann Intern Med* 45: 268-74, 1956.
126. Lowry, T., Schuman, L. M. Silo-filler's disease—a syndrome caused by nitrogen dioxide. *JAMA* 162: 153-60, 1956.

127. Maliszewski, T. F., Bass, D. E. True and apparent thiocyanate in body fluids of smokers and nonsmokers. *J Appl Physiol* 8: 289-91, 1955.
128. Manos, N. E., Cooper, W. C. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
129. McFarland, J. J., Webb, B. M. Special report to the Surgeon General's Advisory Committee on Smoking and Health.
130. Mellors, R. C. Microscopic localization of tobacco smoke products in the respiratory tracts of animals exposed to cigarette smoke. [Abstract] *Proc Amer Ass Cancer Res* 2: 325, 1958.
131. Mendenhall, W. L., Shreeve, K. Effect of tobacco smoke on ciliary action. *J Pharmacol Exp Ther* 69: 295, 1940. The effect of cigarette smoke on the tracheal cilia. *Ibid.* 60: 111-2, 1937.
132. Merrill, M. H. Public health responsibilities and program possibilities in chronic respiratory diseases. *Amer J Public Health* 53: (3) (supp), 25-33, 1963.
133. Mills, C. A. Tobacco smoking: Some hints of its biologic hazards. *Ohio Med J* 46: 1165-70; 1950.
134. Miller, D., Bondurant, S. Effects of cigarette smoke in the surface characteristics of lung extracts. *Amer Rev Resp Dis* 85: 692-6, 1962.
- 134a. Miller, J. M. Special Report to the Surgeon General's Advisory Committee on Smoking and Health.
135. Mitchell, R. I. Controlled measurement of smoke-particle retention in the respiratory tract. *Amer Rev Resp Dis* 85: 526-33, 1962.
136. Mitchell, R. S. Personal communication to the Surgeon General's Advisory Committee on Smoking and Health.
137. Mitchell, R. S., Filley, G. F. Personal communication to the Surgeon General's Advisory Committee on Smoking and Health.
138. Mitchell, R. S., Toll, G., Filley, G. The early lesions in pulmonary emphysema. *Amer J Med Sci* 243: 409-18, 1962.
139. Mork, T. A comparative study of respiratory diseases in England and Wales and Norway. Norwegian Universities Press, 1962. Also: *ACTA Med Scand* 172 (Suppl 384) : 1-100, 1962.
140. Morris, J. N. Uses of epidemiology. Edinburgh, Livingstone, 1957. 135 p.
141. Moriyama, I. M. Chronic respiratory disease mortality in the United States. *Public Health Rep* 78: 743-8, 1963.
142. Motley, H. L., Kuzman, W. J. Cigarette smoke. Its effect on pulmonary function measurements. *Calif Med* 88: 211-21, 1958.
143. Murphy, S. D., Klingshirn, D. A., Ulrich, C. E. Respiratory response of guinea pigs during acrolein inhalation and its modification by drugs. *J Pharmacol Exp Ther* 141: 79-83, 1963.
144. Murphy, S. D., Leng, J. K., Ulrich, C. E., Davis, H. V. Effects on experimental animals on brief exposure to diluted automobile exhaust. Presented at Air Pollution Research Conference, December 9, 1961. California.
146. Nadel, J. A., Comroe, J. H. Acute effects of inhalation of cigarette smoke on airway conductance. *J Appl Physiol* 16: 713-6, 1961.

147. Nakashima, T. Pharmacological studies on ciliary movement. *Nagasaki Igasakkai Zassi* 14: 2219-37, 1936. [Abstract in English] *Jap J Med Sci, Sect pharmacol* 11: 42, 1938.
148. Olsen, H. C., Gilson, J. C. Respiratory symptoms, bronchitis and ventilatory capacity in men. An Anglo-Danish comparison, with special reference to differences in smoking habits. *Brit Med J* 1: 450-6, 1960.
149. Oswald, N. C., Harold, J. T., Martin, W. J. Clinical pattern of chronic bronchitis. *Lancet* 2: 539-43, 1953.
150. Oswald, N. C., Medvei, V. C. Chronic bronchitis; the effect of cigarette smoking. *Lancet* 2: 843-47, 1955.
151. Pattle, R. E. Properties, function, and origin of the alveolar lining layer. *Proc Royal Soc Biol* 148: 217-40, 1958.
152. Pattle, R. E., Burgess, F. Toxic effects of mixtures of sulfur dioxide and smoke with air. *J Path Bact* 73: 411-9, 1957.
153. Payne, M., Kjelsberg, M. Respiratory symptoms, lung function and smoking habits in a total community—Tecumseh, Michigan. Paper presented before the Epidemiology Section of the American Public Health Association in Miami Beach, October 17, 1962.
154. Pemberton, J., Goldberg, C. Air pollution and bronchitis. *Brit Med J* 2: 567-70, 1954.
155. Phelps, H. W., Koike, S. Tokyo-Yokohama asthma. *Amer Rev Resp Dis* 86: 55-63, 1962.
156. Phillips, A. M., Phillips, R. W., Thompson, J. L. Chronic cough: analysis of etiologic factors in a survey of 1,274 men. *Ann Intern Med* 45: 216-31, 1956.
157. Proetz, A. Some preliminary experiments in the study of cigarette smoke and its effect upon the respiratory tract. *Ann Otol* 48: 176-94, 1939.
158. Rakietyen, N., Rakietyen, M. L., Feldman, D., Boykin, M. J., Jr. Mammalian ciliated respiratory epithelium. Studies with particular reference to the effects of menthol, nicotine, and smoke of mentholated and nonmentholated cigarettes. *Arch Otolaryng (Chicago)* 56: 494-503, 1942.
159. Read, J., Selby, T. Tobacco smoking and ventilatory function of the lungs. *Brit Med J* 2: 1104-8, 1961.
160. Reid, D., Fairbairn, A. S. Air pollution and other local factors in respiratory disease. *Brit J Prev Soc Med* 12: 94-103, 1958.
161. Reid, D. D. General epidemiology of chronic bronchitis. *Proc Roy Soc Med* 49: 767-71, 1956.
162. Reid, L. Chronic bronchitis and hypersecretion of mucus. *Lect Sci Basis Med* 8: 235-8, 1958-59.
163. Reid, L. Measurement of the bronchial mucous gland layer: A diagnostic yardstick in chronic bronchitis. *Thorax* 15: 132-41, 1960.
164. Reid, L. M. Pathology of chronic bronchitis. *Lancet* 1: 275-8, 1954.
165. Revotskie, N., Kannell, W., Goldsmith, J. R., Dawber, T. R. Pulmonary function in a community sample. *Amer Rev Resp Dis* 86: 907-11, 1962.

166. Rigdon, R. H. Effect of tobacco condensate on the respiratory tract of the white Pekin duck. *AMA Arch Path (Chicago)* 69: 55-63, 1960.
167. Rivera, J. A. Cilia, ciliated epithelium and ciliary activity. *Int Ser Monogr Pure Appl Biol* 15: 1-167, 1962.
168. Rosen, F. L. Bronchial asthma in the young male adult. *Ann Allerg* 4: 247-60, 1946.
169. Rosen, F. L., Levy, A. Bronchial asthma due to allergy to tobacco smoke in an infant. A case report. *JAMA* 144: 620-1, 1950.
170. Ryan, R. F., McDonald, J. R., Devine, K. D. The pathologic effects of smoking on the larynx. *AMA Arch Path (Chicago)* 60: 472-80, 1955.
171. Sanderud, K. Squamous metaplasia of the respiratory tract epithelium. 2. Relation to tobacco smoking, occupation and residence. *Acta Path Microbiol Scand* 43: 47-61, 1958.
172. Saunders, W. H. Nicotina stomatitis of the palate. *Ann Otol* 67: 618-27, 1958.
173. Schoettlin, C. E. The health effect of air pollution on elderly males. *Amer Rev Resp Dis* 86: 878-97, 1962.
175. Shah, J. R., Warawadekar, M. S., Deshumkh, P. A., Phutane, P. N. Institutional survey of pulmonary tuberculosis with special reference to smoking habits. *Indian J Med Sci* 13: 381-92, 1959.
176. Short, J. J., Johnson, H. J., Ley, H. A., Jr. The effects of tobacco smoking on health. A study of 2,031 medical records. *J Lab Clin Med* 24: 586-9, 1939.
177. Simonsson, B. Effect of cigarette smoking on the forced expiratory flow rate. *Amer Rev Resp Dis* 85: 534-9, 1962.
178. Sollmann, T., Gilbert, A. J. Microscopic observations of bronchiolar reactions. *J Pharmacol Exp Ther* 61: 272-85, 1962.
179. Stokinger, H. E., Wagner, W. D., Dobrogorski, O. J. Ozone toxicity studies. 3. Chronic injury to lungs of animals following exposure at low levels. *AMA Arch Industr Health* 16: 514-22, 1957.
180. Sweet, H. C., Wyatt, J. P., Fritsch, A. J., Kinsella, P. W. Panlobular and centrilobular emphysema: Correlation of clinical findings with pathologic patterns. *Ann Intern Med* 55: 565-81, 1961.
181. Thoma, K. H. Stomatitis nicotina and its effects on the palate. *Amer J Orthodont* 27: 38-47, 1941.
182. Thurlbeck, W. M. A clinico-pathological study of emphysema in an American hospital. *Thorax* 18: 59-67, 1963.
183. Thurlbeck, W. M., Angus, G. E. The relationship between emphysema and chronic bronchitis as assessed morphologically. *Amer Rev Resp Dis* 87: 815-9, 1963.
184. Thurlbeck, W. M., Angus, G. E., Pare, J. A. P. Mucous gland hypertrophy in chronic bronchitis, and its occurrence in smokers. *Brit J Dis Chest* 57: 73-78, 1963.
185. Truhart, H. Ein beitrag zur nicotinwirkung. Dorpat, 1869. Thesis, 70 p.
186. U.S. Department of Health, Education, and Welfare. Disability applicants under the old-age survivors and disability program. 1960 selected data. January 1962.

187. Von Oettingen, W. F. Toxicity and potential dangers of nitrous fumes. *Public Health Bull* 272: 1-34, 1941.
188. Vassar, P. S., Culling, C., Saunders, A. M. Fluorescent histiocytes in sputum related to smoking. *AMA Arch Path (Chicago)* 70: 649-52, 1960.
189. Walker, I. C. The treatment of patients with bronchial asthma with subcutaneous injections of proteins to which they are sensitive. *J Med Res* 36: 423-80, 1917.
190. Westermark, T. Gaseous ions and their possible role in the etiology of lung cancer and some observations on free charges in cigarette smoke. *Acta Med Scand* 170: (Suppl 369) 119-20, 1961.
191. Wolff, W. A., Tuttle, J. G., Godfrey, J. M. Radioautographic method for studying deposition of cigarette smoke in the dog lung. *Abstract Fed Proc* 13: 324, 1954.
192. Wolff, W. A., Purdom, E. G., Isenhower, J. A. The use of radioisotopes as tracers in cigarette smoke. *N Carolina Med J* 15: 159-63, 1954.
193. Wright, G. W., Lloyd, T. The pulmonary reaction of normal and emphysematous persons to inhalation of SO<sub>2</sub>, fly ash, and moisture. 3d Air Pollution Research Seminar, U.S. Public Health Service.
194. Zamel, N., Youssef, H. H., Prime, F. J. Airway resistance and peak expiratory flow-rate in smokers and non-smokers. *New Orleans, 1960. Lancet* 1: 1237-8, 1963.

# Chapter 11

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## Cardiovascular Diseases

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# Chapter 11

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## INTRODUCTION

It has been suggested repeatedly that smoking may have adverse effects on the cardiovascular system. Recently, studies of large groups of people have shown that cigarette smokers in particular are more prone to die early of certain cardiovascular disorders than non-smokers. Chief among these disorders is coronary artery disease, and the present chapter deals mostly with this subject. The chapter begins with a summary of information about the acute effects of smoking on the cardiovascular system. This is followed by a brief account of coronary disease, its frequency in different kinds of people, and the many factors known or thought to affect the likelihood of its development. The aim here is not to review critically our knowledge of coronary disease but only to give background for what follows. Next is summarized the information currently available from study of large population groups on the association of cigarette smoking with an increased tendency to have coronary disease. There follows a brief discussion of smoking and non-coronary cardiovascular disease. Finally, there is a short review of evidence relating to the question of whether cigarette smokers may, as a group, differ from non-smokers in ways not caused by smoking itself. Mortality ratios showing the association between cigarette smoking and deaths from cardiovascular disease, especially coronary disease, do not indicate the magnitude of the burden. This can be better appreciated from consideration of the following facts: cardiovascular disease deaths now total more than 700,000 annually in the United States. Of these more than 660,000 were due to heart disease, with more than 500,000 due to arteriosclerotic heart disease including coronary disease. The remaining approximately 40,000 were ascribed to disease of other parts of the cardiovascular system. Deaths from lung cancer total approximately 39,000. A mortality ratio of 1.7 for coronary heart disease among cigarette smokers in the seven prospective studies represents from 32.9 percent to 51.7 percent of all excess deaths, whereas the much higher lung cancer mortality ratio of 10.8 from the same studies represents only 13.5 percent to 24.0 percent of total excess deaths (Chapter 8, Tables 19, 25).

## PERTINENT PHARMACOLOGY

The acute cardiovascular effects of smoking in man and experimental animals are like those caused by nicotine alone. A smoker who inhales gets usually 1–2 mg of nicotine from a cigarette (56, 57).

Low concentrations of nicotine stimulate sympathetic ganglia, and high concentrations paralyze them. Parasympathetic ganglia respond in the same way but are less sensitive. Nicotine can also have a sympathomimetic effect



by causing the discharge of norepinephrine and epinephrine from chromaffin cells in various tissues, including heart, vessels, and skin (10, 11, 9). In addition, nicotine produces effects reflexly by stimulating the chemoreceptors of the carotid and aortic bodies. When nicotine is given intravenously in increasing doses to dogs or cats the first effects, at about 1 microgram/kg body weight, are increased breathing and sympathetic stimulation, with predominant vasoconstriction, cardiac acceleration, and rise in blood pressure, resulting from stimulation of the aortic and carotid bodies (17). Doses of 4 to 8 micrograms/kg can stimulate pulmonary and coronary chemoreflexes which produce opposite effects. If all these receptors are inactivated, much higher doses are needed to evoke the cardiovascular effects of sympathetic stimulation, presumably through action on sympathetic ganglia or chromaffin tissue. Intravenous administration of nicotine in the experimental animal causes a discharge of epinephrine from the adrenal medulla, and in man heavy cigarette smoking produces an increased urinary excretion of catecholamines (84, 99).

Smoking 1-2 cigarettes causes in most persons, both smokers and non-smokers, an increase in resting heart rate of 15-25 beats per minute, a rise in blood pressure of 10-20 mmHg systolic and 5-15 mmHg diastolic (76, 78, 85, 86), and an increase in cardiac output of about 0.5 l/min/sq.m (75). There is a decrease in digital blood flow and a consequent drop in finger and toe temperature (31, 78, 103). The decrease in peripheral blood flow which normally follows smoking does not occur in a sympathectomized limb, indicating that the effect is mediated primarily by the sympathetic nervous system rather than through the release of catecholamines from other sites or the direct effect of nicotine upon the smooth muscle of the blood vessels themselves (103). Intravenous nicotine, and probably cigarette smoking as well, can produce a slight transitory increase in the blood flow to resting calf muscle (79).

In the dog, nicotine and cigarette smoke cause an increase in coronary flow as the blood pressure, cardiac output, and heart work increase (30, 53). These effects resemble those of epinephrine. Nicotine has been found to cause a transient decrease in cardiac oxygen utilization followed by a slight increase (53). Relatively little information is available about the effect of smoking on coronary blood flow in man. In normal subjects it is reported that cigarette smoking produces an early increase in coronary flow as heart work increases, but there is little change in oxygen utilization by the myocardium (2). With continued "steady state" smoking the coronary flow and cardiac oxygen utilization are maintained at the resting level in both normal subjects and persons with coronary heart disease, despite increased blood pressure, heart rate, and heart work (74). A larger experience must be gathered in this field before statements about the acute effects of smoking on the human coronary circulation can be made with assurance. The atherosclerotic rabbit heart, like the normal rabbit heart, shows an initial drop in coronary flow on administration of nicotine, but demonstrates less of a subsequent increase above the resting level than does the normal heart (97). These effects are said to be equivalent to those produced by norepinephrine in doses one-tenth as large as the nicotine dose.

Little or no change in the electrocardiogram of most normal persons or cardiac patients, except for an increase in rate, is produced by smoking or by the intravenous injection of an equivalent dose of nicotine (82, 98). In some persons there is a slight depression of the S-T segment and a flattening of 1-2 mm in the T wave of the limb leads. These changes are not like those associated with myocardial ischemia. Rarely in persons with true angina, an attack of pain is precipitated by smoking. An ill-defined syndrome consisting of chest pain, palpitation, and shortness of breath, known as "tobacco angina", has been described as occurring in smokers who do not have organic heart disease, but it is rarely diagnosed today (73, 82). Extrasystoles and other cardiac arrhythmias have been reported to be caused by smoking, but such cases appear to be unusual.

The ballistocardiogram obtained from a high-frequency table is sometimes changed by smoking a cigarette from a normal pattern to one said to be typical of coronary disease (78, 91). This phenomenon is rare in healthy persons below 50, becomes increasingly common with advancing years in apparently healthy persons, but is particularly prone to occur at any age in persons with actual coronary disease. The effect has been used as a "stress test" to help uncover coronary disease, but false positive and negative results are common. The ballistocardiographic changes on smoking have been variously interpreted as resulting from impaired myocardial contractility (78), from changes in the peripheral circulation (82), or from uncertain causes related to the physical properties of the high-frequency table as well as changes in the circulation.

Cigarette smoking causes an increase in the concentration of serum-free fatty acids in man (50), apparently mediated by stimulation of the sympathetic nervous system (51). Although continued administration of epinephrine to dogs over many hours can produce substantial increases in serum cholesterol, phospholipids, and triglycerides, such an effect has not yet been reported from nicotine or tobacco smoke (48, 92).

The clotting time of the blood can be decreased 50 percent or more in experimental animals by stimulation of the sympathetic nervous system or by administration of epinephrine (12, 13, 14), but attempts to demonstrate that cigarette smoking alters the clotting properties of the blood in man have been unsuccessful (5, 68). A decrease in platelet survival *in vivo* has been found after smoking (68). Cigarette smokers have been reported to show substantial decreases in hematocrit, hemoglobin, and platelet counts after abstinence of 1-2 weeks (25), but hemoglobin concentrations are alike in smokers and non-smokers of the same population group (4).

Attempts have been made to induce atherosclerosis in rats by the chronic administration of nicotine for periods up to a year without success (93).

Tobacco has antigenic properties (29, 43). Rats can be sensitized to tobacco extracts by intraperitoneal injection. Over a third of smokers demonstrate a positive "immediate" skin reaction to such extracts while only about 10% of non-smokers are said to give positive tests. The presence of serum reagins in persons with positive skin tests has been demonstrated by passive transfer techniques. Persons with thromboangiitis obliterans and smokers with occlusive vascular disease of other types are said to show a much higher incidence of positive skin tests than healthy smokers. The cardiovascular

diseases which have been related to smoking, however, do not in general resemble those usually ascribed to an immune mechanism.

In man and experimental animals smoking or the injection of nicotine causes increased secretion of antidiuretic hormone. The renal effects of this are easily demonstrable but the quantity of hormone secreted in response to smoking is probably too small to have significant vascular effects (17).

In summary, the acute cardiovascular effects of smoking and of nicotine closely resemble those of sympathetic stimulation, and to a considerable extent are mediated by excitation of the sympathetic nervous system. No additional or unique cardiovascular effects have been demonstrated which, in the light of our present understanding, seem likely to account for the observed association of cigarette smoking with an increased incidence of coronary disease.

## GENERAL OBSERVATIONS ON CORONARY HEART DISEASE

Heart disease is the most common cause of death in our population, and coronary disease is the commonest variety of fatal heart disease (59). In 1961 there were 1,701,522 deaths from all causes in the United States. Heart disease deaths numbered 663,391 of which 502,351 were due to arteriosclerotic heart disease.

The disorder consists of obstruction or narrowing of the coronary arteries, reducing the blood supply to the heart muscle. The underlying cause of the obstruction is coronary atherosclerosis, but an acute coronary artery occlusion is often caused by the formation of a blood clot in a diseased artery. The common manifestations of coronary disease are angina pectoris, recurrent brief attacks of chest pain caused by inadequate blood supply to the heart muscle; myocardial infarction, or necrosis of a portion of the heart muscle due to acute loss of blood supply; congestive heart failure, a chronic state caused by inability of the heart to pump enough blood to satisfy the demands of the body; and sudden death resulting from cardiac standstill or ventricular fibrillation.

There are considerable differences in the prevalence of coronary heart disease in different countries, and often in different ethnic and socio-economic groups within a particular country (46, 62). The reported death rate of arteriosclerotic heart disease, which is primarily coronary disease, is higher in the United States than in other countries. It is also quite high in New Zealand, Australia, South Africa, Canada, and Finland, and moderately high in Great Britain. The death rate in Norway, Sweden, and Denmark is roughly half that in the high death rate countries (15). The death rate in Japan appears to be about one-sixth that in the United States, although persons of Japanese origin living in the United States are said to have a death rate similar to that of the general population of this country (52).

Because of changing diagnostic skills and revisions in nomenclature of disease, it is difficult to be certain of the change in incidence of coronary disease in the United States over the past few decades, but there is a general opinion that the incidence is increasing in this country and in England.

particularly in the younger male group (59, 62, 65, 83). In 1955 the mortality rate from arteriosclerotic heart disease was reported to be about 240 per 100,000. Although this is an increase of more than 50% over the rate in 1940, it has been estimated that less than 15% of the increase represented a real change in incidence of the disease, the remainder depending upon changes in diagnosis, in nomenclature and in the age of the population (59). Since 1955 the death rate from coronary disease (ISC 420) and from arteriosclerotic and degenerative heart disease (ISC 420 and 422) has continued to increase gradually. In 1960 the age-adjusted death rate from 420 and 422 was 330 per 100,000 for white males and 150 for white females (55).

Although the basic cause or causes of coronary heart disease are obscure, certain factors other than smoking are known or thought to predispose to the condition or to be associated with an increased incidence.

The incidence of coronary heart disease in men under 45 is about 5 times as great as that in women (Table 1) (15, 20, 59, 62). In both sexes the incidence increases with advancing years. After the menopause the incidence increases rapidly in women, and at age 80 the death rates from coronary disease are about the same for the two sexes. Coronary thrombosis plays a relatively more important role in precipitating myocardial infarction in young men than it does in old men (105). In studies of large population groups coronary disease has been associated with elevation of the serum cholesterol, hypertension, and marked overweight (19, 20, 24, 36, 46, 59, 62).

Some individual characteristics have been said to be associated with coronary disease. There is a significant familial tendency to develop it (36, 69, 81, 96). Persons with a mesomorphic constitution are said to be more vulnerable than endomorphs and ectomorphs (36, 62, 88). A coronary-prone personality has been described as the aggressive, competitive person who takes on too many jobs, fights deadlines, and is obsessed by the lack of adequate time for the performance of his work (33, 34, 35).

TABLE 1.—*Death rates per 100,000 from arteriosclerotic and degenerative heart disease\* by sex and age, United States, 1958-60*

Age Group	Males	Females	Both Sexes
Under 35-----	3.3	1.2	2.2
35-44-----	90.2	18.3	53.3
45-54-----	353.7	79.3	213.5
55-64-----	928.5	314.5	610.2
65-74-----	2129.2	1082.0	1569.5
75 or over-----	4765.1	3738.4	4179.7

\*Includes ISC numbers 420 and 422.

Source: WHO Epidemiological and Vital Statistics Report, Vol. 16, No. 2, 1963.

Certain occupations have been said particularly to favor the development of coronary disease, notably those which feature responsibility and stress (34, 81, 87), and which are sedentary in nature (7). Others (58, 72, 90) have not found that executives are more prone to coronary disease than non-executive personnel. Physicians have been said to have 3 or 4 times as much coronary disease as farmers or laborers (87), and general practitioners to

have 3 times as much as dermatologists (80). Occupations involving much physical activity are said to be protective (66, 67, 77). City life has been said to be more closely associated with coronary disease than suburban life, and men who drove more than 12,000 miles a year seemed, in one study, more prone to the disease than those who drove less (64).

It has been widely held, and occasionally denied, that a diet high in saturated fat predisposes to the development of coronary disease (46, 52, 69, 81). A correlation between the national incidence of coronary disease and the percentage of food calories available as saturated fat has been reported among those countries for which adequate data exist (46). The serum cholesterol tends to rise when saturated fat is added to the diet, and it falls significantly when unsaturated fat is substituted (46). It has also been suggested that general over-nutrition, rather than excess saturated fat predisposes to coronary disease, on the grounds that the correlation of coronary disease with total available calories or sugar consumption per capita is as good as that for percentage of calories in fat (106).

In general, it is apparent that multiple personal and environmental factors can markedly affect the incidence of coronary disease.

## SMOKING AND CORONARY HEART DISEASE

Over the last two decades a considerable number of epidemiologic studies on different populations, employing different techniques, have shown with remarkable consistency a significant relationship between cigarette smoking and an increased death rate from coronary heart disease in males, particularly during middle life. There has been little dissenting evidence. The association of coronary disease with the use of tobacco in other forms has not been striking. The documentation for these statements is given in the following paragraphs. Particularly important is the information in Chapter 8, Mortality.

English et al. (26) found the incidence of coronary disease in male patients at the Mayo Clinic about 3 times greater in cigarette smokers than in non-smokers in the 40-59 year age range, but found little relation to smoking above 60. Russek (81) reported a similar relationship, but less striking, in young men with coronary disease. Mills (64) in a study of reported mortality in a Cincinnati population found that heavy smokers in the 30-59 year age range had twice as high a death rate from coronary disease as non-smokers. Male Seventh Day Adventists, who are non-smokers, were found by Wynder and Lemon (104) in a study based on hospital admissions to have significantly less coronary disease and to develop it later in life than the general male hospital population. Haag and Hanmer (37) reported that employees in the tobacco industry, who tend to smoke heavily, had a lower death rate for cardiovascular disease than the general population in their geographic region, but no report was made of mortality rates within the tobacco-worker group, divided by smoking habits. The study has been criticized on this and other grounds (16).

Large-scale prospective studies of mortality in British physicians (Doll and Hill, 21), United States males 50-69 recruited by volunteer workers

(Hammond and Horn, 38, 39, 40, 42) and V.A. Life Insurance policyholders (Dorn, 22) have confirmed the association of death from coronary disease with cigarette smoking. In the British study, a step-wise association was found between the amount of tobacco consumed (not entirely cigarettes) and the mortality from coronary disease. The association occurred in the 35-54 year age range, but not in older men. Hammond and Horn found a similar graded relationship between coronary deaths and cigarette smoking, the death rate being more than twice as great in men who smoked over a pack a day as in non-smokers. Men who had stopped smoking for more than a year at the start of the study had a coronary death rate lower than those who continued.

Studies on special groups of men, such as longshoremen (Buechley et al. 8) members of a fraternal order (Spain and Nathan, 89) and industrial employees (Paul et al. 71) which, in the latter two instances, incorporated clinical coronary disease, as well as coronary deaths, also have shown a relationship between coronary disease and smoking. The relationship was closer for men under 51 than for older men, and closer for myocardial infarcts and death than for angina pectoris (70, 89).

The long-term prospective studies of cardiovascular disease in Framingham (19) and in Albany (24) which have featured a painstaking search at regular intervals for clinical manifestations of disease, have, on pooling the data (Doyle et al. 23) shown a threefold increase in the incidence of myocardial infarction and coronary deaths in men who are heavy cigarette smokers as compared to non-smokers, pipe and cigar smokers, and former cigarette smokers. In the pooled data the incidence of angina pectoris did not show a significant association with cigarette smoking. The lack of this particular relationship had been suggested on the basis of clinical experience (White and Sharber, 102).

An apparent interplay of factors relating to smoking and occupation turned up in a short-term study of the development of coronary heart disease in a general North Dakota population (Zukel et al., 107). Farmers had about half the incidence of myocardial infarction experienced by others. In farmers, smoking had no appreciable effect on the incidence of infarction, but in others the incidence of infarction was twice as high among smokers as among the non-smokers. The farmers who smoked cigarettes smoked less heavily than males in other occupational groups.

In Chapter 8, Mortality, there is summarized the most recent information available from 7 large completed or current prospective smoking and death rate studies (Doll and Hill; Hammond and Horn; Dorn; Dunn, Linden and Breslow; Dunn, Buell and Breslow; Best, Josie, and Walker; and Hammond). The median mortality ratio for coronary disease of current cigarette smokers to non-smokers is 1.7 (range 1.5-2.0).

Table 2 presents data from some of the large prospective studies on the ratio of mortality rates due to coronary heart disease of male smokers to non-smokers, by age and amount smoked. The ratios tend in general to increase with amount smoked and to decrease with advancing age.

The data from the first 22 months of Hammond's (41) current study help to show the size of the coronary problem. For this purpose, actual numbers of deaths may be more informative than mortality ratios. Of nearly

TABLE 2.—*Ratios of mortality rates for coronary heart disease, male smokers to non-smokers, by age and amount smoked, in selected studies*

HAMMOND AND HORN—1958 (42)

Age Group	Cigarettes smoked per day		
	Less than 10	10-19	20 and over
50-54 .....	1.4	2.0	2.5
55-59 .....	1.4	2.0	2.5
60-64 .....	1.2	1.9	1.9
65-69 .....	1.3	1.6	1.6
Total (age adjusted) .....	1.29	1.89	(20-39) 2.15   (40+) 2.41

BUECHLEY, DRAKE, BRESLOW—1958 (8)\*

35-44 .....		2.0
45-54 .....		2.8
55-64 .....		1.8
65-74 .....		0.9

FRAMINGHAM STUDY—1963 (47)

30-62 .....	(less than 20) 1.5	(20 and over) 3.2
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DORN—1959 (22)

Total (age adjusted) .....	1.32	1.76	1.75
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DOLL AND HILL—1956 (21)

Age Group	Grams of tobacco smoked per day		
	1-14 Grams	15-24 Grams	25 or more Grams
35-54 .....	2.2	3.3	4.2
55-64 .....	0.9	0.6	1.0
65-74 .....	1.0	0.9	1.3
75+ .....	1.3	1.5	1.6
Total (age adjusted) .....	1.1	1.1	1.4

\*Persons smoking 1 pack per day or more compared with those smoking less than 1 pack per day (including non-smokers).

10,000 deaths of men aged 45-79. 46 percent were ascribed to coronary disease. 51.7 percent of the 2,630 "excess deaths" associated with cigarette smoking were caused by coronary disease. In approximate terms, nearly half of middle-aged and elderly males in the United States die of coronary disease. About half of these males smoke cigarettes. Cigarette smokers have been found in several studies to have 1.7 times as high a coronary death rate as non-smokers. If cigarettes actually caused the additional coronary deaths of smokers, they would account for many deaths of middle-aged and elderly males in this country. Like other studies (19, 21, 22, 23, 42) this one shows that the ratio of smokers' coronary death rates to those of non-smokers increases progressively with the daily cigarette consumption. In addition, at each level of consumption the ratio increases with the amount of inhalation reported by the smokers. Others (21, 23, 26, 89) have indicated

that the risk of death from coronary disease in male cigarette smokers relative to that in non-smokers is greater in middle age than old age, and Hammond's current study supports this. The mortality ratio was 3.09 in the age range 40-49, and in successive decades was 2.20, 1.58, and 1.38.

Men who stop smoking have a lower death rate from coronary disease than those who continue (23, 42, 47). In the study of Hammond and Horn (42) the decrease in death appeared only after a year.

Angina pectoris is less closely related to cigarette smoking than myocardial infarction and sudden death. In the combined Albany-Framingham experience (23), angina pectoris showed no over-all relationship with smoking, and the association has not been strong in other studies (71, 89).

In summary, a significant association has been established between cigarette smoking and the incidence of myocardial infarction and sudden death in males, especially in middle life, in population groups whose members appear so far to be similar except for smoking habits. The question of whether they are, in fact, similar except for smoking is, of course, basic to the problem of whether cigarette smoking actually promotes the development of coronary disease or whether it is closely associated with some other factor or factors which promote the development of coronary disease. It has been pointed out that angina pectoris, which indicates advanced coronary atherosclerosis, is less closely associated with cigarette smoking than is myocardial infarction, and that this suggests that any etiologic role of smoking in myocardial infarction should relate more to acute occlusive mechanisms, such as intravascular thrombosis or coronary spasm, than to the development of chronic arterial disease.

## SMOKING AND NON-CORONARY CARDIOVASCULAR DISEASE

In surveys of large groups cigarette smoking has not been found to be associated with an increased prevalence of hypertension (3, 4, 19, 47, 49). The study of Hammond and Horn (40, 42) did not show an increased death rate from hypertension in smokers. However, Dorn (22) found that the death rate of cigarette smokers from hypertension with heart disease was 1.53 times that of non-smokers, and from hypertension without heart disease, 1.41 times that of non-smokers. Hammond's current study shows similar figures (41). Smoking has not been found to be associated with an increased mortality rate from chronic rheumatic heart disease (22, 41, 42).

Hammond and Horn (42) found a moderate increase in the mortality rate from cerebral vascular disease in cigarette smokers as compared to non-smokers (ratio 1.30). Dorn (22) reported a ratio of 1.33, and Hammond (41) a ratio of 1.43. Although non-syphilitic aortic aneurysm is a relatively infrequent cause of death, the mortality ratio for smokers to non-smokers in this diagnostic category is large in relation to the ratios in other cardiovascular disorders. In the study of Hammond and Horn (42) it was 2.72, and in Hammond's current study (41) it is 3.10.