cular states of health in the Negro and white population of Evans County, Georgia. Journal of Chronic Diseases 18(3) : 243–257, March 1965.

(*101*) MAHADEVAN, V., SINGH, H., LUNDBERG, W. O. Effects of saturated and unsaturated fatty acids on blood platelet aggregation *in vitro*. Proceedings of the Society for Experimental Biology and Medicine 121 : 82–85, 1966.

(*102*) MAHLER, R. Diabetes and arterial lipids. Quarterly Journal of Medicine 34(136) : 484, 1965.

(*103*) MALHOTRA, S. L. Serum lipids, dietary factors and ischemic heart disease. American Journal of Clinical Nutrition 20: 462–474, May 1967.

(*104*) MEYER, J. S. Personal communication. 1968.

(*105*) MOSES, D. C., POWERS, D., SOLOFF, L. A. Glucose blockage of the increase in stroke volume produced by smoking. Circulation 29(6) : 820–844, June 1964.

(*106*) MULCAHY, R., HICKEY, N. J. Cigarette smoking habits of patients with coronary heart disease. British Heart Journal 28 : 404–408, 1966.

(*107*) MULCAHY, R., HICKEY, N. J. The role of cigarette smoking in the causation of atherosclerosis. Geriatrics 22(2) : 165–174, February 1967.

(*108*) MULCAHY, R., HICKEY, N. J., MAURER, B. J. The aetiology of coronary heart disease in women. Journal of the Irish Medical Association 60 (335) : 23–29, January 1967.

(*109*) MULCAHY, R., HICKEY, N. J., MAURER, B. J. Coronary heart disease in women. Study of risk factors in 100 patients less than 60 years of age. Circulation 36(4) : 577–586, April 1967.

(*110*) MURCHISON, L. E., FYFE, T. Effects of cigarette smoking on serum-lipids, blood glucose, and platelet adhesiveness. Lancet 2(7456) : 182–184, July 23, 1966.

(*111*) MURPHY, E. A., MUSTARD, J. F. Smoking and thrombosis. In: Wynder, E. L. Hoffmann, D., editors. Toward a Less Harmful Cigarette. Bethesda, U.S. Public Health Service, National Cancer Institute Monograph 28, June 1968. (In press)

(*112*) NADEAU, R. A., JAMES, T. N. Effects of nicotine on heart rate studies by direct perfusion of sinus node. American Journal of Physiology 212(4) : 911–916, April 1967.

(*113*) NATVIG, H. Effekten av umettede fettsyrer pa hyppigheten av hjerteinfarkt M.M. Resultatet av bedriftslegenes "oljeforsok." Tidsskrift for den Norske Laegeforening 87(11) : 1033–1041, June 1967.

(*114*) NIKKILA, E. A., VESENNE, M–R., MIETTINEN, T. A., PELKONEN, R. Plasma-insulin in coronary heart disease: Response to oral and intravenous glucose and to tolbutamide. Lancet 2: 508–511, September 11, 1965.

(*115*) PAGE, I. H., LEWIS, L. A., MOINUDDIN, M. (Clinical Notes) Effect of cigarette smoking on serum cholesterol and lipoprotein concentrations. Journal of the American Medical Association 171(11) : 1500–1502, November 14, 1959.

(*116*) PAPACOSTAS, C. A., REED, J. P. Influence of beta receptor blockade on certain cardiovascular actions of nicotine. Archives Internationales de Pharmacodynamie et de Therapie 164(1) : 167–172, 1966.

(*117*) PENTECOST, B., SHILLINGFORD, J. The acute effects of smoking on myocardial performance in patients with coronary arterial disease. British Heart Journal 26: 422–429, 1964.

(*118*) PETERS, N., HALES, C. N. Plasma-insulin concentrations after myocardial infarction. Lancet 1: 1144–1145, May 29, 1965.

(119) PINCHERLY, G., WRIGHT, H. B. Screening in the early diagnosis and prevention of cardiovascular disease. Journal of the College of General Practitioners 13: 280–289, 1967.

(120) PURI, P. S., ALAMY, D., BING, R. J., Effect of nicotine on the contractility of the intact heart. Journal of Clinical Pharmacology, 1968. (In press)

(121) PURI, P. S., BING, R. J. Influnce of cardiovascular drugs on the force-velocity relation of the intact heart. The Physiologist 10(3): 285, August 1967.

(122) REID, D. D., HOLLAND, W. W., ROSE, G. A. An Anglo-American cardiovascular comparison. Lancet 4(7531): 1375–1378, December 30, 1967.

(123) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, C. D., STRAUS, R., WURM, M., KOSITCHEK, R. Clinically unrecognized myocardial infarction in the Western Collaborative Group Study. American Journal of Cardiology 19(6): 776–782, June 1967.

(124) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, C. D., STRAUS, R., WURM, M., KOSITCHEK, R. Recurring and fatal myocardial infarction in the Western Collaborative Group Study. American Journal of Cardiology 19(6): 771–775, June 1967.

(125) ROSENMAN, R. H., FRIEDMAN, M., JENKINS, C. D., ZYZANSKI, S. J. Personal Communication, 1968.

(126) ROSSI-FANELLI, A., ANTONINI, E. Studies on the oxygen and carbon monoxide equilibria of human myoglobin. Archives of Biochemistry and Biophysics 77: 478–492, 1958.

(127) ROTH, O., BERKI, A., WOLFF, G. D. Long range observations in fifty-three young patients with myocardial infarction. American Journal of Cardiology 19(3): 331–338, March 1967.

(128) ROWSELL, H. C., HEGARDT, B., DOWNIE, H. G., MUSTARD, J. F., MURPHY, E. A. Adrenaline and experimental thrombosis. British Journal of Haematology 12(1): 66–73, 1966.

(129) SELTZER, C. C. An evaluation of the effect of smoking on coronary heart disease. I. Epidemiological evidence. Journal of the American Medical Association 203(3): 193–200, January 15, 1968.

(130) SEN GUPTA, A. N., GHOSH, B. P. Observations on some cardiovascular and biochemical effects of tobacco smoking in health and in ischaemic cardiacs. Bulletin of the Institute of Post-Graduate Medical Education and Research 9(2): 45–57, April 1967.

(131) SHANKS, R. G. The pharmacology of beta sympathetic blockade. American Journal of Cardiology 18(9): 308–316, September 1966.

(132) SHIBATA, S., HOLLANDER, P. H., WEBB, J. L. Effect of nicotine on the transmembrane potential and contractility of isolated rat atria. Experientia 24(3): 236–237, 1968.

(133) SHIMAMOTO, T., ISHIOKA, T., Release of a thromboplastic substance from arterial walls by epinephrine. Circulation Research 12(2): 138–144, February 1963.

(134) SIEVERS, M. L. Myocardial infarction among southwestern American Indians. Annals of Internal Medicine 67(4): 800–807, October 1967.

(135) SLIEGHT, P. A cardiovascular depressor reflex from the epicardium of the left ventricle in the dog. Journal of Physiology 173(3): 321–343, 1964.

(136) SOLOFF, L. A., SCHWARTZ, H. Relationship between glucose and fatty acid in myocardial infarction. Lancet 1: 449–452, February 26, 1966.

(137) STABLES, D. P., RUBENSTEIN, A. H., METZ, J., LEVIN, N. W. The possible role of hemoconcentration in the etiology of myocardial infarction. American Heart Journal 73(2): 155–159, February 1967.

(*138*) STAMLER, J., BERKSON, D. M., LEVINSON, M., LINDBERG, H. A., MOJONNIER, L., MILLER, W. A., HALL, Y., ANDELMAN, S. L. Coronary artery disease. Status of preventive efforts. Archives of Environmental Health 13(3): 322–335, September 1966.

(*139*) STARR, I. The place of the ballistocardiogram in a Newtonian cardiology; and the new light it sheds on certain old clinical problems. Proceedings of the Royal Society of Medicine 60: 1297–1306, December 1967.

(*140*) STROBEL, M., GSELL, O. Mortalitat in Beziehung zum Tabakrauchen: 9 Jahre Beobachtungen bei Arzten in der Schweiz. Helvetica Medica Acta 32(6): 547–593, December 1965.

(*141*) SZANTO, S. Smoking and atherosclerosis. British Medical Journal 3: 178, July 15, 1967.

(*142*) TAYLOR, R. R., CINGOLANI, H. E., GRAHAM, J. P., CLANCY, R. L. Myocardial *oxygen consumption: left ventricular fibre shortening and wall tension.* Cardiovascular Research 1: 219–228, 1967.

(*143*) THOMAS, C. B. On cigarette smoking, coronary heart disease, and the genetic hypothesis. Johns Hopkins Medical Journal 122(2): 69–76, February 1968.

(*144*) TIBBLIN, G. High blood pressure in men aged 50—A population study of men born in 1913. Acta Medica Scandinavica (Supplementum 470): 1–84, 1967.

(*145*) TRUETT, J., CORNFIELD, J., KANNEL, W. A multivariate analysis of the risk of coronary heart disease in Framingham. Journal of Chronic Diseases 20: 511–524, 1967.

(*146*) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Public Health Service Review: 1967. Washington, U.S. Department of Health, Education and Welfare, Public Health Service Publication No. 1696, 1967. 227 pp.

(*147*) U.S. PUBLIC HEALTH SERVICE. National Center for Health Statistics. Monthly Vital Statistic Report. Final Mortality Statistics 16(2) (Supplement): 1–12, March 12, 1968.

(*148*) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service, Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.

(*149*) VALLANCE-OWEN, J. Comments on Dr. Mahler's "Diabetes and Arterial Lipids"). Quarterly Journal of Medicine 34(136): 485, October 1965.

(*150*) VAN BUCHEM, F. S. P. Serum lipids, nutrition and atherosclerotic complications in man. Acta Medica Scandinavica 181(4): 403–461, April 1967.

(*151*) VILLIGER, U., HEYDEN-STUCKY, S. Das Infarktprofil. Unterschiede zwischen infarktpatienten und Kontrollpersonen in der Ostschweiz. Schweizerische Medizinische Wochenschrift 96(23): 748–758, June 11, 1966.

(*152*) WAHLBERG, F. The intravenous glucose tolerance test in atherosclerotic disease with special reference to obesity hypertension, diabetic heredity and cholesterol values. Acta Medica Scandinavica 171(1): 1–7, 1962.

(*153*) WARNER, E. D. HOAK, J. C., CONNOR, W. E. The role of fatty acids in platelet aggregation and thrombosis. In: Brinkland, K. M., editor. *Platelets: Their Role in Hemostasis and Thrombosis.* Chapter 24. Transactions of the Conference held under the auspices of the International Committee on Haemostasis and Thrombosis, Chapel Hill, North Carolina, December 1966. Pp. 249–259.

(*154*) WEBB, W. R., WAX, S. D., SUGG, W. L. Cigarette smoke and fibrillation threshold in dogs. Clinical Research 16(1) : 74, January 1968.

(*155*) WEINBLATT, E. Personal communication. April 1968.

(*156*) WEISSLER, A. M., KRUGER, F. A., BABA, N., SCARPELLI, D. G., LEIGHTON, R. F., GALLIMORE, J. K. Role of anaerobic metabolism in the preservation of functional capacity and structure of anoxic myocardium. Journal of Clinical Investigation 47 : 403–416, 1968.

(*157*) WELBORN, T. A., BRECKENRIDGE, A., RUBENSTEIN, A. H., DOLLERY, C. T., FRASER, T. R. Serum-insulin in essential hypertension and in peripheral vascular disease. Lancet 1(7451) : 1336–1337, June 18, 1966.

(*158*) WESTFALL, T. C., CIPOLLONI, P. B., EDMUNDOWICZ, A. C. Influence of propranolol on hemodynamic changes and plasma catecholamine levels following cigarette smoking and nicotine. Proceedings of the Society for Experimental Biology and Medicine 123 : 174–179, 1966.

(*159*) WITTENBERG, J. B. The molecular mechanism of hemoglobin-facilitated oxygen diffusion. Journal of Biological Chemistry 241(1) : 104–114, January 10, 1966.

(*160*) YAMAMOTO, T. The effect of propranolol on the haemodynamic changes caused by cigarette smoking. Japanese Circulation Journal 31(12) : 1958, December 1967.

SUPPLEMENTAL CARDIOVASCULAR REFERENCES

S1. ANTONINI, E. Hemoglobin and its reaction with ligands. Science 158(3807) : 1417–1425, December 15, 1967.

S2. ARMITAGE, A. K. Effects of nicotine and tobacco smoke on blood pressure and release of catecholamines from the adrenal glands. British Journal of Pharmacology and Chemotherapy 25 : 515–526, October 1965.

S3. ARMITAGE, A. K., MILTON, A. S., MORRISON, C. F. Effects of nicotine and some nicotine-like compounds injected into the cerebral ventricles of the cat. Journal of Physiology (London) 181 : 30P–31P, 1965.

S4. AVIADO, D. M., JR., SCHMIDT, C. F. Cardiovascular and respiratory reflexes from the left side of the heart. American Journal of Physiology 196(4) : 726–730, 1959.

S5. BARER, G. R., HOWARD, P., MCCURRIE, J. R. The effect of carbon dioxide and changes in blood pH on pulmonary vascular resistance in cats. Clinical Science 32 : 361–376, 1967.

S6. BEARD, R. R., WERTHEIM, G. A. Behavioral impairment associated with small doses of carbon monoxide. American Journal of Public Health and the Nation's Health 57(11) : 2012–2022, November 1967.

S7. BECKETT, A. H., TRIGGS, E. J. Enzyme induction in man caused by smoking. Nature 216(5115) : 587, November 11, 1967.

S8. BELLET, S. Adrenergic effects of nicotine on coronary blood flow and blood lipids. IN : Raab, W., editor. Prevention of Ischemic Heart Diseases. Principles and Practice. Springfield, C.C. Thomas, 1966. Pp. 74–84.

S9. BELLET, S., WEST, J. W., MULLER, O. T., MANZOLI, U. C. Effect of nicotine on the coronary blood flow and related circulatory parameters. Correlative study in normal dogs and dogs with coronary insufficiency. Circulation Research 10(1) : 27–34, January 1962.

S10. BELLI, C., ALBERTINI, E., MARTINESI, L., PELIEGRINI, G. F. Studio sperimentale di momenti dell'emocagulazione e della fibrinolisi in corso d'intossicazione nicotinica caronica. Archivio per le Scienze Mediche 120 (6) : 460–478, December 1965.

S11. Bing, R. J., Cohen, A., Bluemchen, G. Tobacco alkaloids and circulation. In: Von Euler, U.S., editor. Tobacco Alkaloids and Related Compounds. Proceedings of the Fourth International Symposium held at the Wenner-Gren Center, Stockholm, February 1964. New York, MacMillan, 1965. Pp. 241–251.

S12. Blaschko, H., Hagen, P., Welch, A. D. Observations on the intracellular granules of the adrenal medulla. Journal of Physiology (London) 129: 27–49, 1955.

S13. Boelling, G. M., Phillips, W. J., Freeking, H. W., Paine, R. Roentgenographic exercise test. A new test of myocardial state. Journal of the American Medical Association 202(4): 275–278, October 23, 1967.

S14. Britman, N. Z., Levine, H. J. Contractile element work: a major determinant of myocardial oxygen consumption. Journal of Clinical Investigation 43(7): 1397–1408, July 1964.

S15. Brox, D., Selvaag, O. The effect of erythritol-tetra-nicotinate on serum-cholesterol levels in man. Acta Medica Scandinavica 182(4): 437–444, 1967.

S16. Burt, R. L. Plasma nonesterified fatty acids in normal pregnancy and the puerperium. Obstetrics and Gynecology 15(4): 460–464, April 1960.

S17. Butkus, A., Page, I. H. Smoking and postabsorptive serum lipid levels. Journal of the American Medical Association 192(1): 52–53, April 5, 1965.

S18. Bygdeman, S., Eliasson, R., Johnson, S. R. Relationship between postoperative changes in adenosine-diphosphate induced platelet adhesiveness and venous thrombosis. Lancet 1: 1301–1302, June 11, 1966.

S19. Byrd, R. B., Divertie, M. B., Spittell, J. A., Jr. Bronchogenic carcinoma and thromboembolic disease. Journal of the American Medical Association 202(11): 1019–1022, December 11, 1967.

S20. Capron, P. Essai d'interprétation des balistocardiogrammes en fonction des traces synchrones type Blomberger. In: Knopp, A.A., editor. Ballistocardiography and Cardiovascular Dynamics. Proceedings, 1st World Congress, Amsterdam, 1965. New York, Karger, 1966. Pp. 155–162.

S21. Christakis, G. J., Rinzler, S. H., Archer, M., Hashim, S. A., Van Itallie, T. B., Mao, P. Effect of a serum cholesterol-lowering diet on composition of depot fat in man. American Journal of Clinical Nutrition 16: 243–251, February 1965.

S22. Christakis, G., Rinzler, S. H., Archer, M., Winslow, G., Jampel, S., Stephenson, J., Friedman, G., Fein, H., Kraus, A., James, G. The anti-coronary club. A dietary approach to the prevention of cornary heart disease—a seven-year report. American Journal of Public Health and the Nation's Health 56(2): 299–314, February 1966.

S23. Clancy, R. L., Graham, T. P., Jr., Powell, W. J., Jr., Gilmore, J. P. Inotropic augumentation of myocardial oxygen consumption. American Journal of Physiology 212(5): 1055–1061, May 1967.

S24. Coburn, R. F., Forster, R. E., Kane, P. B. Considerations of the physiological variables that determine the blood carboxyhemoglobin concentration in man. Journal of Clinical Investigation 44(11): 1899–1910, November 1965.

S25. Coburn, R. F., Williams, W. J., White, P., Kahn, S. B. The production of carbon monoxide from hemoglobin *in vivo*. Journal of Clinical Investigation 46(3): 346–356, March 1967.

S26. Connor, W. E., Hoak, J. C., Warner, E. D. Massive thrombosis produced by fatty acid infusion. Journal of Clinical Investigation 42(6): 860–866, June 1963.

S27. DALDERUP, L. M. Vitamin D, cholesterol, and calcium. (Letter) Lancet 1: 645, March 23, 1968.

S28. DALE, H. H. Nomenclature of fibres in the autonomic system and their effects. Journal of Physiology (London) 80:10P–11P, 1933/1934.

S29. DEBRUIN, A. Carboxyhemoglobin levels due to traffic exhaust. Archives of Environmental Health 15(3): 384–389, September 1967.

S30. DECAMP, P. T., CARRERA, A. E., OCHSNER, A., Jr., The hypercoagulable state. Surgery 63(1): 173–180, January 1968.

S31. DECKER, K., SAMMECK, R. Enzymchemische Untersuchungen zum Nicotinabbau in der Kaninchenleber. Biochemische Zeitschrift 340(3): 326–336, August 1964.

S32. DHALLA, N. S., MCLAIN, P. L. Effect of cardio-active drugs on the rate, contractile force and phosphorylase activity in frog heart. Archives Internationales de Pharmacodynamie et de Therapie 163(2): 272–283, 1966.

S33. DOMINO, E. F. Electroencephalographic and behavioral arousal effects of small doses of nicotine: A neuropsychopharmacological study. Annals of the New York Academy of Sciences 142(Article 1): 216–244, March 15, 1967.

S34. DOYLE, J. T. Etiology of coronary disease. Risk factors influencing coronary disease. Modern Concepts of Cardiovascular Disease 35(4): 81–86, April 1966.

S35. ECCLES, R. M., LIBET, B. Origin and blockade of the synaptic responses of curarized sympathetic ganglia. Journal of Physiology (London) 157: 484–503, 1961.

S36. EDWARDS, M. J., RIGAS, D. A. Electrolyte-labile increase of oxygen affinity during *in vivo* aging of hemoglobin. Journal of Clinical Investigation 45(10): 1579–1588, October 1967.

S37. EL-EBRASHY, N., EL-ASHNAWY, S., ALY, A. Effect of smoking on the index of platelet adhesiveness and blood glucose level in atherosclerotic patients. Journal of the Egyptian Medical Association 50(3): 157–168, 1967.

S38. ELIAKIS, C., COUTSELINIS, A., ELIAKIS, E. Depistage des fumeurs par le dosage des thiocyanures dans le sang: Contribution au diagnostic etiologique de l'oxycarbonisme chronique. Annales de Medecine Legale 47(4): 327–329, July–August 1967.

S39. EMMONS, P. R., HARRISON, M. J. G., HONOUR, A. J., MITCHELL, J. R. A. Effect of dipyridamole on human platelet behaviour. Lancet 2: 603–606, September 25, 1965.

S40. ENGELBERG, H., FUTTERMAN, M. Cigarette smoking and thrombotic coagulation of human blood. Further *in vitro* studies. Archives of Environmental Health 14(2): 266–270, February 1967.

S41. FODOR, J. T., GLASS, L. H., WEINER, J. M. Summary of findings: Immediate effects of smoking. Northridge, California, San Fernando Valley State College, Health Science Research Center, September 8, 1967. [Unpublished]

S42. FORBES, W. H., SARGENT, F., ROUGHTON, F. J. W. The rate of carbon monoxide uptake by normal men. American Journal of Physiology 143: 594–608, 1945.

S43. FRIEDMAN, M., ROSENMAN, R. H., BYERS, S. Serum lipids and conjunctival circulation after fat ingestion in men exhibiting Type–A behavior pattern. Circulation 29: 874–886, June 1964.

S44. FUREY, S. A., SCHAANNING, J., SPOONT, S., BIRKHEAD, N. C. The comparative effects on circulation of smoking tobacco and lettuce leaf cigarettes. Angiology 18(4) : 218–223, April 1967.

S45. GARLAND, H., PEARCE, J. Neurological complications of carbon monoxide poisoning. Quarterly Journal of Medicine 36(144) : 445–455, October 1967.

S46. GOLDSMITH, J. R., TERZAGHI, J., HACKNEY, J. D. Evaluation of fluctuating carbon monoxide exposures. Theoretical approach and a preliminary test of methods for studying effects on human populations of fluctuating exposures from multiple sources. Archives of Environmental Health 7(6) : 647–663, December 1963.

S47. GOLDSTEIN, L., BECK, R. A. Amplitude analysis of the electroencephalogram. Review of the information obtained with the integrative method. International Review of Neurobiology 8 : 265–312, 1965.

S48. HOAK, J. C., CONNOR, W. E., ECKSTEIN, J. W., WARNER, E. D. Fatty acid-induced thrombosis and death : Mechanisms and prevention. Journal of Laboratory and Clinical Medicine 63(5) : 791–800, May 1964.

S49. HOAK, J. C., CONNOR, W. E., WARNER, E. D. Thrombogenic effects of albumin-bound fatty acids. Archives of Pathology 81(2) : 136–139, February 1966.

S50. HOAK, J. C., POOLE, J. C. F., ROBINSON, D. S. Thrombosis associated with mobilization of fatty acids. American Journal of Pathology 43(6) : 987–998, December 1963.

S51. HOFF, E. C., HOCKMAN, C. H. Neurophysiological aspects of the action of nicotine. Annals of the New York Academy of Sciences 142 (Article 1) : 121–125, March 15, 1967.

S52. IRVING, D. W., YAMAMOTA, T. Cigarette smoking and cardiac output. British Heart Journal 25 : 126–132, 1963.

S53. KEDRA, M., DMOWSKI, G. The influence of tobacco smoking on the development of atherosclerosis and on the composition of blood lipids. Polish Medical Journal 5(1) : 37–43, 1966.

S54. KERSHBAUM, A., BELLET, S. Cigarette smoking and blood lipids. Journal of the American Medical Association 187(1) : 32–36, January 4, 1964.

S55. KERSHBAUM, A., BELLET, S. Smoking as a factor in atherosclerosis. A review of epidemiological, pathological, and experimental studies. Geriatrics 21(12) : 155–170, December 1966.

S56. KERSHBAUM, A., PAPPAJOHN, D. J., BELLET, S., HIRABAYASHI, M., SHAFIIHA, H. Effect of smoking and nicotine on adrenocortical secretion. Clinical Research 15 : 261, April 1967.

S57. KIEN, G. A., LASKER, N., SHERROD, T. R. Action of cigarette smoke on cardiovascular hemodynamics and oxygen utilization in the dog. Journal of Pharmacology and Experimental Therapeutics 124 : 35–42, 1958.

S58. KIRKEBY, K. Blood lipids, lipoproteins, and proteins in vegetarians. Acta Medica Scandinavica (Supplement 443) : 1–84, 1966.

S59. KULLER, L., LILIENFELD, A., FISHER, R. Sudden and unexpected deaths in young adults. An epidemiological study. Journal of the American Medical Association 198(3) : 248–252, October 17, 1966.

S60. KONTTINEN, A. Cigarette smoking and serum lipids in young men. British Medical Journal 1 : 1115–1116, April 21, 1962.

S61. LAFRENZ, M. EKG-Veränderungen und begünstigende Faktoren des Angina-pectoris-Syndroms. Zeitschrift fur die Gesamte Innere Medizin und ihre Grenzgebiete 22(23) : 773–780, December 1, 1967.

S62. LANGLEY, J. N., DICKINSON, W. L. III. On the local paralysis of peripheral ganglia, and on the connection of different classes of nerve fibres with

them. Proceedings of the Royal Society ; Series B : Biological Sciences 46 : 423–431, November 21, 1889.

S63. LELLOUCH, J., BEAUMONT, J. L. Enquete epidemiologique sur l'Atherosclerose. Chapitre III. La tension arterielle : distribution et correlations dans ungroupe professionnel. Bulletin de l'Institut National de la Recherche Medicale 22(2) : 203–214, March–April 1967.

S64. LILIENTHAL, J. L., Jr., FUGITT, C. H. The effect of low concentrations of carboxyhemoglobin on the "altitude tolerance" of man. American Journal of Physiology 145 : 359–364, 1946.

S65. LUCCHESI, B. R., SCHUSTER, C. R., EMLEY, G. S. The role of nicotine as a determinant of cigarette smoking frequency in man with observations of certain cardiovascular effects associated with the tobacco alkaloid. Clinical Pharmacology and Therapeutics 8(6) : 789–796, November–December 1967.

S66. MCDONOUGH, J. R., HAMES, C. G., GARRISON, G. E., STULB, S. C., LICHTMAN, M. A., HEFELFINGER, D. C. The relationship of hematocrit to cardiovascular states of health in the Negro and white population of Evans County, Georgia. Journal of Chronic Diseases 18(3) : 243–257, March 1965.

S67. MCFARLAND, R. A. Tobacco and efficiency. In : Human Factors in Air Transportation, Occupational Health and Safety. New York, McGraw-Hill, 1953. Pp. 299–307.

S68. MCFARLAND, R. A., MOORE, R. C. Human factors in highway safety. A review and evaluation. New England Journal of Medicine 256 : 792–799, 837–845, 890–897, April 25, May 2 and 9, 1957.

S69. MCFARLAND, R. A., MOSELEY, A. L. Carbon monoxide in trucks and buses and information from other areas of research on carbon monoxide, altitude and cigarette smoking. In : Conference Proceedings : Health, medical and drug factors in highway safety. Washington, National Academy of Sciences—National Research Council Publication No. 328, 1954. Pp. 4.17–4.33.

S70. MCFARLAND, R. A., ROUGHTON, F. J. W., HALPERIN, M. H., NIVEN, J. I. The effects of carbon monoxide and altitude on visual thresholds. Journal of Aviation Medicine 15(6) : 381–394, December 1944.

S71. MCKENNIS, H., Jr., TURNBULL, L. B., BOWMAN, E. R. N-methylation of nicotine and cotinine *in vivo*. Journal of Biological Chemistry 238(2) : 719–723, February 1963.

S72. MIHOCZY, L. Pulmonary hypertension and BCG. In : Knoop, A. A., editor. Ballistocardiography and Cardiovascular Dynamics. Proceedings, 1st World Congress, Amsterdam, 1965. New York, Karger, 1966. Pp. 265–269.

S73. MILLER, R. L., STEDMAN, R. L. Essential absence of beta-naphthylamine in cigarette smoke condensate. Tobacco 165(8) : 32, August 25, 1967.

S74. MISIRLIOGLU, Y. I. Prevention and cure of arteriosclerosis, essential hypertension by activation of fibrinogenolysis with coenzymes ; a new, reliable, simple diagnostic test for arteriosclerosis. Summary 19 : 1–14, December 1967.

S75. MORRIS, W. H. M. Heart disease in farm workers. Canadian Medical Association Journal 96 : 821–824, March 25, 1967.

S76. MURPHREE, H. B., PFEIFFER, C. C., PRICE, L. M. Electroencephalographic changes in man following smoking. Annals of the New York Academy of Sciences 142(Article 1) : 245–260, March 15, 1967.

S77. Oberman, A., Lane, N. E., Harlan, W. R., Graybiel, A., Mitchell, R. E. Trends in systolic blood pressure in the thousand aviator cohort over a twenty-four year period. Circulation 36(10) : 812–822, December 1967.

S78. Ogston, D., Fullerton, H. W. Plasma fibrinolytic activity following recent myocardial and cerebral infarction. Lancet 2: 99–101, July 17, 1965.

S79. Oram, S. Smoking and ischaemic heart disease. British Heart Journal 30(2) : 145–150, March 1968.

S80. Oram, S., Sowton, E. Tobacco angina. Quarterly Journal of Medicine, New Series 32(126) : 115–143, April 1963.

S81. Pfeiffer, C. C., Beck, R. A., Goldstein, L. The modification of central nervous system (CNS) function by autonomic drugs. Amine shift responses differentiate between CNS nicotinic and muscarinic effects. Annals of the New York Academy of Sciences 142(Article I) : 181–189, March 15, 1967.

S82. Pincherle, G., Shanks, J. Haemoglobin values in business executives. British Journal of Preventive and Social Medicine 21(1) : 40–42, January 1967.

S83. Pincherle, G., Shanks, J. Value of the erythrocyte sedimentation rate as a screening test. British Journal of Preventive and Social Medicine 21(3) : 133–136, July 1967.

S84. Rakusan, K., Du Mesnil De Rochemont, W. Hanlon, J., Braasch, W., Tschopp, H., Bing, R. J. Effect of nicotine and vasopressin on capillary blood flow and capacity of the terminal vascular bed. Medicina et Pharmacologia Experimentalis 17(2) : 119–128, 1967.

S85. Ramsey, J. M. Carboxyhemoglobinemia in parking garage employees. Archives of Environmental Health 15(5) : 580–583, November 1967.

S86. Regan, T. J., Frank, M. J., McGinty, J. F., Zobl, E., Hellems, H. K., Bing, R. J. Myocardial response to cigarette smoking in normal subjects and patients with coronary disease. Circulation 23(3) : 365–369, March 1961.

S87. Rinzler, S. H., Archer, M., Christakis, G. J. Primary prevention of coronary heart disease by diet. (Annotations) American Heart Journal 73(2) : 287–289, February 1967.

S88. Ripka, O. Epidemiologie des hohen Blutdrucks. Medizinische Klinik 63(3) : 89–93, January 19, 1968.

S89. Rosenman, R. H. Emotional factors in coronary heart disease. Postgraduate Medicine 42(3) : 165–171, September 1967.

S90. Sayers, R. R., Yant, W. P. Levy, E., Fulton, W. B. Effect of repeated daily exposure of several hours to small amounts of automobile exhaust gas. Public Health Bulletin No. 186, 1929. 58 pp.

S91. Schievelbein, H., Peter, H., Trautschold, I., Werle, E., Freisetzung von 5-Hydroxytryptamin aus Thrombocyten durch Harmalin. Biochemical Pharmacology 15 : 195–197, 1966.

S92. Schievelbein, H., Werle, E. Mechanism of the release of amines by nicotine. Annals of the New York Academy of Sciences 142(Article 1) : 72–82, March 15, 1967.

S93. Schilling, F. J., Christakis, G. J. Bennett, N. J., Coyle, J. F. Studies of serum cholesterol in 4,244 men and women: an epidemiological and pathogenetic interpretation. American Journal of Public Heath and the Nation's Health 54(3) : 461–476, March 1964.

S94. SCHIMMLER, W., SCHIMERT, G., NEFF, C. Rauchgewohnheiten und Aortenelastizität. (Messung der Pulswellengeschwindigkeit bei männlichen Zigarettenrauchern, Ex- und Nichtrauchern) Vorläufige Mitteilung. Zeitschrift für Kreislaufforschung 56(11) : 1121–1127, November 1967.

S95. SCHMITERLOW, C. G., HANSSON, E., ANDERSSON, G., APPELGREN, L. S., HOFFMANN, P. C. Distribution of nicotine in the central nervous system. Annals of the New York Academy of Sciences 142(Article 1) : 2–14, March 15, 1967.

S96. SCHULTE, J. H. Effects of mild carbon monoxide intoxication. Archives of Environmental Health 7(5) : 524–530, November 1963.

S97. SHILLINGFORD, J. P. The acute effects of smoking on the performance of the heart in normal subjects and patients with coronary heart disease. In : von Euler, U.S., editor. Tobacco Alkaloids and Related Compounds. New York, Pergamon, 1965. Pp. 263–272.

S98. SIEVERS, M. L. Cigarette and alcohol usage by southwestern American Indians. American Journal of Public Health and the Nation's Health 58(1) : 71–82, January 1968.

S99. SILOVE, E. D., GROVER, R. F. Effects of alpha adrenergic blockade and tissue catecholamine depletion on pulmonary vascular response to hypoxia. Journal of Clinical Investigation 47 : 274–285, 1968.

S100. SINGH, J. Effect of nicotine on blood clotting time of albino rats fed atherogenic diet. Archives Internationales de Pharmacodynamie et de Therapie 154(1) : 221–227, March 1965.

S101. SINGH, J., OESTER, Y. T. Nicotine antagonism with heparin. Possible mode of action on human blood coagulation time *in vitro*. Archives Internationales de Pharmacodynamie et de Therapie 149(3–4) : 354–361, June 1, 1964.

S102. SODI-PALLARES, D., DE MITCHELI, A., MEDRANO, G., FISHLEDER, B., BISTENI, A., FRIEDLAND, C., TESTELLI, M. Effets sur l'electrocariogramme de la solution glucose-insuline-potassium au cours de l'insuffisance coronarienne aigue et chronique. Malattie Cardiovasculari 3(1) : 41–79, 1962.

S103. SONNENBLICK, E. H., ROSS, J., Jr., COVELL, J. W., KAISER, A., BRAUNWALD, E. Velocity of contraction as a determinant of myocardial oxygen consumption. American Journal of Physiology 209(5) : 919–927, May 1965.

S104. SPECKMANN, K., KLENSCH, H., MAETZEL, F. K., MEYER, J. D. Untersuchungen zur Frühdiagnose der Angina Pectoris. Deutsche Medizinische Wochenschrift 92 : 1493–1947, August 25, 1967.

S105. STEIN, P. D., ALSHABKHOUN, S., HATEM, C., PUR-SHAHRIARI, A. A., HAYNES, F. W., HARKEN, D. E., DEXTER, L. Coronary artery blood flow in acute pulmonary embolism. American Journal of Cardiology 21(1) : 32–37, January 1968.

S106. STERN, S., RAPAPORT, E. Comparison of the reflexes elicited from combined or separate stimulation of the aortic and carotid chemoreceptors on myocardial contractility, cardiac output and systemic resistance. Circulation Research 20(2) : 214–227, February 1697.

S107. TALBOT, S. A., HARRISON, W. K., Jr., GINN, W. M., Jr. Features of ULF–BCG pertinent to coronary heart disease. In : Knoop, A. A., editor. Ballistocardiography and Cardiovascular Dynamics. Proceedings. 1st World Congress, Amsterdam, 1965. New York, Karger, 1966. Pp. 55–68.

S108. TALBOTT, G. D. Influence of environmental factors on lipid-response curves. Cigarette smoking, salt, alcohol, and high-fat diet effecting healthy males. Geriatrics 19(8) : 575–584, August 1964.

S109. TAYLOR, L., SCHILLING, R. S. F. The health and habits of higher executives. Journal of the Royal College of General Practitioners 14(3): 262–281, November 1967.

S110. TRAVELL, J., RINZLER, S. H., KARP, D. Cardiac effects of nicotine in the rabbit with experimental coronary atherosclerosis. Part VII. Effects of nicotine and smoking in cardiovascular disorders. Annals of the New York Academy of Sciences 90(1): 290–301, September 27, 1960.

S111. TROUTON, D., EYSENCK, H. The effects of drugs on behavior. In: Eysenck, H. J., editor. Handbook of Abnormal Psychology. New York, Basic Books, 1961. Pp. 634–696.

S112. WENZEL, D. G. Drug-induced cardiomyopathies. Journal of Pharmaceutical Sciences 56(10): 1209–1224, October 1967.

S113. WENZEL, D. G., KAMAL, J. S. TURNER, J. A. The chronic effects of orally administered nicotine in cholesterol-fed rabbits. Annals of the New York Academy of Sciences 90(1): 302–307, September 27, 1960.

S114. WERTLAKE, P. T., WILCOX, A. A., HALEY, M. I., PETERSON, J. E. Relationship of mental and emotional stress to serum cholesterol levels. Proceedings of the Society for Experimental Biology and Medicine 97: 163–165, January 1958.

S115. WESTFALL, T. C., ANDERSON, G. P. Influence of nicotine on catecholamine metabolism in the rat. Archives Internationales de Pharmacodynamie et de Therapie 169(2): 421–428, October 1967.

S116. WHELAN, R. F. Alcohol, nicotine and man. Medical Journal of Australia 1(3): 77–83, January 20, 1968.

CHAPTER 2

Smoking and Chronic Bronchopulmonary Diseases (Non-Neoplastic)

Contents

INTRODUCTION

The primary purpose of the 1968 Supplemental Report is to review the pertinent literature that has become available subsequent to the 1967 report. Brief mention of the conclusions of the 1964 report and the highlights of the 1967 report is made to facilitate an understanding of the significance of the newer information. The current research findings should be considered in the perspective of the research evidence previously reported in the 1964 (*59*) and 1967 (*57*) reports.

Conclusions of the 1964 Report (*59*)

1. Cigarette smoking is the most important of the causes of 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 nonsmokers.
5. Cigarette smoking is associated with a reduction in ventilatory function. Among males, cigarette smokers have a greater prevalence of breathlessness than nonsmokers.
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.

Highlights of the 1967 Report (*57*)

1. New data confirm and to some extent strengthen the conclusions of the Surgeon General's 1964 Report.
2. Cigarette smoking is the most important of the causes of chronic non-neoplastic bronchopulmonary diseases in the United States. It greatly increases the risk of dying not only from both chronic bronchitis but also from pulmonary emphysema.
3. Cessation of smoking is followed by a reduction in mortality from chronic bronchopulmonary disease relative to the mortality of those who continue to smoke.

4. Even relatively young cigarette smokers frequently have demonstrable respiratory symptoms and reduction in ventilatory function.

GENERAL BRONCHOPULMONARY DISEASE MORTALITY AND MORBIDITY

The 1967 report (*57*) pointed out the alarming rate of increase in emphysema and/or chronic bronchitis mortality (table 1). There were 25,416 deaths from emphysema and/or chronic bronchitis in 1966 which represent a 25 percent increase over 1964. The increasing death rates for chronic bronchitis and emphysema since 1950 are shown in figure 1. Death rates for these diseases are increasing more rapidly than are the death rates for lung cancer as illustrated in figure 2.

Last year, payments made by the Social Security Administration to men and women totally disabled because of emphysema amounted to about 90 million dollars; this was 7 percent of all disability payments, making chronic lung disease second only to heart disease in this regard.

TABLE 1.—*Mortality from emphysema and/or chronic bronchitis: United States, each year 1950–1964*

[ISC codes 501, 502, 527.1]

Year	Number of deaths	Year	Number of deaths	Year	Number of deaths
1950	3, 157	1955	5, 616	1960	12, 426
1951	3, 660	1956	6, 535	1961	13, 302
1952	3, 846	1957	8, 136	1962	15, 915
1953	4, 657	1958	9, 328	1963	19, 443
1954	4, 877	1959	10, 433	1964	20, 208

SOURCE: Vital Statistics of the United States, 1950-1964 (*58*).

POPULATION STUDIES

Several papers published in the past year reported the results of surveys of pulmonary function and respiratory symptoms in different populations. All of those which were reviewed and which included a comparison of findings between smokers and nonsmokers reported similar observations. In all instances, smokers had respiratory symptoms such as cough, phlegm production, and dyspnea more often than nonsmokers or ex-smokers of the same age and sex. In surveys which included pulmonary function tests, it was found that smokers did not perform as well as nonsmokers or ex-smokers. Substantially, these observations confirm those of earlier years without indicating new associations.

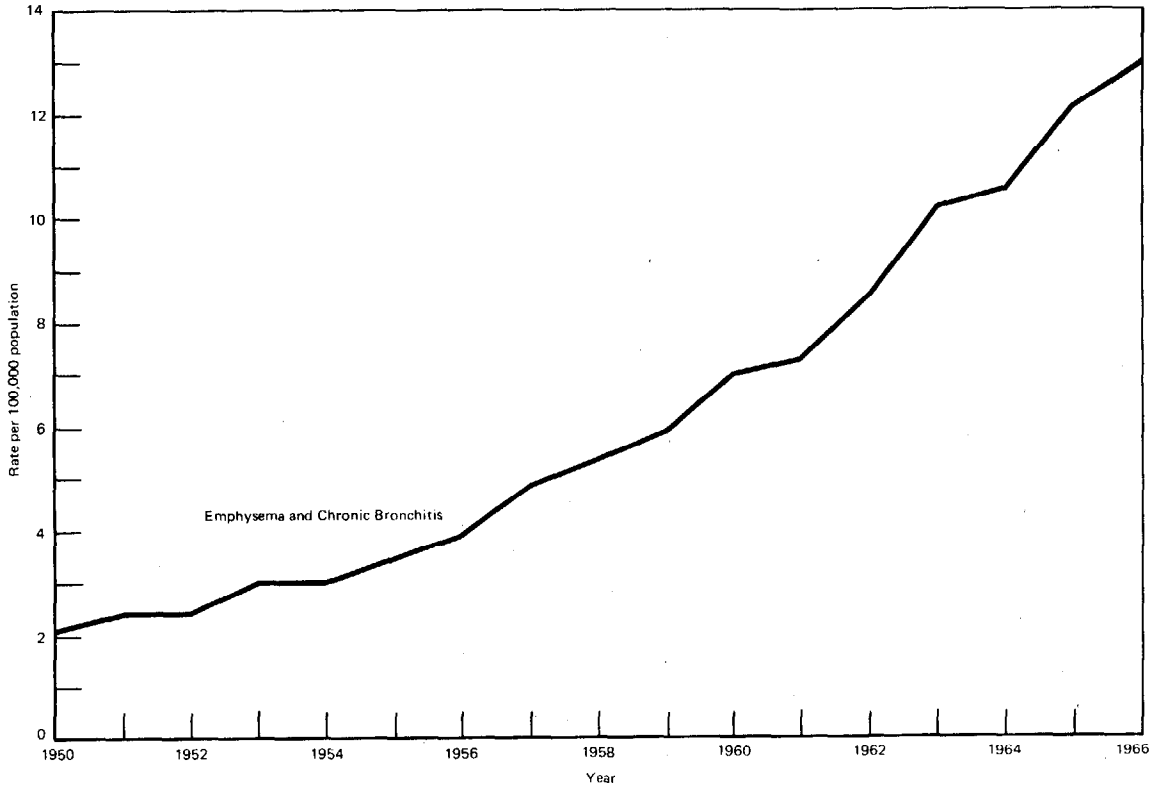

FIGURE 1—Death rates for emphysema and chronic bronchitis. United States, 1950–1966 (Arthritic scale).
SOURCE: National Center for Chronic Disease Control.

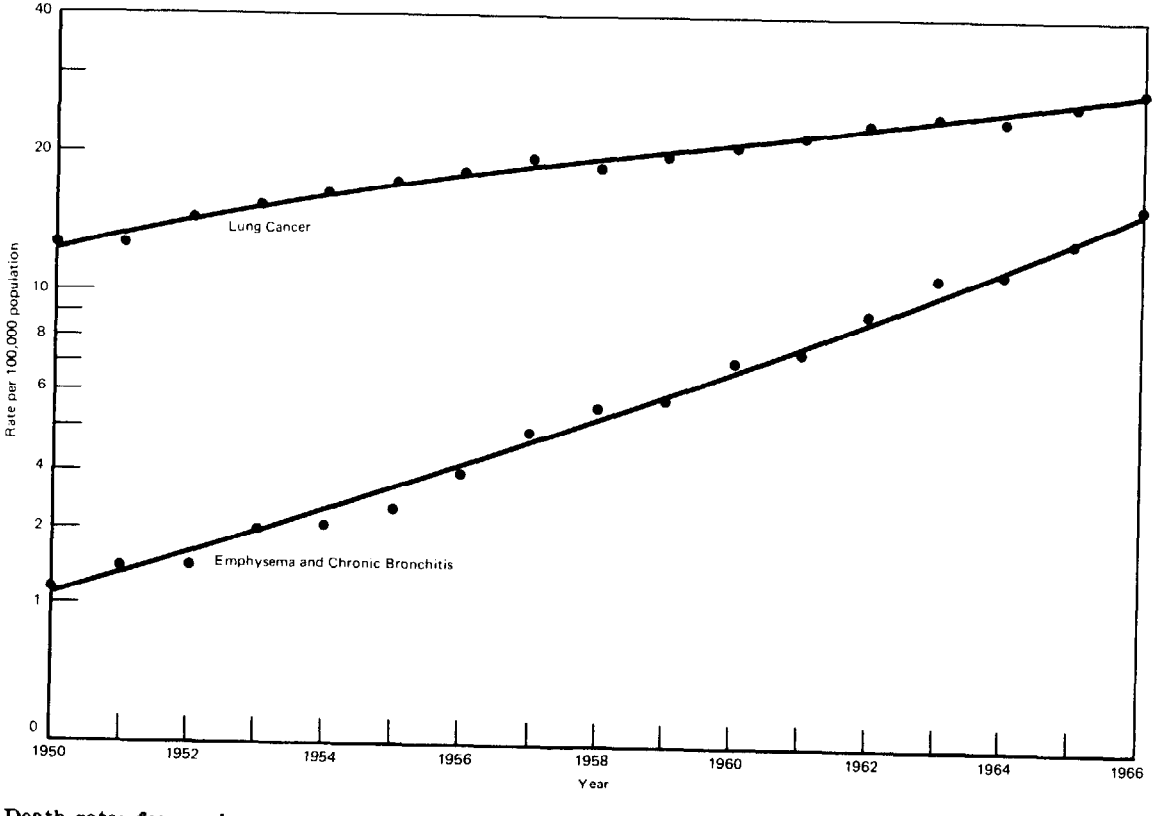

FIGURE 2—Death rates for emphysema and chronic bronchitis and for lung cancer: United States, 1950–1966 (Logarithmic scale).
SOURCE: National Center for Chronic Disease Control.

A few specific surveys might be mentioned. Huhti (*27*) surveyed 1,028 men and women in a village in Finland. None of the women smoked. In men the one-second forced expiratory volume ($FEV_{1.0}$) and the peak expiratory flow (PEF) were significantly lower among those men who smoked 15 or more cigarettes a day than those who smoked less or not at all. No difference in forced vital capacity (FVC) was observed.

Edelman, et al. (*14*) studied 410 men and found lower values of $FEV_{1.0}$, FVC, and maximal voluntary ventilations among current smokers than among nonsmokers. They also reported an inverse relationship between the number of cigarettes smoked and pulmonary function.

Stanek, et al. (*54*) noted a definite association between chronic cough and phlegm production (chronic bronchitis) and cigarette smoking among a random sample of 443 men surveyed in Prague. Freour, et al. (*21*) in Bordeaux also reported a much greater frequency of symptoms of chronic bronchitis among smokers than nonsmokers in a preliminary report based on 1,055 examinations.

Higgins and his associates (*25*) reported observations from a nine year followup study of men in an industrial town in England. Among the 385 men who were age 55–64 at the start of the study, mortality during the nine years was twice as high for smokers as nonsmokers. Ex-smokers had the same mortality experience as nonsmokers. Among the survivors of all ages who were tested initially and nine years later, the average decline in lung function as measured by the $FEV_{.75}$ was smallest in nonsmokers, slightly greater in ex-smokers, and greatest in smokers. The findings suggested that smoking was a more important factor than occupation in respiratory disability.

Industrial air pollution studies have been performed by Lowe (*32*) using a population of steelworkers at Ebbw Vale and Port Talbot, with smoking and chronic bronchitis data presented in a subsequent publication (*31*). It was noted that for each age group, chronic bronchitis was about three times more prevalent among men who smoked 25 or more cigarettes per day, than among those who had never smoked. Cigarette smokers appear to be more adversely affected by pulmonary exposure to dusts at work than the nonsmokers. The authors pointed out that studies to evaluate the interaction between smoking and industrial air pollution require occupational subgroups large enough to permit standardization for both age and smoking habits. In this way, the interaction between smoking and other air pollutants can be analyzed more definitively.

Most surveys have been of adults, but Holland, et al. (*26*) reported the findings of an investigation of smoking and respiratory symptoms among more than 10,000 school children, age eleven or more, in England. The survey was conducted in 1965 and repeated in 1966. Ciga-

rette smokers (at least one cigarette per week) more frequently reported symptoms of cough and phlegm production than nonsmokers and the prevalence of symptoms increased with increases in the amount smoked. Children who smoked one year but did not smoke in the subsequent year had a lower frequency of symptoms in the second year.

Relationships to Pulmonary Infection

The relationship between smoking and pulmonary infection is unclear. It is evident that cigarette smoking is a major cause of chronic bronchitis. Much of the symptomatology of chronic bronchitis of smokers, particularly cigarette smokers, results from the harmful effects of inhaled tobacco smoke on the bronchial ciliary apparatus and the mucous glands. These effects tend to impair mucous removal from the bronchial and bronchiolar airways and possibly may, in turn, increase susceptibility to pulmonary infections.

In a study of 191 boys, age 14 to 19, in a preparatory school, the incidence of all respiratory illness over a one-year period was positively correlated with smoking habits within each age group. "Severe" (purulent sputum) lower respiratory tract illnesses were nine times more frequent in regular smokers than nonsmokers (age-adjusted) (*24*).

A study in Cairo of the relation between smoking and infection and appearance of mucous gland hypertrophy in the main bronchi was reported by Megahed and his colleagues (*34*). They studied 50 men with chronic bronchitis and found substantially more mucous gland hypertrophy among the 43 smokers than the 7 nonsmokers. This hypertrophy seemed unrelated to the presence of potential pathogenic organisms isolated from a single bronchial lavage, although the authors believed that infection might have an initiating or potentiating effect.

Fletcher (*17*) studied the relationship between frequency of respiratory illness as measured by sputum purulence and histories of "chest illnesses" and "chest colds" and the rate of decline of FEV in slightly more than 900 men who were followed at least four years. He concludes that illnesses and sputum purulence have no significant effect on FEV regression. (This study will be discussed again later in this chapter).

It appears that, in patients with chronic obstructive bronchopulmonary disease caused by cigarette smoking or other pulmonary irritants, superimposed infections may cause exacerbations of the chronic disease process. There is no substantial evidence that infections per se cause much of the chronic obstructive bronchopulmonary disease seen in cigarette smokers.

Wynder (*62*) reported that the hyperplastic and metaplastic effects of Swine influenza virus could not be enhanced by subsequent exposure

of mice to cigarette smoke. Previous literature indicates that the sequence of events may be of some importance, since there have been reports that cigarette smoke increases the bronchial epithelial reaction to influenza virus. Spurgash (*53*) reported that pre-exposure to cigarette smoke did not have any significant effect on resistance of mice to subsequent influenza virus infection inoculated by aerosol inhalation. But, the subsequent exposure of pre-infected mice to cigarette smoke resulted in significantly higher mortality rates, thus suggesting that cigarette smoke can aggravate an existing respiratory viral infection. However, smoke-exposed mice subsequently challenged with certain bacteria, *Klebsiella pneumoniae* or *Diplococcus pneumoniae*, also exhibited a decreased resistance to respiratory infection as shown by a decreased survival time and a higher mortality (*53*).

The tobacco plant can be diseased by a variety of fungi (*33*). Of these the *Alternaria* species and *Aspergillus niger* were recently shown to increase the toxicity of cigarette smoke (*20*). Mice exposed to smoke from hay previously inoculated with *Alternaria* or *Aspergillus niger*, showed progressive pulmonary congestion, edema and tissue destruction confirmed by autopsy. Those mice in a hay-smoke control group were normal clinically and showed only chronic pulmonary inflammation on autopsy.

SMOKING AND BRONCHOPULMONARY PHYSIOLOGY

Animal and Experimental Studies

The ciliatoxic effects of cigarette smoke were presented in the 1964 (*59*) and 1967 Reports (*57*). Discussants in a recent symposium (*29*), pointed out that both volatile and particulate components of cigarette smoke can adversely affect ciliary activity. In short-term *in vivo* experiments, Dalhamn (*11*) showed that the ciliostatic effect of cigarette smoke was direcly related to the "tar" content if the gas phase was held constant.

Rylander (*44*) reported that in guinea pigs exposed to cigarette smoke, the reduction of killed, radioactive bacteria was lower than in controls, presumably due to a decrease in mucus flow. There was no significant difference in reduction of viable bacteria.

A study by Dalhamn, et al. (*10*) suggests that lack of oxygen in the external environmental *in vitro* can reduce ciliary activity. The main problem in the evaluation of studies related to ciliary activity is to determine to what extent the *in vitro* studies can relate to the *in vivo* studies in animals and in man. For instance, the ciliatoxic effects of hydrogen cyanide in cigarette smoke were dose-related in experiments on clam gills *in vitro*, but the same results could not be reproduced with *in vivo* experiments in cats (*12*). Volatile (gas phase) components have been shown to be retained to a large extent by wet surfaces (*28*),

which raises the question of how much of the volatile ciliatoxic agents in cigarette smoke entering the moist oral cavity actually enter the lower respiratory tract.

Davis, et al. (*13*) in experiments with respiratory irritants including cigarette smoke in guinea pigs, have implicated the nasopharynx and larynx as sources of receptor stimulation leading to increased upper airway resistance, and decreases in respiration rate and minute volume. These effects were not present when a tracheostomy was performed to bypass the smoke directly into the trachea. However, Guillerm (*23*) noted increased airway resistance and decreased compliance in the tracheotomized and spinal guinea pig after smoke inhalation.

Aviado and his co-workers (*2*, *3*, *4*, *19*, *38*, *45*, *46*, *47*, *48*) have continued their studies on bronchoconstriction and bronchodilation in animals and recently have further investigated the role of histamine in a study of inhibitors for histamine decarboxylase in rabbits, dogs, and cats (*39*). These species have variations in response to cigarette smoking as previously noted. Cats have a uniphasic bronchoconstrictor response to inhaled cigarette smoke (somewhat like man's) and dogs have a biphasic response. Rabbits were observed to behave differently than cats or dogs. Histamine has been implicated as mediating part of the bronchoconstrictive effect of cigarette smoke. The rabbit does not respond to histamine by bronchoconstriction. This study (*39*) suggests that the rabbit lacks a histamine sensitive system in the airways, in contrast to cats and dogs. Alpha-hydrazino histidine, which inhibits the enzyme histamine decarboxylase, was demonstrated to prevent much of the bronchoconstrictive effect in cats and dogs. By analogy, this suggests the possibility that histamine may mediate some of the bronchoconstrictive response to inhaled tobacco smoke noted in humans. Pretreatment with atropine has been shown to block the bronchoconstriction caused by cigarette smoke (*36*) and by histamine inhalation in humans (*7*, *8*, *52*).

There is experimental evidence (*48*) in dogs, that the pulmonary exposure to inhaled cigarette smoke or injected nicotine can result in pulmonary vasoconstriction, causing increased pulmonary arterial pressure. This effect is thought to be due to histamine release from lung tissue (*48*). Autopsy studies in humans, by Auerbach (*1*), showed considerably greater fibrous thickening of the arterioles and small arteries in smokers, occurring not only in the lungs, but other organs as well. The degree of fibrous thickening increased with age and the amount of cigarette smoking.

Participants in a recent international symposium on the mechanism of elimination of deposited particles from the lungs (*15*), discussed the relationships among alveolar surfactant, alveolar macrophages, the alveolar transport mechanisms, and the mucociliary apparatus; which may also relate to the pathoetiology of pulmonary emphysema.

Giammona (*22*) reports that cigarette smoke consistently lowers the maximal surface tension without altering the minimal surface tension of lung extracts after *in vitro* exposure to cigarette smoke. *In vivo* changes were noted in guinea pigs, but not in dogs or cats, which he thought may have been due to insufficient exposure. Additional information concerning surfactant has been discussed by Sekulic, et al. (*49*, *50*). Yeager, et al, (*63*) have reported that cigarette smoke has a depressant effect on protein synthesis of human alveolar cells *in vitro*.

Studies in Humans

Fletcher (*17*) in the study mentioned earlier in this chapter, correlated the rate of decline of FEV in over 900 men followed for at least four years, with respect to starting FEV, cigarette smoking, sputum purulence, and histories of respiratory infections. He tested FEV's in response to the acute effect of smoking cigarettes, and found that the mean regression of FEV in those subjects who had a higher prevalence of cough and sputum was not significantly different from those with a lower prevalence. The men with higher initial standardized levels of FEV had less steep regressions than those with lower levels. Cigarette smoking had a significant effect on decline of FEV. Sputum eosinophilia was also related but apparently to a lesser degree, and Fletcher stated that there was no confirmation of the possible role of tobacco allergy in chronic obstructive bronchitis. With regard to the decline in FEV, more information on controls and on the quantity of cigarettes usually smoked would be helpful. While contributing important information, this study does not fully describe the progression of declining FEV in cigarette smokers in relation to the quantity that they smoked before and over the time-period studied. In a detailed study of 58 bronchitics (50 of whom had positive smoking histories) Simonsson (*51*) found a positive correlation between the degree of obstructive status and the reactivity to exposure to nebulized acetylcholine; and noted that a larger decrease in airflow seems to occur in previously obstructed airways than in normal ones.

Peterson (*42*) studies pulmonary function in a group of 12 individuals who had stopped cigarette smoking for 18 months, and compared their pulmonary function test before and after cessation. These individuals showed significant improvements in their pulmonary functions as measured by timed vital capacity and expiratory flow rates. Ex-smokers reported a decrease in cough and breathlessness after cessation of smoking. (This study confirms the findings of Krumholz reported in the 1967 report). The mean FEV of Peterson's ex-smokers was markedly greater than that observed in another group of individuals who had continued to smoke cigarettes during the same 18 month period, measured at the same time intervals.

Wilhelmsen (*60*) found in a small study of 16 persons who had smoked over 10 cigarettes a day for a mean of 25 years that cessation of cigarette smoking for an average of 40 days was accompanied by a marked decrease of sputum production, coughing and wheezing, and a significant increase in FEV_1.

Bates (*5, 6*) has reviewed the reliability and constancy of pulmonary function tests. He notes the importance of making pathological diagnoses with lungs inflated at autopsy. Morphologic considerations of emphysema are correlated with functional abnormalities and current biochemical research. He discusses derangement of pulmonary ventilation-perfusion distribution in relation to bronchial and/or alveolar damage from cigarette smoking with consequent stresses on right ventricular function. He emphasizes the fact that obstructive bronchitis appears to lead more frequently to right heart failure than does "pure" emphysema.

Although instances of "pure" emphysema or "pure" bronchitis exist, most patients with respiratory obstruction appear to have both emphysema and bronchitis. Bates suggests the theory that one of cigarette smoking's harmful effects may be destruction of bronchiolar structure. This could lead to disturbed ventilation-perfusion (V/Q) relationships. As enough lung tissue breaks down, causing centrilobular emphysema, there is impairment of gas equilibration within the centrilobular spaces. Increasing derangement of the V/Q distribution in turn can lead to hypercapnia and hypoxemia. Clinically, what may seem to be respiratory decompensation, may actually be incipient cardiopulmonary decompensation due to the deranged V/Q and gas imbalance resulting from the obstructive bronchiolitis.

Postural hypoxemia has also been noted (*55*) in young asymptomatic cigarette smokers with no evidence of chronic lung disease when in the supine position as compared with nonsmoking controls.

THEORIES INTERRELATING CIGARETTE SMOKING AND CHRONIC OBSTRUCTIVE BRONCHOPULMONARY DISEASE WITH PULMONARY HYPERTENSION AND COR PULMONALE

Hypercapnia and hypoxemia are capable of causing pulmonary vasoconstriction with a resultant increase in pulmonary arterial pressure and right ventricular work. Stuart-Harris, in a review article (*56*), relates these phenomena to the clinical picture of pulmonary hypertension and right heart failure seen in patients with pulmonary insufficiency caused by chronic obstructive bronchitis. Since the pathologic changes in the small pulmonary vessels are not usually as severe as those found in congenital heart disease, it is believed that the pulmonary hypertension seen in chronic obstructive lung disease is of the vasoconstrictive type. Although most patients with severe chronic

bronchitis have some emphysema, it is the airway obstruction of chronic bronchitis which may relate most strongly to the development of cor pulmonale. It is now apparent that cor pulmonale can be a sequel to severe obstructive bronchitis without emphysematous changes (*9*, *17*, *35*, *37*). Studies (*16*, *18*, *43*) indicate that patients with hypercapnia and hypoxemia due to abnormal pulmonary ventilation-perfusion relationships are likely to develop cardiac complications. As indicated in the preceding section of this report, recent studies (*40*, *41*, *43*) have demonstrated the presence of ventilation-perfusion imbalances in patients with chronic bronchitis—the extent of imbalances being related to the severity of bronchitic process. Penman, et al. (*41*) determined the gas tensions in expired air and arterial blood and used them to calculate the alveolar dead space and alveolar blood shunt, permitting estimation of three theoretical "compartments" of the lung: (1) Ventilated but unperfused (alveolar dead space) "compartment," (2) unventilated perfused (alveolar blood shunt) "compartment" and (3) "normal" ventilated perfused "compartment." Chronic bronchitics were found to have abnormalities of ventilation and perfusion with a marked reduction in the "normal" "compartment." In patients with decompensated cor pulmonale, further studies of the correlations between cardiac output, arterial oxygen tension, and arterial carbon dioxide tension with the above "compartments" lead Penman, et al. (*41*) to believe that in cases of decompensated cor pulmonale a considerable fraction of the cardiac output is shunted without exposure to aerated alveoli.

It was further hypothesized that this increased shunting of blood through non-aerated regions of lung would result in increasing hypoxemia and hypercapnia with consequent further constriction of the pulmonary vasculature and further encroachment of the alveolar dead space upon the normally ventilated and perfused lung. Williams, et al. (*61*) in determining the acute effects of cigarette smoking, found an increase in the "alveolar dead space" in 11 patients with obstructive airway disease. They postulate this to be due to "the effect of nicotine on the vasculature of the lung in this group of patients."

Since pulmonary vasoconstriction will also increase the pulmonary arterial pressure and right ventricular work, it may also lead to right ventricular failure and the classic picture of cor pulmonale. The beneficial effects of correcting (to the extent that this is possible) the ventilatory problems in these patients is well known, and it is thought that the basis of the improvement is the correction of the hypoxemia and hypercapnia which allows a reversal of the pulmonary vasoconstriction, thereby permitting better perfusion of underperfused areas and also decreasing the workload of the right ventricle. Stuart-Harris also pointed out that the relief of myocardial anoxia with appropriate therapy may help the right ventricle recompensate.