

Similar types of diverse effects on drug disposition caused by marijuana have been found in man. Vessell and Passananti (78) found that oral doses (0.6 mg/kg/day) of Δ^9 -THC for 7 days caused a slight increase in the antipyrine $t_{1/2}$. Dalton, et al. (18) examined the effects of smoking a marijuana cigarette containing 0, 150, and 500 $\mu\text{g}/\text{kg}$ cannabidiol (a major cannabinoid constituent of *Cannabis sativa*) and found that cannabidiol did not alter secobarbital disposition.

Lemberger, et al. (41) found that chronic marijuana users eliminated Δ^9 -THC from blood plasma with a $t_{1/2}$ of 28 hours compared to 57 hours in nonusers. The apparent volume of distribution did not significantly differ between the two groups.

Purified cannabinoid appears to inhibit the induction of the drug-metabolizing enzyme, but the marijuana smoke is generally inhaled; the chronic inhalation of marijuana smoke results in enzyme induction caused by the PAHs in the smoke. The multiple components in the smoke of a "joint" may play an additive or an inactive role in altering drug disposition as does tobacco smoking. Therefore, the chronic use of marijuana must be considered as a source of pharmacological drug interaction not only because of its psychoactive actions, but also because of its ability to stimulate or to inhibit the metabolic rate of susceptible drugs used in man.

Summary

Despite the warning "The Surgeon General Has Determined That Cigarette Smoking Is Dangerous To Your Health" on each pack of cigarettes, the use of tobacco is still "enjoyed" by one out of three adults in the United States. This extensive use of tobacco and the frequency of altered disposition and pharmacological effects of many drugs in smokers make it apparent that smoking of tobacco should be considered as one of the primary sources of drug interactions in man.

The majority of the *in vivo* and *in vitro* experimental work conducted to the present time indicates that the dominant effect of smoking is enhanced drug disposition caused by an induction of hepatic microsomal enzymes. The primary causal agent for this induction is probably the PAHs which are potent enzyme inducers and which are persistent in the tissues. Many other ingredients of tobacco smoke are capable of inducing (nicotine, cadmium, and insecticides) or inhibiting (carbon monoxide and hydrogen cyanide) drug-metabolizing enzymes. Inhibition of the drug-metabolizing enzymes is apparently overridden by the inducers in tobacco smoke, because presently there are no reports of diminished rates of drug metabolism in man or animals treated with tobacco smoke. Alteration of drug-transport processes can occur, as seen by the enhanced bioavailability of glutethimide by smokers, but this does not appear to be a common pathway. Diminished protein binding of drugs in smokers could occur, but there is no evidence for this at the present time. Factors such as the volume of

distribution of drugs in smokers and nonsmokers have been examined. The variability in drug disposition for antipyrine and theophylline was appreciable. There is evidence for genetic control of the degree of enzyme induction from smoking which may also be a common factor in the carcinogenicity of inhaled chemicals.

Reports of altered pharmacological or toxicological effects of drugs in smokers can sometimes be explained by induced metabolism of the drug (pentazocine, theophylline). On the other hand, smokers differ from nonsmokers in their pain threshold, psychosomatic characteristics, and drug consumption; the presence of substances, such as nicotine, which cause competing or additive pharmacological effects, may complicate the action of drugs used in treating pain or anxiety (propoxyphene, benzodiazepine, chlorpromazine).

In addition to the identification of a wider array of drugs, enzymatic pathways, and clinical effects which are altered by tobacco smoking, future studies should investigate the role of smoking in affecting other clearance processes. Even though it is known that some of the hepatic microsomal drug-metabolizing enzymes are stimulated in smokers, the selectivity of this induction is unpredictable and the effects of smoking on other potential rate-limiting disposition processes, such as the effect of smoking on protein binding of various drugs, and the contribution of nonhepatic tissue such as kidney, lung, and intestine are largely unexplored.

Effects on Pharmacokinetics and Pharmacodynamics: References

- (1) ABRAMOWICZ, M. (Editor). Marijuana. *Medical Letter on Drug and Therapeutics* 18(17): 69-70, August 13, 1976.
- (2) AKIN, F.J., SNOOK, M.E., SEVERSON, R.E., CHAMBERLAIN, W.J., WALTERS, D.B. Identification of polynuclear aromatic hydrocarbons in cigarette smoke and their importance as tumorigens. *Journal National Cancer Institute* 57(1): 191-195, July 1976.
- (3) AMBRE, J., GRAEFF, D., BURES, F., HAUPT D., DEASON, K. Antipyrine metabolism and bronchogenic carcinoma. *Journal of Medicine* 8(1): 57-70, 1977.
- (4) BACHMANN, K., TARLOFF, J. Influence of 3, 4-benzo(a)pyrene on warfarin hypoprothrombinemia and disposition in the rat. *Toxicology and Applied Pharmacology* 42: 157-165, 1977.
- (5) BECKETT, A.H., ROWLAND, M., TRIGGS, E.J. Significance of smoking in investigations of urinary excretion rates of amines in man. *Nature* 207(4993): 200-201, July 10, 1965.
- (6) BECKETT, A.H., TRIGGS, E.J. Enzyme induction in man caused by smoking. *Nature* 216: 587, November 11, 1967.
- (7) BENNETT, J.R. Progress Report. Smoking and the gastrointestinal tract. *Gut* 13: 658-665, 1972.
- (8) BERMAN, M.L., BOCHANTIN, J.F. Effect of delta-9 tetrahydrocannabinol (marihuana) on liver microsomal dechlorinase activity: A preliminary report. *Anesthesia and Analgesia* 51(6): 929-932, November/December, 1972.
- (9) BOSTON COLLABORATIVE DRUG SURVEILLANCE PROGRAM. Clinical depression of the central nervous system due to diazepam and chlorodiazepoxide in relation to cigarette smoking and age. *New England Journal of Medicine* 288(6): 277-280, February 8, 1973.
- (10) BOSTON COLLABORATIVE DRUG SURVEILLANCE PROGRAM. Decreased clinical efficacy of propoxyphene in cigarette smokers. *Clinical Pharmacology and Therapeutics* 14(2): 259-263, 1973.
- (11) BURNEY, S.W., BONUS, L. Cross-sectional assessment of laboratory variables in a healthy male population. II. Cigarette smoking and laboratory values. *Aging and Human Development* 3: 89-94, 1972.
- (12) CARRUTHERS, M. Modification of the noradrenaline related effects of smoking by beta blockade. *Psychological Medicine* 6: 251-256, 1976.
- (13) COFFMAN, J.D. Effect of propranolol on blood pressure and skin blood flow during cigarette smoking. *Journal of Clinical Pharmacology* 9(1): 39-44, January/February, 1969.
- (14) CONNEY, A.H., PANTUCK, E.J., HSIAO, K.-C., KUNTZMAN, R., ALVARES, A. P., KAPPAS, A. Regulation of drug metabolism in man by environmental chemicals and diet. *Federation Proceedings* 36(5): 1647-1652, April 1977.
- (15) CONNEY, A.H., WELCH, R., KUNTZMAN, R., CHANG, R., JACOBSON, M., MUNRO-FAURE, A.D., PECK, A.W., BYE, A., POLAND, A., POPPERS, P.J., FINSTER, M., WOLFF, J.A. Effects of environmental chemicals on the metabolism of drugs, carcinogens and normal body constituents in man. *Annals of the New York Academy of Science* 179: 155-172, 1971.
- (16) CROW, J.W., LAIN, P., BOCHNER, F., SHOEMAN, D. W., AZARNOFF, D.L. Glutethimide and 4-OH glutethimide: Pharmacokinetics and effect on performance in man. *Clinical Pharmacology and Therapeutics* 22(4): 458-464, 1977.
- (17) DALES, L.G., FRIEDMAN, G.D., SIEGELAUB, A.B., SELTZER, C.C. Cigarette smoking and serum chemistry tests. *Journal of Chronic Disease* 27: 293-307, 1974.

- (18) DALTON, W.S., MARTZ, R., RODDA, B.E., LEMBERGER, L., FORNEY, R.B. Influence of cannabidiol on secobarbital effects and plasma kinetics. *Clinical Pharmacology and Therapeutics* 20(6): 695-700, 1976.
- (19) FERGUSON, D. Smoking, drinking and non-narcotic analgesic habits in an occupational group. *Medical Journal of Australia* 1: 1271-1274, June 30, 1973.
- (20) FRANKL, W.S., SOLOFF, L.A. The hemodynamic effects of propranolol hydrochloride after smoking. *American Journal of Medical Sciences* 254: 623-628, November 1967.
- (21) GIBALDI, M., PERRIER, D. *Pharmacokinetics*. New York, Marcel Dekker, 1975, pp. 243-250.
- (22) HAGEDORN, B., KOSTENBAUDER, H.B. Studies on the effect of tobacco smoke on the biotransformation of vasoactive substances in the isolated perfused rabbit lung. I. Prostaglandin F_{2α}. *Research Communications in Chemical Pathology and Pharmacology* 18(3): 495-504, November 1977.
- (23) HART, P., FARRELL, G.C., COOKSLEY, W.G.E., POWELL, L.W. Enhanced drug metabolism in cigarette smokers. *British Medical Journal* 2: 147-149, July 17, 1976.
- (24) HUNT, S. N., JUSKO, W.J., YURCHAK, A.M. Effect of smoking on theophylline disposition. *Clinical Pharmacology and Therapeutics* 19(5) Part I: 546-551, 1976.
- (25) ISAAC, P.F., RAND, M.J. Cigarette smoking and plasma levels of nicotine. *Nature* 236: 308-310, April 7, 1972.
- (26) JENNE, J., NAGASAWA, H., McHUGH, R., MacDONALD, F., WYSE, E. Decreased theophylline half-life in cigarette smokers. *Life Sciences* 17(2): 195-198, 1975.
- (27) JICK, H. Smoking and clinical drug effects. *Medical Clinics of North America* 58(5): 1143-1149, September 1974.
- (28) JUSKO, W.J. Role of tobacco smoking in pharmacokinetics. *Journal of Pharmacokinetics and Biopharmaceutics* 6(1): 7-39, 1978.
- (29) JUSKO, W.J., KOUP, J.R., SCHENTAG, J.J., VANCE, J.W. Surveillance of factors affecting theophylline clearances in patients. American Pharmaceutical Association, Academy of Pharmaceutical Sciences Meeting, New Orleans, 1976, p. 145. (Abstract)
- (30) KEERI-SZANTO, M., POMEROY, J.R. Atmospheric pollution and pentazocine metabolism. *Lancet* 1: 947-949, May 8, 1971.
- (31) KELLERMANN, G., LUYTEN-KELLERMANN, M. Phenobarbital-induced drug metabolism in man. *Toxicology and Applied Pharmacology* 39: 97-104, 1977.
- (32) KELLERMANN, G., LUYTEN-KELLERMANN, M., HORNING, M.G., STAFFORD, M. Correlation of aryl hydrocarbon hydroxylase activity of human lymphocyte cultures and plasma elimination rates for antipyrine and phenylbutazone. *Drug Metabolism and Disposition* 3(1): 47-50, 1975.
- (33) KELLERMANN, G., LUYTEN-KELLERMANN, M., HORNING, M.G., STAFFORD, M. Elimination of antipyrine and benzo(a)pyrene metabolism in cultured human lymphocytes. *Clinical Pharmacology and Therapeutics* 20(1): 72-80, 1976.
- (34) KERSHBAUM, A., OSADA, H., PAPPAJOHN, D.J., BELLET, S. Effect of nicotine on the mobilization of free fatty acids from adipose tissue in vitro. *Experientia* 25: 128, 1969.
- (35) KERSHBAUM, A., PAPPAJOHN, D.J., BELLET, S. Smoking effect on dexamethasone suppression test. *Clinical Research* 17(2): 287, April 1969. (Abstract)

- (36) KERSHBAUM, A., PAPPAJOHN, D.J., BELLET, S., HIRABAYASHI, M., SHAFIHA, H. Effect on smoking and nicotine on adrenocortical secretion. *Journal of the American Medical Association* 203 (4): 275-278, January 22, 1968.
- (37) KLOTZ, U., AVANT, G.R., HOYUMPA, A., SCHENKER, S., WILKINSON, G.R. The effects of age and liver disease on the disposition and elimination of diazepam in adult man. *Journal of Clinical Investigation* 55: 347-359, February 1975.
- (38) KOPUN, M., PROPPING, P. The kinetics of ethanol absorption and elimination in twins and supplementary repetitive experiments in singleton subjects. *European Journal of Clinical Pharmacology* 11: 337-344, 1977.
- (39) KUNTZMAN, R., PANTUCK, E.J., KAPLAN, S. A., CONNEY, A.H. Phenacetin metabolism: Effect of hydrocarbons and cigarette smoking. *Clinical Pharmacology and Therapeutics* 22(5): 757-764, 1977.
- (40) LELLOUCH, J., SCHWARTZ, D., TRAN, M.H., BEAUMONT, J.L. The relationships between smoking and levels of serum urea and uric acid. Results of an epidemiological survey. *Journal of Chronic Disease* 22: 9-15, 1969.
- (41) LEMBERGER, L., TAMARKIN, N.R., AXELROD, J., KOPIN, I.J. Delta-9-Tetrahydrocannabinol: Metabolism and disposition in long-term marijuana smokers. *Science* 173: 72-73, July 2, 1971.
- (42) LEVINE, R.R., PELIKAN, E.W., KENSLER, C.J. The effect of cigarette smoking on the excretion of phenol red. *Federation Proceedings* 20: 414, 1961. (Abstract)
- (43) LOHMAN, S.M., MIECH, R.P. Theophylline metabolism by the rat liver microsomal system. *Journal of Pharmacology and Experimental Therapeutics* 196(1): 213-225, 1976.
- (44) LUBAWY, W.C., GRIFFITH, R.B., KOSTENBAUDER, H.B., PERRIER, D. An isolated perfused lung (IPL)-smoke system for studying the inhibition of benzo(a)pyrene (BAP) metabolism by smoke. *Federation Proceedings* 77: 970, 1977. (Abstract)
- (45) MA, J.K.H., FU, P.P., LUZZI, L.A. Protein-binding of benzo(a)anthracene and benz(a)pyrene. *Journal of Pharmaceutical Sciences* 66(2): 209-213, February 1977.
- (46) MARCOTTE, J., SKELTON, F.S., COTE, M.G., WITSCHI, H. Induction of aryl hydrocarbon hydroxylase in rat lung by marijuana smoke. *Toxicology and Applied Pharmacology* 33: 231-245, 1975.
- (47) MATHER, L.E., TUCKER, G.T., PFLUG, A.E., LINDOP, M.J., WILKERSON, C. Meperidine kinetics in man: Intravenous injection in surgical patients and volunteers. *Clinical Pharmacology and Therapeutics* 17(1): 21-30, 1975.
- (48) MCGOVREN, J.P., LUBAWY, W.C., KOSTENBAUDER, H.B. Uptake and metabolism of nicotine by the isolated perfused rabbit lung. *Journal of Pharmacology and Experimental Therapeutics* 199(1): 198-207, 1976.
- (49) MITCHELL, A.A. Smoking and warfarin dosage. *New England Journal of Medicine* 287(22): 1153-1154, November 1972.
- (50) MITRA, G., PODDAR, M.K., GHOSH, J.J. In vivo and in vitro effects of Δ^9 -tetrahydrocannabinol on rat liver microsomal drug-metabolizing enzymes. *Toxicology and Applied Pharmacology* 35: 523-530, 1976.
- (51) NORMAN, T.R., BURROWS, G.D., MAGUIRE, K.P., RUBINSTEIN, G., SCOGGINS, B.A., DAVIES, B. Cigarette smoking and plasma nortriptyline levels. *Clinical Pharmacology and Therapeutics*, 21(4): 453-456, 1977.
- (52) NYMAND, G. Maternal smoking and neonatal hyperbilirubinaemia. *Lancet* 2: 173, July 20, 1974.

- (53) PANTUCK, E.J., HSIAO, K.-C., KAPLAN, S.A., KUNTZMAN, R., CONNEY, A.H. Effects of enzyme induction on intestinal phenacetin metabolism in the rat. *Journal of Pharmacology and Experimental Therapeutics* 191(1): 45-52, 1974.
- (54) PANTUCK, E.J., HSIAO, K.-C., MAGGIO, A., NAKAMURA, K., KUNTZMAN, R., CONNEY, A.H. Effect of cigarette smoking on phenacetin metabolism. *Clinical Pharmacology and Therapeutics* 15(1): 9-17, 1974.
- (55) PANTUCK, E.J., KUNTZMAN, R., CONNEY, A.H. Decreased concentration of phenacetin in plasma of cigarette smokers. *Science* 175: 1248-1250, March 17, 1972.
- (56) PARSONS, W.D., ALDRIDGE, A. Stimulation of caffeine metabolism in the rat by 3-methylcholanthrene. *Federation Proceedings* 35: 665, 1976. (Abstract)
- (57) PATON, W.D.M., PERTWEE, R.G. Effect of cannabis and certain of its constituents on pentobarbitone sleeping time and phenazone metabolism. *British Journal of Pharmacology* 44: 250-261, 1972.
- (58) PELLETIER, O. Vitamin C and cigarette smokers. *Annals of New York Academy of Science* 258: 156-168, 1975.
- (59) PELLETIER, O., KEITH, M.O. Bioavailability of synthetic and natural ascorbic acid. *Journal of the American Dietetic Association* 64: 271-275, March 1974.
- (60) PEREL, J.M., HURWIC, M.J., KANZLER, M.B. Pharmacodynamics of imipramine in depressed patients. *Psychopharmacology Bulletin* 11(4): 16-18, 1975.
- (61) PEREL, J.M., SHOSTAK, M., GANN, E., KANTOR, S.J., GLASSMAN, A.H. Pharmacodynamics of imipramine and clinical outcome in depressed patients. In: Gottschalk, L.A., Merlis, S. (Editors). *Pharmacokinetics of Psychoactive Drugs*. New York, Spectrum Publications, 1976, pp. 229-241.
- (62) PFEIFER, H.J., GREENBLATT, D.J. Clinical toxicity of theophylline in relation to cigarette smoking. *Chest* 73(4): 455-459, April 1978.
- (63) POWELL, J.R., THIERCELIN, J.-F., VOZEH, S., SANSOM, L., RIEGELMAN, S. The influence of cigarette smoking and sex on theophylline disposition. *American Review of Respiratory Disease* 116: 17-23, 1977.
- (64) ROSE, J.Q., BARRON, S.A., JUSKO, W.J. Phenytoin disposition in smokers and nonsmokers. *American Pharmaceutical Association, Academy of Pharmaceutical Sciences Meeting*. New York, 1977, p. 162. (Abstract)
- (65) ROTTENSTEIN, H., PEIRCE, G., RUSS, E., FELDER, D., MONTGOMERY, H. Influence of nicotine on the blood flow of resting skeletal muscle and of the digits in normal subjects. *Annals of the New York Academy of Sciences* 90(1): 102-113, 1960.
- (66) SCHUMACHER, J.N., GREEN, C.R., BEST, F.W., NEWELL, M.P. Smoke composition. An extensive investigation of the water-soluble portion of cigarette smoke. *Journal Agricultural and Food Chemistry* 25(2): 310-320, 1977.
- (67) SELTZER, C.C. Constitution and heredity in relation to tobacco smoking. *Annals of New York Academy of Sciences* 142: 322-330, March 15, 1967.
- (68) SELTZER, C.C., FRIEDMAN, G.D., SEIGELAUB, A.B. Smoking and drug consumption in white, black, and oriental men and women. *American Journal of Public Health* 64(5): 466-473, May 1974.
- (69) SELTZER, C.C., FRIEDMAN, G.D., SEIGELAUB, A.B., COLLEN, M.F. Smoking habits and pain tolerance. *Archives of Environmental Health* 29: 170-172, September 1974.
- (70) SEVERSON, R.F., SNOOK, M.E., ARRENDALE, R.F., CHORTYK, O.T. Gas chromatographic quantitation of polynuclear aromatic hydrocarbons in tobacco smoke. *Analytical Chemistry* 48(13): 1866-1871, November 1976.
- (71) SIEMENS, A.J., KALANT, H., KHANNA, J.M., MARSHMAN, J., HO, G. Effect of cannabis on pentobarbital-induced sleeping time and pentobarbital metabolism in the rat. *Biochemical Pharmacology* 23: 477-488, 1974.

- (72) SOFIA, R.D., BARRY, H. Interactions of chronic and acute Δ^1 tetrahydrocannabinol pretreatment with zoxazolamine and barbiturates. *Research Communications in Chemical Pathology and Pharmacology* 5(1): 91-98, January 1973.
- (73) SWETT, C., Jr., COLE, J.O., HARTZ, S.C., SHAPIRO, S., SLONE, D. Hypotension due to chlorpromazine. Relation to cigarette smoking, blood pressure, and dosage. *Archives of General Psychiatry* 34: 661-663, June 1977.
- (74) TSCHANZ, C., HIGNITE, C.E., HUFFMAN, D.H., AZARNOFF, D.L. Metabolic disposition of antipyrine in patients with lung cancer. *Cancer Research* 37: 3881-3886, November 1977.
- (75) UOTILA, P., HARTIALA, J. Drug and steroid metabolism in the isolated perfused rat lung. In: Duncan, W.A.M., Leonard, B.J. (Editors). *Proceedings of the European Society of Toxicology. Excerpta Medica. Amsterdam* 18: 201-202, 1977.
- (76) VAPAATALO, H.I., NEUVONEN, P.J., TISSARI, A., MANSNER, R., PAASONEN, M.K. Effect of cigarette smoking on diuresis induced by furosemide. *Annals of Clinical Research* 3: 159-162, 1971.
- (77) VAUGHAN, D.P., BECKETT, A.H., ROBBIE, D.S. The influence of smoking on the inter-subject variation in pentazocine elimination. *British Journal of Clinical Pharmacology* 3: 279-283, 1976.
- (78) VESELL, E.S., PASSANANTI, G.T. Inhibition of drug metabolism in man. *Drug Metabolism and Disposition* 1(1): 402-410, 1973.
- (79) VESTAL, R.E., McGUIRE, E.A., TOBIN, J.D., ANDRES, R., NORRIS, A.H., MEZEY, E. Aging and ethanol metabolism. *Clinical Pharmacology and Therapeutics* 21(3): 343-354, 1977.
- (80) VESTAL, R.E., NORRIS, A.H., TOBIN, J.D., COHEN, B.H., SCHOCK, N.W., ANDRES, R. Antipyrine metabolism in man: Influence of age, alcohol, caffeine, and smoking. *Clinical Pharmacology and Therapeutics* 18(4): 425-432, 1975.
- (81) WEITMAN, M., SCHEBLE, R., JOHNSON, K.G., ABBEY, H. Correlations among use of drugs. *American Journal of Public Health* 62: 166-170, February 1972.
- (82) WELCH, R.M., CAVALLITO, J., GILLESPIE, D.D. Effect of analgesics and exposure to cigarette smoke on the metabolism of acetophenetidin by rat tissues. *Drug Metabolism and Disposition* 1(1): 211-215, 1973.
- (83) WELCH, R.M., CAVALLITO, J., LOH, A. Effect of exposure to cigarette smoke on the metabolism of benzo(a)pyrene and acetophenetidin by lung and intestine of rats. *Toxicology and Applied Pharmacology* 23: 749-758, 1972.
- (84) WELCH, R.M., DeANGELIS, R.L., WINGFIELD, M., FARMER, T.W. Elimination of antipyrine from saliva as a measure of metabolism in man. *Clinical Pharmacology and Therapeutics* 18(3): 249-258, 1975.
- (85) WELCH, R.M., HSU, S.Y., DeANGELIS, R.L. Effect of Aroclor 1254, phenobarbital, and polycyclic aromatic hydrocarbons on the plasma clearance of caffeine in the rat. *Clinical Pharmacology and Therapeutics* 22(5): 791-798, 1977.
- (86) WELCH, R.M., HUGHES, C.R., DeANGELIS, R.L. Effect of 3-methylcholanthrene pretreatment on the bioavailability of phenacetin in the rat. *Drug Metabolism and Disposition* 4(4): 402-406, 1976.
- (87) WELCH, R.M., LOH, A., CONNEY, A.H. Cigarette smoke: Stimulatory effect on metabolism of 3,4-benzopyrene by enzymes in rat lung. *Life Sciences* 10(4): 215-221, 1971.
- (88) WENZEL, D.G., BROADIE, L.L. Stimulatory effect of nicotine on the metabolism of meprobamate. *Toxicology and Applied Pharmacology* 8: 455-459, 1966.

- (89) WILSON, J.T., VAN BOXTEL, C.J., ALVAN, G., SJOQVIST, F. Failure of vitamin C to affect the pharmacokinetic profile of antipyrine in man. *Journal of Clinical Pharmacology* 16: 265-270, May/June 1976.
- (90) WOOD, A.J.J., VESTAL, R.E., BRANCH, R.A., WILKERSON, G.R., SHAND, D.G. Age-related effects of smoking on elimination of propranolol (P), antipyrine (Ap), and indocyanine green (ICG). *Clinical Research* 26: 297A, 1978. (Abstract)
- (91) YACOBI, A., UDALL, J.A., LEVY, G. Serum protein binding as a determinant of warfarin body clearance and anticoagulant effect. *Clinical Pharmacology and Therapeutics* 19(5): 552-558, 1976.
- (92) YAMAMOTO, I., NAGAI, K., KIMURA, H., IWATSUBO, K. Nicotine and some carcinogens in special reference to the hepatic drug-metabolizing enzymes. *Japanese Journal of Pharmacology* 16: 183-190, 1966.
- (93) ZUSKIN, E., MITCHELL, C.A., BOUHUYS, A. Interaction between effects of beta blockade and cigarette smoke on airways. *Journal of Applied Physiology* 36(4): 449-452, April 1974.

Specific Drug Interactions

Oral Contraceptives

In early 1970, Frederiksen and Ravenholt (8) presented data showing an association between thromboembolism and smoking. Sartwell (16), however, reported that he could find no evidence that smoking enhanced the effect of oral contraceptives to produce increased blood clotting. In 1973, the Collaborative Group for the Study of Stroke in Young Women (5) stated that cigarette smoking may potentiate the effect of oral contraceptives on thromboembolism or cardiovascular disease. A subsequent report by this Group (6) showed that women who took the pill and smoked one pack of cigarettes had a 200 percent increased risk of a stroke. Perhaps the most important articles published on smoking and oral contraceptives were published by Mann, et al. (12, 13). In these articles, the authors quantitated the association between cigarette smoking and oral contraceptives. They showed that the relative risk of myocardial infarction increased from 1.2 in women smoking fewer than 15 cigarettes a day, to 4.1 in women smoking 15 to 24 cigarettes a day, and to 11.3 in women smoking 25 or more cigarettes a day. Jain (9) reanalyzed the data from the United States and Great Britain and reported that: (1) the use of oral contraceptives in the absence of smoking is considerably safer than no fertility control for all ages, including the group aged 40-44; (2) the use of oral contraceptives among smokers aged 40 and over is substantially more hazardous than no fertility control, although there is little difference for light smokers; (3) the use of oral contraceptives among heavy smokers in the group aged 30-39 may be more hazardous than no fertility control; and (4) the use of oral contraceptives among heavy smokers in the group aged 15-29 may be more hazardous than any other method of fertility regulation. Ory (15) has stated that his analyses show "that cigarette smoking is the most important factor in increasing the likelihood of myocardial infarction." The effect is independent of oral contraceptive use, but oral contraceptive use also appears to be a risk factor. The use of oral contraceptives in the absence of other predisposing factors appears, however, to have only a small effect in increasing the risk of dying from myocardial infarction.

Beral (2) has shown that the death rate from diseases of the circulatory system in women who used oral contraceptives was 5 times that of controls who had never used them; the death rate in those who had taken the pill continuously for 5 years or more was 10 times that of controls. The author concluded that the excess annual deaths were 1 per 10,000 for oral contraceptive users who had quit smoking and 1 per 3,000 users who smoke.

In a recent article, Jick, et al. (11), comparing oral contraceptive users with nonusers, stated that, in otherwise healthy young women, the relative risk of a myocardial infarction is 14. While myocardial

infarction is rare in most healthy women, the risk in women older than 37 years who smoke and take oral contraceptives appears to be high.

Tietze (18) has updated his findings on mortality related to pregnancy. His article shows that up to the age of 30 the risk to life from pregnancy and childbirth among noncontraceptors is far in excess of that experienced by users of any method. After age 30, the mortality risk experienced by pill users who smoke rises dramatically, but among nonsmokers the risk remains relatively low—and is lower than the risk of death among noncontraceptors even after age 40.

In another recent study Slone, et al. (17) investigated the smoking habits of women under the age of 50 who had survived a recent myocardial infarction. The subjects had not been using oral contraceptives, and other identifiable risk factors were excluded. A dose-response relationship was evident; among women smoking 35 or more cigarettes per day the rate of myocardial infarction was estimated to be some 20-fold higher than among those who had never smoked. This study demonstrates quite strongly that cigarette smoking is a risk factor for myocardial infarction in young women who are otherwise apparently healthy.

Estrogens

A recent report (10) of apparently healthy women aged 39 to 45 who were taking noncontraceptive estrogens estimated a relative risk of 7.5 for nonfatal myocardial infarction, when comparing estrogen users with nonusers. All but one of the nonfatal myocardial infarction patients were cigarettes smokers. Although this is only one report, it appears that women aged 39 to 45 may have a substantial risk when they both smoke and take estrogens. Further study on this subject is needed.

Cardiovascular Drugs

There is comparatively little clinical evidence of interactions between smoking and cardiovascular drugs. The ability of smoking to stimulate various hepatic microsomal enzymes is a potentially important effect and affects numerous drugs, but, thus far, few such interactions have been recognized. A second, potentially important set of interactions could arise from interactions with the pharmacologic effects of nicotine.

As summarized in detail in *The Health Consequences of Smoking*(19) nicotine causes increased heart rate, blood pressure, cardiac output, stroke volume, myocardial contractility, myocardial oxygen consumption, and arrhythmia formation, most of which is explained by release of catecholamines from both neuronal and extraneuronal sites. Apart from potential toxicity of elevated catecholamines, some interesting potential interactions with drugs can be postulated; these have been

studied to some extent, although not definitively. Aronow, et al. (1) have shown increased angina in patients who smoke.

Frankl and Soloff (7) studied the interaction of smoking and propranolol. They reported that, in four of five normal subjects, smoking two cigarettes led to a small increase in blood pressure associated with increased cardiac output, increased heart rate, and decreased peripheral resistance (cigarettes are usually found to increase peripheral resistance). When cigarettes were smoked after treatment with propranolol, blood pressure increased further, heart rate and cardiac output fell, and peripheral resistance increased. These results are compatible with the predicted effects of propranolol, viz. beta-blockade blocks the chronotropic, inotropic, and vasodilator effects of the catecholamines (all beta effects), but does not affect their peripheral vasoconstrictor effects (an alpha effect), thus unmasking or exaggerating this effect. Propranolol is known to increase peripheral resistance even in the absence of nicotine, however, and it would have been helpful to examine the contribution of propranolol alone to increased peripheral resistance by studying a group treated with propranolol alone, in addition to the nicotine and nicotine—propranolol groups. The results suggest, however, that the increase in resistance was greater than that caused by propranolol alone; propranolol normally decreases blood pressure, despite the increase in resistance it causes in the absence of smoking, but in this study blood pressure rose after propranolol administration. The reported hemodynamic changes are in a direction generally considered harmful, especially for persons with underlying cardiac disease.

Subsequently, Coffman (4) examined a closely related question, measuring blood pressure and vascular resistance in the foot in 13 smoking volunteers before and after propranolol. He found that while nicotine or smoking increased blood pressure and foot resistance over baseline, the addition of propranolol did not seem to exaggerate these effects, as the author felt would have been expected if propranolol unmasked an alpha-adrenergic effect of smoking. This analysis may be incorrect. An unusual finding of this study, similar to that of Frankl and Soloff, is that propranolol increased both foot resistance (expected) and blood pressure (not expected). Propranolol, despite increasing peripheral resistance, is normally a hypotensive agent, presumably because the vasoconstriction it causes is offset by decreased cardiac output. The rise in pressure seen here suggests that the increased catecholamines provoked by smoking were still present when propranolol was given (it was always given after the first smoking period) and that alpha-effects were in fact unmasked by propranolol-inhibition of beta-mediated vasodilation. This explanation is strengthened by the observation that the pre-smoking baseline blood pressure and foot resistance were higher for the second (propranolol) phase of the study, suggesting persistent cigarette effect.

The Frankl and Soloff and the Coffman studies are thus not necessarily incompatible, but their small size and lack of concurrent controls render them inconclusive.

In a more recent study, Carruthers (3) examined the effects of smoking low and high nicotine cigarettes on 12 normal volunteer smokers given oxprenolol (a beta-blocker) and placebo on a crossover basis before smoking. Oxprenolol prevented the smoking-induced rise in heart rate and systolic and diastolic pressure seen in placebo-treated subjects. There was no suggestion that it exaggerated this effect. While this study certainly does not demonstrate unmasking of alpha-stimulation, the blood pressure after high-nicotine smoking in oxprenolol-treated patients was equal to the blood pressure before oxprenolol or smoking in these patients. The nicotine thus obliterated the hypotensive effect of oxprenolol.

The possibility that smoking reverses or blocks, even in part, the antihypertensive effect of beta-blockers, a major antihypertensive class, is obviously a suitable subject for study and a matter for concern. We are not aware of any hypertension clinical trial that has analyzed smoking as a covariant. It should also be noted that a "cardioselective" beta-blocker, which would not block the beta-mediated peripheral vasodilating effects of catecholamines, might behave differently from propranolol.

Zuskin, et al. (21) studied the interaction on airways of beta-blockade and smoking. They found that, in nonsmokers and light smokers, cigarettes cause decreases in flow rates on maximum or partial expiratory flow-volume curves, evidence of slight obstruction of small airways, and that propranolol alone has no effect on these rates. Propranolol did not add to these effects in light smokers or nonsmokers, but potentiated the constricting effect of smoking in regular smokers, who had little response to smoking alone. This was interpreted as suggesting that beta-adrenergic stimuli protect smokers against vasoconstriction, and that this protection can be removed by beta-blockade. The interaction at this point appears to be of marginal importance, but deserves further study, especially in persons with impaired pulmonary function. Here too, it is likely that cardioselective beta-blockers would behave differently from nonselective ones.

Furosemide

Vapaatalo, et al. (20) have reported a reduced diuretic effect of furosemide in smokers, probably related to nicotine-stimulated increased secretion of ADH. This interaction is of negligible clinical significance.

Negative Findings

The ability of cigarette smoke to alter drug metabolism has led to concern that it might alter anticoagulant metabolism and, therefore,

anticoagulant dosage requirements. While many drugs affect warfarin metabolism, Mitchell (14) reported that maintenance doses of warfarin were not different in nonsmokers, light smokers, or heavy smokers.

Specific Drug Interactions: References

- (1) ARONOW, W.S., KAPLAN, M.A., JACOB, D. Tobacco: A precipitating factor in angina pectoris. *Annals of Internal Medicine* 69(3): 529-536, September 1968.
- (2) BERAL, V. Mortality among oral contraceptive users. *Lancet* 2: 727-731, October 8, 1977.
- (3) CARRUTHERS, M. Modification of the noradrenaline related effects of smoking by beta-blockade. *Psychological Medicine*, 6: 251-256, 1976.
- (4) COFFMAN, J.D. Effect of propranolol on blood pressure and skin blood flow during cigarette smoking. *Journal of Clinical Pharmacology* 9: 39-44, January/February 1969.
- (5) COLLABORATIVE GROUP FOR THE STUDY OF STROKE IN YOUNG WOMEN. Oral contraception and increased risk of cerebral ischemia or thrombosis. *New England Journal of Medicine* 288(17): 871-878, April 26, 1973.
- (6) COLLABORATIVE GROUP FOR THE STUDY OF STROKE IN YOUNG WOMEN. Oral contraceptives and stroke in young women: Associated risk factors. *Journal of the American Medical Association* 231(7): 718-722, February 17, 1975.
- (7) FRANKL, W.S., SOLOFF, L.A. The hemodynamic effects of propranolol hydrochloride after smoking. *American Journal of the Medical Sciences* 254: 623-628, November 1967.
- (8) FREDERIKSEN, H., RAVENHOLT, R.T. Thromboembolism, oral contraceptives, and cigarettes. *Public Health Reports* 85(3): 197-205, March 1970.
- (9) JAIN, A.K. Mortality risk associated with the use of oral contraceptives. *Studies in Family Planning* 8(3): 50-54, March 1977.
- (10) JICK, H., DINAN, B., ROTHMAN, K.J. Noncontraceptive estrogens and nonfatal myocardial infarction. *Journal of the American Medical Association* 239(14): 1407-1408, April 3, 1978.
- (11) JICK, H., DINAN, B., ROTHMAN, K.J. Oral contraceptives and nonfatal myocardial infarction. *Journal of the American Medical Association* 239(14): 1403-1406, April 3, 1978.
- (12) MANN, J.I., INMAN, W.H.W. Oral contraceptives and death from myocardial infarction. *British Medical Journal* 2: 245-248, May 3, 1975.
- (13) MANN, J.I., VESSEY, M.P., THOROGOOD, M., DOLL R. Myocardial infarction in young women with special reference to oral contraceptive practice. *British Medical Journal* 2: 241-245, May 3, 1975.
- (14) MITCHELL, A.A. Smoking and warfarin dosage. *New England Journal of Medicine* 287(22): 1153-1154, November 30, 1972.
- (15) ORY, H.W. Association between oral contraceptives and myocardial infarction - A review. *Journal of the American Medical Association* 237(24): 2619-2622, June 13, 1977.
- (16) SARTWELL, P.E. Oral contraceptives and thromboembolism: A further report. *American Journal of Epidemiology* 94(3): 192-201, September 1971.
- (17) SLONE, D., SHAPIRO, S., ROSENBERG, L., KAUFMAN, D.W., HARTZ, S.C., ROSSI, A.C., STOLLEY, P.D., MIETTINEN, O.S. Relation of cigarette smoking to myocardial infarction in young women. *New England Journal of Medicine* 298(23): 1273-1276, June 8, 1978.
- (18) TIETZE, C. New estimates of mortality associated with fertility control. *Family Planning Perspectives* 9(2): 74-76, March/April 1977.
- (19) U.S. PUBLIC HEALTH SERVICE. *The Health Consequences of Smoking. A Reference Edition: 1976.* Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, HEW Publication No. (CDC) 78-8357, 1976, 657 pp.
- (20) VAPAATALO, H.I., NEUVONEN, P.J., TISSARI, A., MANSNER, R., PAASONEN, M.K. Effect of cigarette smoking on diuresis induced by furosemide. *Annals of Clinical Research* 3: 159-162, 1971.

- (21) ZUSKIN, E., MITCHELL, C.A., BOUHUYS, A. Interaction between effects of beta blockade and cigarette smoke on airways. *Journal of Applied Physiology* 36(4): 449-452, April 1974.

Biologicals

Viral Vaccines

Most viral vaccines, such as poliovirus, measles virus, mumps virus, and rubella virus, are primarily administered to children. Some viral vaccines, such as influenza, are administered to persons of all ages in the general population during pandemic periods. During other periods, those persons at high risk, such as the elderly or persons with chronic upper respiratory and other debilitating diseases, are vaccinated. Other vaccines are given to groups of people at high risk; for example, adenovirus vaccine to military recruits or yellow fever vaccine to those individuals travelling in areas of endemic infection.

Very little attention has been paid to whether or not smoking influences the response of individuals to vaccination. Several studies have found increased incidences of respiratory illness in smokers (21). On the other hand, Monto and Ross (15), in a study of the relationship between the frequency of acute respiratory infections, smoking, and chronic pulmonary disease, found an increase in infections in subjects with chronic lung disease which was independent of the smoking factor.

Studies in Humans

Finklea, et al. (2), in a study involving 289 volunteers, reported a significant decrease in the persistence of hemagglutination inhibition antibody among cigarette smokers after natural infection or vaccination with influenza A₂ antigens. Although this investigation suggests a rapid decrease in antibodies to influenza vaccination in the group that smoked when compared to the nonsmoking group, the results obtained in this study have to be criticized for two reasons: the 289 volunteers were subdivided into very small groups making the assessment of statistical significance difficult and the data were not presented in a manner which allowed a judgment regarding the validity of the presumption that the response of the two populations, nonsmokers and smokers, was functioning under the same multinomial distribution upon which the investigators based their statistical analyses.

The only other report in the literature on smoking, vaccines, and the immune response is a study by MacKenzie, et al. (12). These investigators studied the effects of cigarette smoking on the response to vaccination against influenza. Their results indicate that a higher number of cigarette smokers than nonsmokers sero-converted after vaccination with live attenuated influenza vaccine as measured by the hemagglutination inhibition test. There was no difference in response between smokers and nonsmokers to killed subunit vaccine. However, when the investigators studied the longevity of the immune response over a period of 50 weeks, they found that the smokers vaccinated with killed subunit vaccine had a significant depression ($t = 2.35$, 111 D.F.,

$P \leq 0.05$) in antibody titer. No significant difference was found between titers of smokers and nonsmokers who received the live attenuated vaccine. Again, although there are indications that smoking influences the immune response, this study has limitations: because of the small number of subjects in each group, significance of differences is difficult to assess; inconsistencies were found in the immune response of subjects to live vaccine versus killed vaccine; and, in the strictest sense, there was a control group for the live influenza vaccines that received injections of saline, but there was no placebo or control group for the subjects administered the killed subunit vaccine by intranasal spray. The one control group was used as the control for both experimentally vaccinated groups.

Animal Model Systems

Thomas, et al. (19) reported testing the effects of fresh cigarette smoke on the immune response of mice. They found that the antibody response to sheep red blood cells was inhibited, depending on the concentration of the cigarette smoke solution.

MacKenzie (11) developed a model system in mice to study the influence of smoking on influenza virus. He reported that short exposures to cigarette smoke enhanced the response of mice to vaccination while prolonged exposure depressed the humoral response as measured by the hemagglutination inhibition test.

Bacterial Products

There are no reports of studies on the influence of and response to bacterial vaccines or bacterial products in humans who smoke. Campbell and Hilsenroth (1) investigated the response of mice immunized with tetanus toxoid after the mice had been exposed to nitrogen dioxide (a byproduct of cigarette smoke) or ozone. The mice were then challenged with tetanus toxin. The results indicated that there was more mortality and morbidity in the animals exposed to the two gases when compared to the controls.

Carcinoembryonic Antigen Test

Gold and Freedman (4) reported finding tumor-specific antigens in adenocarcinoma of the human colon. These antigens are not found in normal adult colonic tissues. When rabbits are immunized with these antigens, tumor-specific antibodies can be demonstrated by different immunologic methods, such as agar gel diffusion, immunoelectrophoresis, passive cutaneous anaphylaxis, and the hemagglutination inhibition test. Gold and Freedman (5) characterized the antigens and found that, for the most part, they could be detected in cancerous tissues of the human digestive organs. The origin of these organs in fetal life is the endodermally derived epithelium. The antigens were detected in

human fetal gut, liver, and pancreas tissues obtained between 2 and 6 months of gestation. Normal adult colon and the other adult tissues tested, as well as fetal gut, liver, and pancreas in the third trimester, were devoid of these antigens. Gold and Freedman termed these antigenic components of the human digestive system, carcinoembryonic antigen (CEA), and suggested that CEA represented cellular components found in the normal developing (embryonic) digestive system epithelium. These components are repressed after the sixth month of embryonic life but reappear in colon malignancy by derepression of differentiation as the adult colon cells metastasized. Krupey, et al. (9) characterized CEA as a protein-polysaccharide complex. It is a glycoprotein of high molecular weight (200,000) normally found as a constituent of the glycocalyx of embryonic endodermal epithelium and is also present in extracts of colon carcinoma cells. Thomson, et al. (20) developed a radioimmunoassay to detect CEA circulating in the blood of patients. This test permits the detection of nanogram (ng) amounts of CEA. To obtain more specific antiserum and thereby reduce false positive results in the radioimmunoassay, Krupey, et al. (10) developed a procedure to purify CEA used to immunize the rabbits. Originally the CEA test was only sensitive enough to detect concentrations of 2.5 ng/ml but by this improved procedure 1.0-2.0 ng/ml could be detected.

Gold (3) reported on a study of 212 sera. Seventy percent (30/43) of the patients with non metastatic cancer had hemagglutination inhibition titers $> 1:80$ to CEA.

Moore, et al. (16) and Rule, et al. (18) reported finding elevated CEA levels in patients with inflammatory bowel disease. Holyoke, et al. (8) reviewed the literature on CEA and cancers of the gastrointestinal tract and reported that evidence was accumulating that the detection of elevated CEA levels could be used as a tool in prognosis of colon carcinoma after surgical removal of the tumor. However, the use of CEA as a diagnostic tool was doubtful because of the finding of elevated levels of CEA in disease states, such as Crohn's disease and other chronic inflammatory bowel diseases. Meeker, et al. (14) reported finding 90 percent (66/73) of patients with gastrointestinal tract cancer with CEA levels above 2.5 ng/ml. In a joint study of the National Cancer Institute of Canada and the American Cancer Society (17), the sera of 503 patients were examined for CEA titers to determine whether or not the results of the test were reproducible in different laboratories and whether or not patients with colon tumors could be distinguished from patients with other malignancies. The results indicated that the CEA test was reproducible in different laboratories and that determination of CEA titers was an important aid in the diagnosis of colon cancer.

The results of a large double-blind study by Gold, et al. (6), which involved 597 individuals, showed that over 95 percent (83/87) of patients with malignant colon tumors had CEA levels over 2.5 ng/ml.

Hansen, et al. (7) have reported on a collaborative study involving some 35,000 plasma samples from more than 10,000 patients. In this study 97 percent (865/892) of the healthy nonsmokers had CEA levels below 2.6 ng/ml and 3 percent (25/892) had CEA levels of 2.6 to 5.0 ng/ml, while 15 percent (93/620) of smokers had levels of 2.6 to 5.0 ng/ml. In the same study, 883 subjects at high risk (uranium miners) were examined: 19 percent (91/484) had CEA levels above 2.5 ng/ml while 3.9 percent (19/484) had CEA levels over 5.0 ng/ml. In an attempt to further correlate elevated CEA levels, these investigators extended their studies to look at the sputum cytology of 581 uranium miners of whom 456 were smokers with a history of smoking (289) or former smokers (167). Uranium miners were considered to be a high risk population for the development of pulmonary cancer. Eighteen percent (52/289) of the subjects had CEA levels above 2.5 ng/ml. The sputum cytological examination revealed nine of these 52 individuals had carcinoma *in situ* and three had carcinoma, while the remaining 28 individuals had mild to marked atypic sputum reports. These results confirmed the previous findings of elevated CEA levels in patients with pulmonary cancers. These investigators were the first to report elevated CEA levels in people who were chronic, heavy smokers.

Meeker, et al. (14) reported finding CEA levels greater than 2.5 ng/ml in 11 percent (19/176) of individuals classified as healthy subjects. These investigators examined a number of factors such as sex, age, and so forth, to determine those which might influence CEA levels. The only factor found to influence CEA levels was smoking. When CEA levels of those who did not smoke and those who smoked were compared; a highly significant difference ($P = .005$) was found. The mean level of 1.5 ± 0.96 ng/ml was found in the nonsmokers whereas the smokers had a mean level of 2.1 ± 1.2 ng/ml.

McCartney and Hoffer (13) mentioned that chronic cigarette smoking was associated with elevated CEA levels in the absence of other specific diseases, but they did not elaborate further on the subject.

Summary

There is suggestive evidence that antibody titers to natural infection or vaccination with influenza virus in cigarette smokers decrease more rapidly than the titers of nonsmokers. To confirm these findings, studies need to be done with larger groups of individuals.

Carcinoembryonic antigen levels found in many smokers are elevated to the levels observed in patients with proven carcinoma of the colon. The significance of these elevated levels is not clear at this

time. However, when the CEA test is used as an adjunct in diagnosis, this fact needs to be considered when interpreting the results obtained.

Biologicals: References

- (1) CAMPBELL, K.I., HILSENROTH, R.H. Impaired resistance to toxin in toxoid-immunized mice exposed to ozone or nitrogen dioxide. *Clinical Toxicology* 9(6): 943-954, December 1976.
- (2) FINKLEA, J.F., HASSELBLAD, V., RIGGAN, W.B., NELSON, W.C., HAMMER, D.I., NEWILL, V.A. Cigarette smoking and hemagglutination inhibition response to influenza after natural disease and immunization. *American Review of Respiratory Disease* 104(3): 368-376, September 1971.
- (3) GOLD, P. Circulating antibodies against carcinoembryonic antigens of the human digestive system. *Cancer* 20(10): 1663-1667, October 1967.
- (4) GOLD, P., FREEDMAN, S.O. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. *Journal of Experimental Medicine* 121(3): 439-462, March 1, 1965.
- (5) GOLD P., FREEDMAN, S.O. Specific carcinoembryonic antigens of the human digestive system. *Journal of Experimental Medicine* 122(3): 467-481, September 1, 1965.
- (6) GOLD, P., WILSON, T., ROMERO, R., SHUSTER, J., FREEDMAN, S.O. Immunology and colonic cancer: Further evaluation of the radioimmunoassay for carcinoembryonic antigen of the human digestive system as an adjunct in cancer diagnosis. *Diseases of the Colon and Rectum* 16(5): 358-365, September/October 1973.
- (7) HANSEN, H.J., SNYDER, J.J., MILLER, E., VANDEVOORDE, J.P., MILLER, O.N., HINES, L.R., BURNS, J.J. Carcinoembryonic antigen (CEA) assay. A laboratory adjunct in the diagnosis and management of cancer. *Human Pathology* 5(2): 139-147, March 1974.
- (8) HOLYOKE, E.D., CHU, T.M., MURPHY, G.P. Carcinoembryonic antigen (CEA) and gastrointestinal malignancy. *Review of Surgery* 30(5): 305-311, September/October 1973.
- (9) KRUYEY, J., GOLD, P., FREEDMAN, S.O. Physicochemical studies of the carcinoembryonic antigens of the human digestive system. *Journal of Experimental Medicine* 128(3): 387-398, September 1, 1968.
- (10) KRUYEY, J., WILSON, T., FREEDMAN, S.O., GOLD, P. The preparation of purified carcinoembryonic antigen of the human digestive system from large quantities of tumor tissue. *Immunochemistry* 9(4): 617-622, April 1972.
- (11) MACKENZIE, J.S. The effect of cigarette smoke on influenza virus infection: A murine model system. *Life Sciences* 19(3): 409-412, August 1, 1976.
- (12) MACKENZIE, J.S., MACKENZIE, I.H., HOLT, P.G. The effect of cigarette smoking on susceptibility to epidemic influenza and on serological responses to live attenuated and killed subunit influenza vaccines. *Journal of Hygiene (Cambridge)* 77(3): 409-417, December 1977.
- (13) MCCARTNEY, W.H., HOFFER, P.B. The value of carcinoembryonic antigen (CEA) as an adjunct to the radiological colon examination in the diagnosis of malignancy. *Radiology* 110(2): 325-328, February 1974.
- (14) MEEKER, W.R., JR., KASHMIRI, R., HUNTER, L., CLAPP, W., GRIFFEN, W.O., JR. Clinical evaluation of carcinoembryonic antigen test. *Archives of Surgery* 107(2): 266-274, August 1973.
- (15) MONTO, A.S., ROSS, H.W. The Tecumseh study of respiratory illness. X. Relation of acute infections to smoking, lung function and chronic symptoms. *American Journal of Epidemiology* 107(1): 57-64, January 1978.
- (16) MOORE, T.L., KANTROWITZ, P.A., ZAMCHECK, N. Carcinoembryonic antigen (CEA) in inflammatory bowel disease. *Journal of the American Medical Association* 222(8): 944-947, November 20, 1972.

- (17) NATIONAL CANCER INSTITUTE OF CANADA/AMERICAN CANCER SOCIETY. A collaborative study of a test for carcinoembryonic antigen (CEA) in the sera of patients with carcinoma of the colon and rectum. A joint National Cancer Institute of Canada/American Cancer Society investigation. *Canadian Medical Association Journal* 107(1): 25-33, July 8, 1972.
- (18) RULE, A.H., STRAUS, E., VANDEVOORDE, J., JANOWITZ, H.D. Tumor-associated (CEA-reacting) antigen in patients with inflammatory bowel disease. *New England Journal of Medicine* 287(1): 24-26, July 6, 1972.
- (19) THOMAS, W.R., HOLT, P.G., KEAST, D. Antibody production in mice chronically exposed to fresh cigarette smoke. *Experientia* 30(12): 1469-1470, December 15, 1974.
- (20) THOMSON, D.M.P., KRUPPEY, J., FREEDMAN, S.O., GOLD, P. The radioimmunoassay of circulating carcinoembryonic antigen of the human digestive system. *Proceedings of the National Academy of Sciences, U.S.A.* 64(1): 161-167, September 1969.
- (21) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. A Reference Edition: 1976. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, HEW Publication No. (CDC) 78-8357, 1976, 657 pp.

Nutrients Interactions

Epidemiology data have long linked smoking with increased risks of cardiovascular disease, increased osteoporosis, amblyopia, and other disorders (5, 9, 14, 18, 24, 29, 43, 53, 56, 68). As early as 1939 (65), scientists demonstrated that smoking causes changes in levels of nutrients, which may help to explain the impact smoking has on health. Since the complete "cause and effect" relationships of these nutritional changes have not been clearly identified, only those of nutrients for which the effect is more clearly understood will be considered in this section.

Macronutrients

Lipids

Because smoking has been established epidemiologically as a major factor in cardiovascular disease, the interaction between smoking and lipid metabolism has been extensively investigated. Several studies demonstrate that blood cholesterol levels are higher in smokers than in nonsmokers (52, 55, 72). In carefully controlled studies, however, Elwood, et al. (20) reported that the differences are not statistically significant. An explanation for these observations, proposed by several investigators, is that they are associated with vitamin C metabolism (35, 38, 62, 63). These researchers claim that vitamin C has a role in the transport of cholesterol to the liver where catabolism and excretion take place. Smoking has been shown to increase plasma triglyceride levels (52, 55, 58) and differences between smokers and nonsmokers are highly significant. Yeung (72) has reported that smoking together with oral contraceptives results in even higher plasma triglyceride levels.

Carbohydrates

Several investigators have demonstrated that alterations in carbohydrate metabolism are frequently associated with smoking (24, 27, 37, 52, 55, 61). Orsetti, et al. (44) supported epidemiological observations in a clinical nutrition study in which both smokers and nonsmokers were required to smoke two cigarettes in a 10 minute period. Of the 18 subjects studied, 10 showed a significant rise in somatotrophic hormone for 20 minutes post smoking. Plasma catecholamine levels increased for five of six subjects tested.

Proteins

Albanese, et al. (3) in a study involving 7 nonsmokers and 10 smokers, reported a significant difference in protein utilization. Nonsmokers were more efficient in retaining nitrogen than were smokers. The authors concluded that the apparent difference in protein metabolism was associated with impairment of tryptophan utilization. As discussed later, an impairment in protein metabolism may also be partially

responsible for low birthweight found in infants born to smoking mothers. Crosby, et al. (16) have shown that smoking mothers had lower leukocyte RNA synthesis and lower plasma levels of 14 amino acids than did non-smoking mothers.

Micronutrients

Vitamin C

Strauss and Scheer (65) reported that the urinary excretion of vitamin C was lower in heavy smokers than it was for nonsmokers. Several investigators later showed that smoking causes changes in the vitamin C levels found in plasma and leukocytes (9, 10, 20, 25, 30, 33, 40, 45, 46, 47, 48, 60, 72, 73). The reasons for these observed changes have not been completely established. Keith and Pelletier (34) have demonstrated a decrease in vitamin C absorption when high levels of nicotine were administered to laboratory animals. Dewhurst and Kitchen (19) and Sprince, et al. (64) have postulated that there is increased oxidation of vitamin C from compounds, such as acetaldehyde, which are derived from smoking. Other scientists postulate that increased secretion of adrenaline and adrenal steroids stimulated by nicotine causes increased utilization of vitamin C. Vitamin C is known to be essential for the metabolism of tyrosine which, in turn, is a precursor of adrenalin and noradrenalin. The importance of vitamin C in the formation of collagen, the synthesis of neurotransmitters, and in many other biochemical functions has stimulated several hypotheses for the pathogenesis of degenerative diseases for which smoking is known to be a risk factor (6, 35, 38, 62, 63).

Vitamin B₁₂

The observation that tobacco amblyopia and nutrition-induced amblyopia respond to hydroxycobalamin, a form of vitamin B₁₂, led to the discovery that smoking lowers both blood and tissue levels of vitamin B₁₂ (2, 11, 15, 22, 32, 36, 49, 50, 51). The loss of vitamin B₁₂ is attributed to the use of this vitamin in the detoxication of cyanide derived from inhaled tobacco smoke (23, 26, 28, 70, 72). Predictably, vegetarians have been shown to have lower vitamin B₁₂ levels than nonvegetarians, and vegetarians who smoke have the lowest levels of this vitamin (17, 69). Schrauzer and Lee (57) have postulated that carbon monoxide in tobacco smoke reacts with Co + + + in vitamin B₁₂ to form Co + + (57). The occurrence of amblyopia is believed to be associated with individuals having a genetic or acquired error of cyanide or vitamin B₁₂ metabolism in that cyanide is not converted to thiocyanate, but remains as cyanocobalamin (13, 27, 54, 71). Agamanolis, et al. (1) have suggested that the occurrence of amblyopia is an early symptom of vitamin B₁₂ deficiency and that pernicious anemia and other symptoms occur at a much later stage.

Vitamin B₆

El-Zoghby, et al. (21) have reported the possible existence of a smoking-induced vitamin B₆ deficiency, as indicated by the finding that tryptophan metabolites follow different excretion patterns in smokers and nonsmokers. Supplementation with vitamin B₆ restores the excretion of some metabolites for smokers to the levels found in nonsmokers; however, other metabolites remain at abnormal levels despite the additional vitamin B₆. A report by Mitchell and Schandl (42) suggests a possible mechanism for vitamin B₆ loss which involves a reaction between vitamin B₆ and carbon monoxide.

Minerals

Some observations have been made that bone mineral losses associated with postmenopause are accelerated with smoking. In two studies involving 72 and 80 women, osteoporosis in nonobese smokers was significantly higher than for nonobese nonsmokers (8). Obese women showed no similar effect between smoking and nonsmoking. The increased loss of bone mineral may be a secondary effect induced by other nutritional conditions such as low vitamin C levels.

Other

Obesity

Although many individuals have reported significant weight gains when smoking was terminated, there appears to be no scientific evidence to support the existence of a thermogenesis effect. In a carefully controlled study, Sims (61) observed no change in resting metabolic rate, thermic response to exercise or meals, and no change in serum T-3 or T-4. Subjects participating in this study revealed, however, that their appetite ratings were lower during periods of smoking.

Smoking in Pregnancy

Fetal malnutrition associated with smoking mothers has been observed both in the United States and in Great Britain. Results of these studies demonstrate that babies born to smoking mothers are smaller and have a greater risk of perinatal mortality when compared to babies of nonsmoking mothers (4, 7, 16, 28, 39, 59). The exact causes of these observations have not been established. It is likely that a combination of nutritional factors, such as lower levels of amino acids, vitamins B₁₂ and C, and glucose and fatty acids in maternal blood, contribute to the causes of these observations (12, 41). In addition, it has been postulated that higher levels of carbon monoxide, nicotine, and cyanides result in decreased oxygen for the fetus.