Summary

Epidemiologic data have long linked smoking with increased risk of cardiovascular disease, increased osteoporosis, amblyopia, and other disorders. Recent data demonstrate that smoking during pregnancy results in a greater risk of smaller birth weight and perinatal mortality among pregnant women. Smoking causes changes in plasma and leukocyte concentrations of vitamin C and impairs biochemical functions of this vitamin. Vitamin B_{12} is metabolized in the detoxification process of cyanide derived from smoking. Some heavy smokers develop an amblyopia which is reversed by either vitamin B_{12} supplementation or termination of smoking. Evidence is also presented suggesting that smoking may alter the metabolism of lipids, carbohydrates, proteins, and other vitamins such as vitamin B_6.

Nutrient Interactions: References

(1) AGAMANOLIS, D.P., CHESTER, E.M., VICTOR, M., KARK, J.A., HINES, J.D., HARRIS, J.W. Neuropathology of experimental vitamin B-12 deficiency in monkeys. Neurology 26(10): 905-914, October 1976.

(2) AINLEY, R.G. The Farnsworth-Munsell 100 hue test in tobacco amblyopia. Transactions of the Ophthalmological Society of the United Kingdom 90: 765-772, 1970.

(3) ALBANESE, A.A., ORTO, L.A., WEIN, E.H., ZAVATTARO, D.N. Effect of cigarette smoking on protein and amino acid metabolism. I. Tryptophan. Nutrition Reports International 5(4): 245-258, April 1972.

(4) ANDREWS, J., MCGARRY, J.M. A community study of smoking in pregnancy. The Journal of Obstetrics and Gynaecology of the British Commonwealth 79(12): 1057-1073, December 1972.

(5) ARMSTRONG, B., LEA, A.J., ADELSTEIN, A.M., DONOVAN, J.W., WHITE, G.C. RUTTLE, S. Cancer mortality and saccharin consumption in diabetics. British Journal of Preventive and Social Medicine 30(3): 151-157, September 1976.

(6) BAILEY, D.A., CARRON, A.V., TEECE, R.G., WEHNER, H.J. Vitamin C supplementation related to physiological response to exercise in smoking and nonsmoking subjects. American Journal of Clinical Nutrition 23(7): 905-912, July 1970.

(7) BRITISH MEDICAL JOURNAL. Cigarette smoking in pregnancy. British Medical Journal 2(6034): 492, August 28, 1976.

(8) BRITISH MEDICAL JOURNAL. Smokers' bones. British Medical Journal 2(8029): 201, July 24, 1976.

(9) BURR, M.L., ELWOOD, P.C., HOLE, D.J., HURLEY, R.J., HUGHES, R.E. Plasma and leukocyte ascorbic acid levels in the elderly. American Journal of Clinical Nutrition 27(2): 144-151, February 1974.

(10) BURR, R.G., RAJAN, K.T. Leucocyte ascorbic acid and pressure sores in paraplegia. British Journal of Nutrition 28(2): 275-281, 1972.

(11) CANADIAN MEDICAL ASSOCIATION JOURNAL. Tobacco amblyopia. Canadian Medical Association Journal 102(4): 420, February 1970. (Editorial)

(12) CHAMOT, A.P.H. BAZARBACHI, H. Agents toxiques et grossesse (Toxic agents and pregnancy). Gynaecologia 168(5): 318-327, 1969.

(13) CHISHOLM, I.A., PETTIGREW, A.R. Biochemical observations in toxic optic neuropathy. Transactions of the Ophthalmological Society of the United Kingdom 90: 827-838, 1970.

(14) CLEGG, K.M., MACDONALD, J.M. L-ascorbic acid and d-isoascorbic acid in a common cold survey. American Journal of Clinical Nutrition 28(9): 973-976, September 1975.

(15) CREWS, S.J., JAMES, B., MARSTERS, J.B., WEST, R.H. Drug and nutritional factors in optic neuropathy. Transactions of the Ophthalmological Society of the United Kingdom 90: 773-794, 1970.

(16) CROSBY, W.M., METCOFF, J., COSTILOE, J.P., MAMEESH, M., SANDSTEAD, H.H., JACOB, R.A., MCCLAIN, P.E., JACOBSON, G., REID, W., BURNS, G. Fetal malnutrition: An appraisal of correlated factors. American Journal of Obstetrics and Gynecology 128(1): 22-31, May 1, 1977.

(17) DASTUR, D.K., QUADROS, E.V., WADIA, N.H., DESAI, M.M., BHARUCHA, E.P. Effect of vegetarianism and smoking on vitamin B-12, thiocyanate, and folate levels in the blood of normal subjects. British Medical Journal 3: 260-263, July 29, 1972.

(18) DELAHAYE, J.P., BESSET C., TOUBOUL, P. Evolution spontanee et pronostic des arteriopathies atherosclereuses des membres inferieurs (Spontaneous evolution and prognosis of atherosclerotic arterial diseases of the lower limbs). Archives des Maladies du Coeur et des Vaisseaux 63 (Supplement 1): 64-78, 1970.

(19) DEWHURST, F., KITCHEN, D.A. Effect of some 6-substituted benzo(a)pyrene derivatives upon liver enzymes and ascorbic acid excretion in mice. Biochemical Pharmacology 22(7): 789-796, April 1973.

(20) ELWOOD, P.C., HUGHES, R.E., HURLEY, R.J. Ascorbic acid and serum-cholesterol. Lancet 2(7684): 1197, December 5, 1970.

(21) EL-ZOGHBY, S.M., EL-SHAFEI, A.K., ABDEL-TAWAB, G.A., KELADA, F.S. Studies on the effect of reserpine therapy on the functional capacity of the tryptophan-niacin pathway in smoker and non-smoker males. Biochemical Pharmacology 19(5): 1661-1667, May 1970.

(22) FOULDS, W.S. Visual disturbances in systemic disorders, optic neuropathy, and systemic disease. Transactions of the Ophthalmological Society of the United Kingdom, 1969 Session, 89: 125-146, 1970.

(23) FREEMAN, A.G. Thiocyanate metabolism in human vitamin B-12 deficiency. British Medical Journal 1(5847): 231-232, January 27, 1973.

(24) GASTARD, J., JOUBAUD, F., FARBOS, T., LOUSSOUARN, J., MARION, J. PANNIER, M., RENAUDET, F., VALDAZO, R., GOSSELIN, M. Etiology and course of primary chronic pancreatitis in Western France. Digestion 9(5): 416-428, 1973.

(25) GRANT, F.W., COWEN, M.A., OZERENGIN, M.F., BIGELOW, N. Nutritional requirements in mental illness. 1. Ascorbic acid retention in schizophrenia. A reexamination. Biological Psychiatry 5(3): 289-294, December 1972.

(26) HALAWA, B., MAZUREK, W. Wplyw palenia tytoniu na poziom witaminy B-12 w surowicy u ludzi (Effect of Tobacco smoking on vitamin B-12 level in human serum). Wiadomosci Lekarskie 29(6): 469-472, March 15, 1976.

(27) HARRIS, J.O., SWENSON, E.W., JOHNSON, J.E. Human alveolar macrophages: Comparison of phagocytic ability, glucose utilization, and ultrastructure in smokers and nonsmokers. Journal of Clinical Investigation 49(11): 2086-2096, November 1970.

(28) HAUSER, G.A. Genussmittel in der schwangerschaft (Voluptuaries in pregnancy). Therapeutische Umschau 28(7): 430-434, July 1971.

(29) HELMAN, N. Macrocytosis and cigarette smoking (Letter). Annals of Internal Medicine 79(2): 287-288, August 1973.

(30) HUGHES, R.E., JONES, P.R., NICHOLAS, P. Some effects of experimentally-produced cigarette smoke on the growth, vitamin C metabolism, and organ weights of guinea-pigs. Journal of Pharmacy and Pharmacology 22(11): 823-827, November 1970.

(31) ILEBEKK, A., MILLER, N.E., MJOS, O.D. Effects of nicotine and inhalation of cigarette smoke on total body oxygen consumption in dogs. Scandinavian Journal of Clinical and Laboratory Investigation 35(1): 67-72, 1975.

(32) JAYLE, G.E., METGE, P., CHAIX, A., VOLA, J.L., TASSY, A. Exploration fonctionnelle des nevrites optiques alcoolo-tabagiques (Functional exploration of alcohol-tobacco optic neuritis). Archives D'Ophtalmologie 32(1): 79-86, 1972.

(33) KAMPENG, V., VASINARAVONGSE, V., SIDDHIKOL, C. Level of vitamin C in plasma in smokers and nonsmokers among medical students. Sibiraj Hospital Gazette 25(6): 964-971, June 1973.

(34) KEITH, M.O., PELLETIER, O. The effect of nicotine on ascorbic acid retention by guinea pigs. Canadian Journal of Physiology and Pharmacology 51(12): 879-884, December 1973.

(35) KEVANY, J., JESSOP, W., GOLDSMITH, A. The effect of smoking on ascorbic acid and serum cholesterol in adult males. Irish Journal of Medical Science 144(12): 474-477, December 1975.

(36) KNOX, D.L. Neuro-ophthalmology. Annual review. Archives of Ophthalmology 83(1): 103-127, January 1970.

(37) KRISHNASWAMY, K., NADAMUNI NAIDU, A. Microsomal enzymes in malnutrition as determined by plasma half life of antipyrine. British Medical Journal 1(6060): 538-540, February 26, 1977.

(38) LOH, H.S. Cigarette smoking and the pathogenesis of atherosclerosis—a hypothesis. Irish Journal of Medical Science 142(4): 174-178, July 1973.

(39) LUBCHENCO, L.O. The infant who is small for gestational age. Major Problems in Clinical Pediatrics. Volume XIV. The High Risk Infant. Philadelphia, W.B. Saunders, 1976, pp. 181-201.

(40) MCCLEAN, H.E., DODDS, P.M., ABERNETHY, M.H., STEWART, A.W., BEAVEN, D.W. Vitamin C concentration in plasma and leucocytes of men related to age and smoking habit. New Zealand Medical Journal 83(561): 226-229, April 14, 1976.

(41) MCGARRY, J.M., ANDREWS, J. Smoking in pregnancy and vitamin B-12 metabolism. British Medical Journal 2(5805): 74-77, April 8, 1972.

(42) MITCHELL, D.A., SCHANDL, E.K. Carbon monoxide, vitamin B-6, and multiple sclerosis: a theory of interrelationship. American Journal of Clinical Nutrition 26(8): 890-896, August 1973.

(43) MOLLER, E., KLEIN, B. Herzinfarkt und subklinishcer diabetes (Myocardial infarct and subclinical diabetes). Medizinische Welt 21(26): 1191-1194, June 27, 1970.

(44) ORSETTI, A., AMARA, F., COLLARD, F., MIROUZE, J. Influence du tabac sur les hormones essentielles de la glycoregulation (The influence of tobacco on hormones essential to glycoregulation). Nouvelle Press Medicale 4(21): 1571-1572, May 24, 1975.

(45) PELLETIER, O. Cigarette smoking and vitamin C. Nutrition Today 5(3): 12-15, Autumn 1970.

(46) PELLETIER, O., Vitamin C and cigarette smokers. Annals of the New York Academy of Sciences 258: 156-168, 1975.

(47) PELLETIER, O. Vitamin C status of cigarette smokers and nonsmokers. American Journal of Clinical Nutrition 23(5): 520-524, May 1970.

(48) PELLETIER, O., KEITH, M.O. Bioavailability of synthetic and natural ascorbic acid. Journal of the American Dietetic Association 64(3): 271-275, March 1974.

(49) PETTIGREW, A.R., FELL, G.S., CHISHOLM, I.A. Red cell glutathione in tobacco amblyopia. Experimental Eye Research 14(2): 87-90, 1972.

(50) PHILLIPS, C.I., AINLEY, R.G., VAN PEBORGH, P., WATSON-WILLIAMS, E.J., BOTTOMLEY, A.C. Vitamin B-12 content of aqueous humour. Nature 217(5123): 67-68, January 6, 1968.

(51) POTTS, A.M. Tobacco amblyopia. Survey of Ophthalmology 17(5): 313-339, March/April, 1973.

(52) RATZMANN, K.-P., RIEMER, D., SPOERL, L., WEBER, L., WITTKOPF, E. Untersuchungen zur wirkung des zigaretten rauchens auf metaboliten des kodlenhyhrat-und fettstoffwechsels (Investigation of the effect of cigarette smoke on intermediates in carbohydrate and lipid metabolism). Deutsche Gesundheitswesen 34(28): 1618-1620, August 4, 1973.

(53) ROBERTS, D.M. Chronic gastritis, alcohol, and non-ulcer dyspepsia. Gut 13(10): 768-774, October 1972.

(54) ROSSMANN, H. Vitamin B-12 resorption bei der sogenannten tabak-amblyopie (Vitamin B-12 resorption in the so-called tobacco amblyopia). Deutsche Medizinische Wochenschrift 95(8): 419-420, February 20, 1970.

(55) SALAZAR, E., MORAGREGA, J.L., MAGOS, C., ZORRILLA, E., SERRANO, P.A. Alteraciones metabolicas en sobrevivientes de infarto del miocardio (Metabolic changes in survivors of myocardial infarction). Archivos del Instituto de Cardiologia de Mexico 43(1): 4-17, January/February 1973.

(56) SCHETTLER, G., MOERL, H. Risikofaktoren der atherosklerose in beziehung zur lebenserwartung heute und den lebensaussichten morgan (Risk factors of atherosclerosis in relation to life expectancy today and in the future). Medizinische Welt 27(46): 2201-2205, November 12, 1976.

(57) SCHRAUZER, G.N., LEE, L.P. The reduction of vitamin B-12a by carbon monoxide. Archives of Biochemistry and Biophysics 138(1): 16-25, May 1970.

(58) SHANKAR, R. Effect of chronic nicotine administration on the intestinal mucosal alkaline phosphatase in rats. Indian Journal of Experimental Biology 13(4): 360-362, July 1975.

(59) SILVERMAN, H.M. Fetal and newborn adverse drug reactions. A survey of the recent literature. Drug Intelligence and Clinical Pharmacy 8(12): 690-693, December 1974.

(60) SIM, A.K. Ascorbic acid—a survey, past and present. Chemistry and Industry 8(4): 160-165, February 19, 1972.

(61) SIMS, E.A.H. Experimental obesity, dietary-induced thermogenesis, and their clinical implications. Clinics in Endocrinology and Metabolism 5(2): 377-395, July 1976.

(62) SPITTLE, C.R. The action of vitamin C on blood vessels. American Heart Journal 88(3): 387-388, September 1974.

(63) SPITTLE, C.R. Atherosclerosis and vitamin C. Lancet 2(7737): 1280-1281, December 11, 1971.

(64) SPRINCE, H., PARKER, C.M., SMITH, G.G., GONZALES, L.J. Protective action of ascorbic acid and sulfur compounds against acetaldehyde toxicity: Implications in alcoholism and smoking. Agents and Actions 5(2): 164-173, 1975.

(65) STRAUSS, L.H., SCHEER, P. Ueber die Einwirkungen des Nikotins auf den Vitamin C-Haushalt (On the influence of nicotine on the composition of vitamin C). Zeitschrift fur Vitaminforschung 9: 39-48, 1939.

(66) TAMURA, T., INOUE, H. IIDA, T., ONO, H. Studies on the antidotal action of drugs. Part 1. Vitamin C and its antidotal effect against alcoholic and nicotine poisoning. Journal of Nihon University School of Dentistry 11: 149-151, 1969.

(67) TOPORKOVA, I.B. Vitamin C balance in connection with chronic exposure of tobacco industrial workers to tobacco dust. Leningradskii Sanitarno-Gigienicheskii Meditsinskii Institut, Trudy 47: 243-253, 1959.

(68) TSARFIS, T.P., SVERDLOVA, P.S., ILYUSHINA, I.P., GLAZUNOV, I.S., METELITSA, V.I. Disturbance in tolerance to carbohydrates in males 50-59 years old. Terapevticheskii Arkhiv 41(12): 77-80, December 1969.

(69) WADIA, N.H., DESAI, M.M., QUADROS, E.V., DASTUR, D.K. Role of vegetarianism, smoking and hydroxocobalamin in optic neuritis. British Medical Journal 3: 264-267, July 29, 1972.

(70) WELLS, D.G., LANGMAN, M.J.S., WILSON, J. Thiocyanate metabolism in human vitamin B-12 deficiency. British Medical Journal 4(5840): 588-590, December 9, 1972.

(71) WILSON, J., LINNELL, J.C., MATTHEWS, D.M. Plasma-cobalamins in neuro-ophthalmological diseases. Lancet 1(7693): 259-261, February 6, 1971.

(72) YEUNG, D.L. Relationships between cigarette smoking, oral contraceptives, and plasma vitamins A, E, C, and plasma triglycerides and cholesterol. American Journal of Clinical Nutrition 29(11): 1216-1221, November 1976.

(73) YEW, M.-L.S., LO, Y. Levels of optimal vitamin C intake in individuals as estimated by the lingual tests. Proceedings of the Society for Experimental Biology and Medicine 144(2): 626-627, 1973.

Trace Constituents in Smoke

Trace elements in tobacco that are sublimated at the temperature of smoking may interact with dietary components. These elements include organic compounds that are not pyrolyzed at these temperatures and compounds that may be formed during pyrolysis. The interaction may result because cigarette smoke contains: (1) significant amounts of trace components normally present in the food, e.g., heavy metals, pesticides, and naturally occurring carcinogens, which may represent an important additional source of exposure to these compounds; and (2) components that alter the metabolism of food additives or constituents. Because of the large number of components that may occur in cigarette smoke, only those considered significant are discussed here.

Trace Metals

Nadkarni (*12*) has reported that toxic elements in tobacco smoke include cadmium, lead, arsenic, and selenium. Cadmium from cigarettes represents a very substantial additional burden for smokers when compared with that normally present in the diet and other non-industrial sources. For a person smoking two to three packs of cigarettes a day, the estimated respiratory cadmium intake ranges from 4 to 6 μg. The retention of cadmium via this route is high; it has been estimated that of the 4-6 μg of the cadmium in the inhaled smoke, up to 2.82 μg would be absorbed. This represents a very significant exposure when compared with the proportion of cadmium retained from other sources, e.g., of the 50 μg/day cadmium ingested in food, retention may be of the order of only 3.0 μg. The significantly greater retention of cadmium by smokers is clearly reflected in greater levels of tissue cadmium in smokers compared to nonsmokers. Smokers accumulate more cadmium in the kidney cortex, liver, pancreas and other tissues than nonsmokers (*13*). For a person smoking one pack of cigarettes a day for 50 years, Elinder, et al. (*5*) estimated an increase in body burden of cadmium of about 8 mg. In another study, Johnson, et al. (*9*) estimated the body burden of cadmium in nonsmokers to be 10.3 mg compared to 14.9 mg for smokers.

Studies on the contribution of smoking to the body burden of other metals are limited. Cigarette smokers have been shown to have higher lead concentrations in the liver, pancreas, and kidney tissues, and slightly higher levels of lead in muscle and fat than nonsmokers (*6*). Johnson, et al. (*9*) have reported that zinc and mercury concentrations were significantly higher in the pancreas and fat tissues of smokers, but lower in the kidney tissue than in the case of nonsmokers.

^{210}Polonium, which is present in the leaves of tobacco and volatizes at the temperature at which cigarettes burn, is deposited in smoke particles and enters the lung with the particles. The ^{210}Po concentration

in cigarettes varies from 0.15 to 0.63 p Ci/g. Approximately 20 percent of the ^{210}Po content of a cigarette enters the lungs with the smoke stream, with one cigarette yielding about 0.08 p Ci of ^{210}Po to the body. This is almost as much ^{210}Po as a person inhales from the atmosphere in 24 hours (*14*).

There is no information to indicate that the increased body burden of these toxic elements results in toxic effects related to increased exposure to the elements. It is possible that subclinical effects may occur, although these effects cannot be demonstrated by the presently available methodology.

Nitrosamines

Tobacco smoke not only represents a source of exposure to nitrosable amines which can undergo nitrosation, but it is also a major source of exposure to preformed N-nitrosonornicotine (NNN), which is present in processed tobacco. Its concentration ranges from 0.3-90 ppm in smoking tobacco, chewing tobacco, and snuff. Hilfrich, et al. (*8*) have estimated exposure to NNN from tobacco smoke at 140-250 ng/cigarette. Fine (*6*) has estimated the exposure to nitrosamines from tobacco smoke, primarily NNN, to be 4.1 μg/day (from 20 cigarettes) compared to 6 μg/day (nitropyrollidine and other nitrosamines) from food. NNN induces tumors of the esophagus, pharynx, and the nasal cavity in rats, and it is possible that the increased incidence of cancer in tobacco smokers and chewers may be related to the carcinogenicity of this compound (*5*). In addition, it is not known if the possible carcinogenic action of this compound may be additive or may potentiate the effect of nitrosamines occasionally found in the diet.

Schmeltz, et al. (*15*) have detected N-nitrosodiethanolamine in cured tobacco at concentrations ranging from 0.1 to 173 ng/g. They postulate that it is derived from the use of diethanolamine, a solubilizing agent for the plant growth regulator, maleic hydrazide. Schmeltz and Hoffmann (*16*) have reviewed the occurrence of nitrogen-containing compounds in tobacco and tobacco smoke. Included in the list of compounds reported are numerous aliphatic amines, notably secondary and tertiary amines, as well as aromatic amines, which have the potential of being converted to nitrosamines in the presence of nitrite or nitrogen oxide. Because saliva normally contains low levels of nitrite (*18*), there is a potential for nitrosation of the amines to occur *in vivo*. In addition, nitrite in certain processed foods may represent a source of nitrite for nitrosation of these amines. The synthesis of nitrosamines may be further catalyzed by the presence of thiocyanate in saliva. Because thiocyanate levels are greatly increased in the saliva, as well as in the stomach content, of smokers compared to that of nonsmokers, the potential for *in vivo* nitrosation is greatly increased in smokers (*5*). However, other dietary components, e.g. ascorbic acid (*1*) or α-

tocopherol (*10*), may reduce the potential for nitrosation, primarily by reacting with the free nitrite.

Nicotine is a major constituent of tobacco smoke, but Lijinsky and Singer (*11*) report that it is only very slowly nitrosated in aqueous solutions and thus does not provide a significant source for amines that may be nitrosated in the stomach.

Pesticide Residues

Atallah and Dorough (*2*) have reported on studies with cigarettes impregnated with ^{14}C-labelled pesticides (carbaryl, carbofuran, leptophos, DDT, and mirex) and have provided information on both the stability of these pesticides under smoking conditions as well as the amount transferred to mainstream smoke. Mirex was reported to be the most stable compound (70 percent of ^{14}C in mainstream was unchanged mirex). Carbofuran was almost as stable as mirex. From 40 to 45 percent of the ^{14}C in mainstream smoke from carbaryl and DDT was in the form of the parent compound. Leptophos was the least stable, with only 21 percent of the ^{14}C in the mainstream smoke present as the parent compound. Rats which inhaled the ^{14}C-labelled smoke derived from the treated cigarettes did not show patterns or tissue distribution of inhaled ^{14}C-labelled pesticides which could be considered characteristic for a particular type of pesticide. In contrast, Atallah and Dorough (*2*) cited a report by Guthrie (*7*) which states that carbamates and organophosphate pesticides were almost completely degraded during the smoking process.

More information is needed on the nature and ultimate fate of insecticide residues inhaled in tobacco smoke. Based on the information reviewed, it is not possible to assess the health significance of pesticide residues in tobacco.

In addition to the active principals contained in pesticides, other subtances such as surfactants or solubilizing agents of inert carriers may, if transferred to tobacco smoke, interact with compounds in the diet or undergo conversion to potentially hazardous substances in the tobacco leaf itself, e.g., nitrosation of diethanolamine which is used as a solubilizing agent for maleic hydrazide. Very little is known regarding these potential interactions and the effects, if any, in humans.

There is also little information on the fate of N-containing agricultural chemicals after their application to tobacco. Maleic hydrazide is present in cured tobacco (20-30 ppm) and a small portion (4–10 percent) is transferred unchanged to mainstream smoke.

Metabolic Effects

Constituents of tobacco smoke may inhibit or induce enzyme activity in human tissues and alter the rate of metabolism of food additives or food constituents.

Nicotine has been shown to cause significant reduction in rats' intestinal alkaline phosphatase activity. The significance of the reduced activity of this marker enzyme of intestinal mucosa is not known, but it may be indicative of a reduced metabolic activity of the mucosal cells. Shankar (*17*) has postulated that this may be one of the factors causing sensitivities of mucosal cells to acid destruction.

A large number of polynuclear aromatic hydrocarbon (PNAs) have been identified in tobacco smoke. Wynder and Hoffmann (*19*) have reported that the concentration of PNA in the smoke of one cigarette ranges from 0.6-70.0 ng. In addition to their well-known effects as initiating carcinogens, PNAs are well-known inducers of mixed function oxidases. The effect of PNAs on the proliferation of microsomal enzymes and on subsequent increases in cytochrome P-450 has already been discussed in detail. However, it is of interest to note that cigarettes contain substances that may depress the activity of microsomal enzymes at one site and increase them at another site, e.g., cigarette smoke depresses pulmonary aryl hydrocarbon hydroxylase (AHH) activity in guinea pigs but increases liver AHH activity (*3*). The depression of pulmonary AHH activity may be due to the presence of carbon monoxide or cyanide in tobacco smoke combining directly with the cytochromes and rendering them unavailable for their role in the enzymatic action.

It is not known if these metabolic changes can affect the metabolism of food chemicals or food constituents, or if the level of changes that can occur are significant in relation to the inhibition or increase of microsomal activity by normal dietary constituents or contaminants in the diet. Another area of concern relates to the possible effect of enzyme inducers of the developing fetus. Enzyme inducers that cross the placental barrier may effect changes in the enzyme patterns of the developing fetus. Such changes or biochemical imprints may persist throughout life and could possibly result in altered patterns of metabolism of food additives and contaminants. It is not known to what extent, if any, constituents of tobacco smoke may cause these changes. However, a major problem in evaluating any possible effect due to the constituents of tobacco smoke is the lack of knowledge of the quantitative aspect of the relative amounts and activities of the components in tobacco smoke compared with those active substances normally present in the diet or present as contaminants (e.g., environmental contaminants, PCBs, DDT) of the diet, and the possible interactions between such compounds.

Summary

Although cigarette smoking will result in an additional body burden of Cd and Pb, there is little evidence that this will result in known adverse effects. The effects of nitrosamines and inhibitors and activators of enzymes in tobacco smoke have not been established.

Trace Constituents in Smoke: References

(1) ARCHER, M.C., TANNENBAUM, S.R., FAN, T.-Y., WEISMAN, M. Reaction of nitrite with ascorbate and its relation to nitrosamine formation. Journal of the National Cancer Institute, 54(5): 1203-1205, May 1975.

(2) ATALLAH, Y.H., DOROUGH, H.W. Insecticide residues in cigarette smoke. Transfer and fate in rats. Journal of Agriculture and Food Chemistry, 23(1): 64-71, 1975.

(3) BILIMORIA, M.H., JOHNSON, J., HOGG, J.C., WITSCHI, H.P. Pulmonary aryl hydrocarbon hydroxylase: Tobacco smoke-exposed guinea pigs. Toxicology and Applied Pharmacology 41: 433-440, 1977.

(4) BOYLAND, E., WALKER, S.A. Effect of thiocyanate on the nitrosation of amines. Nature, 248: 601-602, April 12, 1974.

(5) ELINDER, C.G., KJELLSTROM, T., FRIBERG, L., LIND, B., LINNMAN, L. Cadmium in kidney cortex, liver, and pancreas from Swedish autopsies. Archives of Environmental Health 31(6): 292-302, November/December 1976.

(6) FINE, D.H. An assessment of human exposure to N-nitroso compounds. Presented at the Fifth meeting on Analysis and Formation of N-nitroso Compounds, International Agency for Research on Cancer, Durham, N.H., August 22-24, 1977, 15 pp.

(7) GUTHRIE, F.E. The nature and significance of pesticide residues on tobacco and in tobacco smoke. Beitrage zur Tabakforschung 4(6): 229-246, November 1968.

(8) HILFRICH, J., HECHT, S.S., HOFFMANN, D. A study of tobacco carcinogenesis. XV. Effects of N'-nitrosonornicotine and N'-nitrosoanabasine in Syrian golden hamsters. Cancer Letters 2: 169-175, 1977.

(9) JOHNSON, D.E., PREVOST, R.J., TILLERY, J.B., THOMAS, R.E. The Distribution of Cadmium and Other Metals in Human Tissue. San Antonio, Southwest Research Institute, September 1977, 231 pp.

(10) KAMM, J.J., DASHMAN, T., NEWMARK, H., MERGENS, W.J. Inhibition of amine-nitrite hepatotoxicity by α-tocopherol. Toxicology and Applied Pharmacology 41: 575-583, September 1977.

(11) LIJINSKY, W., SINGER, G.M. Formation of nitrosamines from tertiary amines and nitrous acid. In: Bogovski, P. and Walker, E.A. (Editors). N-Nitroso Compounds in the Environment. Proceedings of a Working Conference held at the International Agency for Research on Cancer, Lyon, France, October 17-20, 1973. Lyon, International Agency for Research on Cancer, 1975, pp. 111-114.

(12) NADKARNI, R.A. Some considerations of metal content of tobacco products. Chemistry and Industry 17: 693-696, September 7, 1974.

(13) OFFICE OF TOXIC SUBSTANCES. Multimedia Levels—Cadmium. Environmental Protection Agency, Office of Toxic Substances, September 1977, pp. 5-1-5-21, 6-1-6-14.

(14) PARFENOV, Y.D. Polonium-210 in the environment and in the human organism. Atomic Energy Review 12(1): 75-143, 1974.

(15) SCHMELTZ, I., ABIDI, S., HOFFMANN, D. Tumorigenic agents in unburned processed tobacco; N-Nitrosodiethanolamine and 1,1-Dimethylhydrazine. Cancer Letters 2: 125-131, 1977.

(16) SCHMELTZ, I., HOFFMANN, D., Nitrogen-containing compounds in tobacco and tobacco smoke. Chemical Reviews 77(3): 295-311, June 1977.

(17) SHANKAR, R. Effect of chronic nicotine administration on the intestinal mucosal alkaline phosphatase in rats. Indian Journal of Experimental Biology 13: 360-362, July 1975.

(18) TANNENBAUM, S.R., WEISMAN, M., FETT, D. The effect of nitrate intake on nitrite formation in human saliva. Food and Cosmetics Toxicology (Oxford) 14: 549-552, 1976.

(*19*) WYNDER, E.L., HOFFMANN, D. Tobacco and tobacco smoke. Seminars in Oncology 3(1): 5-15, March 1976.

Smoker and Nonsmoker Responses to Diagnostic Tests

Numerous epidemiological studies have indicated that cigarette smokers have increased mortality ratios for lung cancer, coronary heart disease, and nonmalignant respiratory disease. That the relationship is causal, and not purely statistical, was determined through examination of evidence on the biochemical, cytological, pathological, and pathophysiological effects of cigarette smoking (*22*). As more prospective screening studies involving clinical laboratory analyses have been done on apparently healthy subjects (*5, 6, 8, 12*), more differences at the biochemical level have become apparent between smokers and nonsmokers. As discussed in the 1976 *The Health Consequences of Smoking* (*22*), some of the differences in analytical values of clinical/diagnostic tests may be due to the fact that the nicotine in cigarette smoke causes increased levels of serum catecholamines, which in turn lead to increased levels of serum free fatty acids. Other effects, particularly those involving the erythrocyte, are probably the results of the relatively high levels of carbon monoxide in cigarette smoke.

The major portion of the experimental results and data to be presented here was obtained by testing individuals who were apparently normal and healthy and not suffering from any of the smoking-related diseases listed above or from other diseases. The evidence indicates that smoking causes significant changes in the "normal" values in various biochemical and clinical tests that may be done routinely in the clinical laboratory. In addition, values obtained in certain less routine analyses, such as platelet aggregation and carcinoembryonic antigen tests, may depend upon the smoking status of the individual subject. Although conflicting results have been obtained in some of the experimental reports, it is apparent that the smoking status of an individual should be reported along with parameters such as age and sex.

Leukocytes

Results from a large number of studies have shown that smokers have higher numbers of white blood cells than nonsmokers (*3, 4, 5, 12, 13, 16, 17, 20*).

In a study on 108 males aged 20 to 39, Okuno (*17*) found that the leukocyte count was significantly higher in smokers than in nonsmokers. Okuno (*17*) stated that, since his subjects were healthy and completely free of symptoms, smoking alone appeared to be the cause of the increased leukocyte counts. Similar results in leukocyte counts were found by Sagone, et al. (*20*) in a study of 27 healthy white men between the ages of 20 and 32. The 9 men in this study who smoked one or more packs of cigarettes per day had higher white cell counts than the 18 nonsmokers (*20*).

Friedman, et al. (*8*), in a study involving 86,488 ambulatory patients undergoing multiphasic examinations, related the leukocyte count to (1) quantity smoked, (2) inhalation, and (3) smoking duration. Cigarette smokers showed the highest leukocyte counts and nonsmokers showed the lowest. Differences in the mean leukocyte count were shown by Friedman, et al. (*8*) to be present in all ages from 15 to 79, in both sexes, and in all three races tested (yellow, black and white). Data from Friedman, et al. (*8*) showing the leukocyte patterns discussed above are presented in Table 9. These authors suggest that the increased leukocyte counts in smokers might be due to nicotine-induced release of catecholamines or to an irritant effect of smoke on the respiratory tree with resultant inflammation. They state that the age, sex, racial composition, and smoking habits of the reference population should be taken into account in arriving at "normal" values for the leukocyte count.

Corre, et al. (*5*), in a study of 4,264 men, showed that the number of leukocytes is increased in smokers as compared to nonsmokers. Investigation of a subgroup revealed that the increase was in granulocytes, lymphocytes, and monocytes. The authors found no real change in the differential leukocyte count, thus excluding the hypothesis of involvement of an infectious process. As shown in Table 10, their data indicated that the average number of leukocytes is greater in smokers who inhale than in those who do not, regardless of the amount smoked. They also stated that the leukocyte count is higher in light smokers who inhale than in heavy smokers who do not inhale.

Parulkar, et al. (*18*), in an examination of 130 healthy Indian males aged 16 to 60 of different social and economic status, found a direct relationship between smoking and an increase in the lymphocyte count. They suggested the presence of a chronic inflammatory process, such as bronchitis, based on data in which the lymphocyte count was higher in smokers than in nonsmokers, with little change in other types of cells. The data also showed an increase in lymphocyte count with increasing numbers of cigarettes smoked per day. Parulkar, et al. (*18*) noted the difference between results of their work and that of Corre, et al. (*5*).

Helman and Rubenstein (*12*) examined 1,000 patients randomly selected from the clinic population. By chart review, the authors excluded the following: overt or chronic debilitating illness, known chronic respiratory disease, hepatic disease, hematologic disorders, hematinic therapy, history of splenectomy, gastric surgery, and small intestinal surgery. Following complete blood counts, the authors eliminated women with hemoglobin outside the limits of 11.0 to 17.0 gm per 100 ml and men with hemoglobin outside the limits of 13.0 to 19.0 gm per 100 ml. They also eliminated those with gross erythrocytic abnormalities. They stated that, when both sexes and all ages were grouped, it was clear that the heavier the smoking, the higher the

TABLE 9.—Mean leukocyte count in 1,000s (WBC) according to race, sex, and smoking category

Smoking category	Study group: White		Black		Yellow	
	Men	Women	Men	Women	Men	Women
Nonsmokers						
No.	8,246	18,438	1,108	3,199	709	1,308
Mean WBC/cu mm	7.2	7.4	6.3	6.8	7.0	7.3
SD	1.6	1.7	1.5	1.8	1.6	1.7
% ≥ 11,000	1.9	.0	0.5	2.3	2.1	2.3
Cigar or pipe (noncigarette)						
No.	1,573	. . .	214	. . .	42	. . .
Mean WBC/cu mm	7.2	. . .	6.2	. . .	6.7	. . .
SD	1.6	. . .	1.5	. . .	1.3	. . .
% ≥ 11,000	2.2	. . .	0.9	. . .	0.0	. . .
Ex-cigarette→none						
No.	6,065	5,379	503	487	143	136
Mean WBC/cu mm	7.3	7.7	6.7	7.2	7.0	7.5
SD	1.7	2.1	1.7	1.8	1.5	1.8
% ≥ 11,000	3.0	4.9	2.2	3.9	2.1	2.2
Ex-cigarette→cigar or pipe						
No.	1,776	. . .	184	. . .	59	. . .
Mean WBC/cu mm	7.6	. . .	6.7	. . .	7.4	. . .
SD	1.7	. . .	1.9	. . .	2.0	. . .
% ≥ 11,000	4.2	. . .	1.6	. . .	3.4	. . .
Current established cigarette smokers						
No.	14,416	15,972	2,590	2,847	651	441
Mean WBC/cu mm	8.4	8.4	7.2	7.6	7.8	7.9
SD	2.0	2.0	1.9	2.1	1.8	1.8
% ≥ 11,000	10.0	10.0	3.9	6.4	5.8	5.0

SOURCE: Friedman, G.D. (*8*).

white cell count. The authors (*12*) concluded that the cause of smoking-associated leukocytosis is unknown.

Billimoria, et al. (*4*) examined 187 volunteers aged 30 to 60 years divided into heavy and light smokers and nonsmokers. In the male heavy smokers, they found, a significant increase in the leukocyte count, with the differential count indicating rises in neutrophils and lymphocytes. The changes were not significant in the female heavy smoking group.

In an extensive study of erythrocytosis, Sagone and Balcerzak (*19*) noted an increased leukocyte count among the parameters they examined.

TABLE 10.—Number of leukocytes per cu mm in smokers as a function of quantity smoked and of inhalation (number of subjects in parentheses)

Quantity smoked (g./day)	Inhalation status		Significance (p)
	No inhalation	Inhalation	
1–9	5801 (539)	6321 (208)	0.001
10–19	6130 (546)	6930 (563)	0.001
20–29	6263 (397)	7287 (610)	0.001
30 +	6276 (121)	7397 (199)	0.001
Significance (p)	0.05	0.001	

SOURCE: Corre, F. (*5*).

Noble and Penny (*16*) examined leukocyte function and other hematological measurements in a group of 27 healthy white males 20 to 30 years of age. Total leukocyte counts were significantly higher in smokers and temporarily abstaining smokers as compared to the nonsmoking group. Although leukocyte chemotaxis was depressed in the smoking subjects, smoking was not observed to affect the whole blood bactericidal and phagocytic tests with either Staphylococcus aureus or Klebsiella pneumoniae. Anderson, et al. (*2*) observed higher readings in the nitroblue-tetrazolium test among smokers than in nonsmokers and concluded that smoking may give rise to false positive results in this test.

Erythrocytes and Intraerythrocytic Parameters

Okuno (*17*) observed that smokers showed increases in hemoglobin, hematocrit, and mean corpuscular volume when compared to nonsmokers. Similar differences were obtained (*17*) between heavy smokers and light smokers.

In a study of the effects of smoking on tissue oxygen, Sagone, et al. (*20*) demonstrated that smokers had higher values for carboxyhemoglobin, hematocrit, hemoglobin, red cell count, and red cell mass. Red cell 2,3-diphosphoglycerate was not changed in smokers while ATP and P_{50} were significantly lower. The authors suggested that, in cases where a decreased oxygen-hemoglobin affinity has been observed, the hypoxia due to exposure to low levels of carbon monoxide is different from hypoxia due to other causes. It was concluded that adaptation to carbon monoxide in cigarettes is reflected by an increased red cell mass and hemoglobin. In a study by Isager and Hagerup (*14*), a positive correlation between cigarette smoking and hematocrit was found in a group composed of 394 men and 339 women.. Hematocrit values above normal were shown to be more common in cigarette smokers than in nonsmokers, with the differences statistically significant in the male

group. Cigarette consumption and lung function were negatively correlated in both sexes, but there was no evidence of any correlation between lung function and hematological variables (*14*). As Sagone, et al. (*20*) have done, these authors (*14*) suggest that the increase in packed cell volume and hemoglobin in cigarette smokers may be caused by elevated blood levels of carbon monoxide.

Helman and Rubenstein (*12*) related blood parameters to sex, age, and smoking habits. Although Helman and Rubenstein felt that the difference was not clinically significant, they showed that, under age 50, men who smoke have slightly higher hemoglobin levels than nonsmokers. After age 50, the hemoglobin of nonsmokers increases while that of smokers decreases. After age 60, the nonsmoker has a higher hemoglobin level than the smoker. Women smokers were shown (*12*) to have clearly higher levels of hemoglobin than nonsmoking women. These authors (*12*) found higher erythrocyte counts in nonsmoking men than in smoking men, but in women the RBC was independent of smoking. Smokers, both men and women, had higher hematocrit values than nonsmokers. It was found (*12*) that mean corpuscular volume and mean corpuscular hemoglobin are higher in smokers than in nonsmokers in both sexes and increase with age. Further, nonsmoking men were shown to have a slightly higher mean corpuscular hemoglobin concentration than men smokers and women. The authors (*12*) suggest that carbon monoxide and cyanide in cigarette smoke may be responsible for the increased hemoglobin and hematocrit in smokers with no increase in red cell count.

Heavy smoking was suggested as a reversible cause of polycythemia by Sagone and Balcerzak (*19*). They evaluated five smokers who were found to have very high values for hemoglobin, hematocrit, and erythrocyte mass as compared to nonsmokers. They reported that the patients did not have lung disease, shunt physiology, hemoglobin with increased oxygen affinity, erythropoietin-producing tumor, renal disease, or polycythemia rubra vera. In the period of 3 to 3 1/2 months after two of the subjects stopped smoking, it was observed that they both showed large decreases in erythrocyte mass and hematocrit values. The erythrocytosis found by these authors (*19*) appeared to be an adaptation to carboxyhemoglobin and a decreased oxygen-carrying capacity.

Cholesterol, Triglycerides, Lipoproteins

The effects of smoking on serum lipid levels are discussed in *The Health Consequences of Smoking* (*22*) with respect to coronary heart disease and immediate or acute effects of cigarette smoking. Inconsistencies in results described there are still prevalent. Howell (*13*) found no significant variation in either serum cholesterol or beta lipoprotein levels between heavy smokers, nonsmokers, and ex-smokers. On the other hand, Billimoria, et al. (*4*) found that male heavy smokers showed

increases in most indices associated with lipids. Compared with male nonsmokers, the male heavy smokers had a higher fasting serum turbidity and higher levels of cholesterol, serum phopholipids and triglycerides. The esterified fatty acid index of beta and pre-beta lipoprotein was also higher in male heavy smokers. Changes in cholesterol levels, the beta-esterified fatty acid index, phospholipids, and serum fasting turbidity were not observed in female heavy smokers in this study.

Other Chemistry Tests

Dales, et al. (*6*) studied levels of eight serum components in more than 65,000 cigarette smokers and nonsmokers. Creatinine and albumin levels were lower in smokers in both sexes, while the opposite was true for 1-hour post-challenge serum glucose. Globulin levels were consistently lower in women smokers, while uric acid levels were lower in male smokers. Cholesterol levels were higher in white men who smoked, but not in black male smokers. Calcium and serum glutamic oxalacetic transaminase (SGOT) levels of smokers were similar to those of nonsmokers. While alcohol consumption played a role in smoker-nonsmoker differences in serum glucose concentration, no additional factors were identified that could explain relationships to smoking for the other chemistries studied.

Glauser, et al. (*9*) examined seven subjects during a period in which they were smoking and 1 month after cessation of smoking. Statistically significant decreases were observed in protein-bound iodine level, 30-minute postprandial blood glucose level, and serum calcium level.

Clotting Factors

In a controlled, double-blind study, Levine (*15*) showed that the smoking of a single cigarette increased the platelet's response to a standard aggregating stimulus (Figure 7). The platelet effect appeared to be independent of the rise in plasma-free fatty acid which followed cigarette smoking. It was suggested that potentiation of platelet aggregation might help explain the increased incidence of arterial thrombi in cigarette smokers.

Hawkins (*11*) examined the relationship between smoking, platelet function, and thrombosis in a group of healthy young men divided into nonsmokers, light smokers, and heavy smokers. It was observed that platelets from smoking subjects seemed to be more active when aggregated with ADP than those from nonsmokers. When samples from each group were compared, a lower concentration of ADP was required in the two smoking groups to induce permanent platelet aggregates. The coagulation time of whole blood of smokers during a nonsmoking period was significantly shorter than that of nonsmokers. In the heavy smoking group there was an increase in maximum tensile

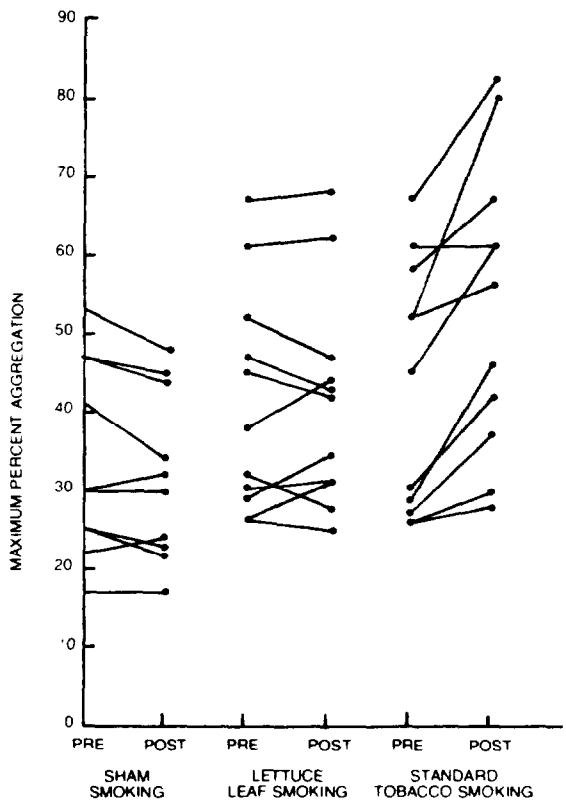

FIGURE 7.—Maximum platelet aggregation in response to a fixed dose of ADP. Paired experiments before and after sham smoking, non-nicotine cigarette smoking, and standard cigarette smoking
SOURCE: Levine, P.H. (*15*).

strength of the clot, when compared with the clot strength of nonsmokers.

Billimoria, et al. (*4*) observed no changes in fibrinogen levels or platelet adhesiveness. However this group of workers did find euglobulin lysis times significantly longer for both male and female heavy smokers. It was also determined that Stypven clotting times of heavy smokers were significantly shortened in both males and females.

Dintenfass (*7*) examined a group of blood viscosity factors in 125 healthy male Caucasian smokers and nonsmokers of 45 to 55 years of age. Hematocrit values, fibrinogen levels, plasma viscosity, blood viscosity, and red cell aggregation were elevated in the smokers.

Table 11.—CEA titers in selected groups of 2107 healthy subjects*

	Number	0.0–2.5 mg/ml	2.6–5.0 mg/ml	5.1–10.0 mg/ml	> 10.0 mg/ml
Nonsmokers	892	865	25	2	0
Presently smoking	620	502	93	19	6
Former smokers	235	219	12	2	2
Pregnant females	369	316	11	3	0

*Individuals with no known disease.
SOURCE: Hansen, H.J. (*10*).

Carcinoembryonic Antigen

In a study by Stevens and MacKay (*21*), sera from 955 unselected persons aged 60 years and older, obtained as part of a population survey, were tested for carcinoembryonic antigen (CEA). Among the 903 current smokers, ex-smokers, and nonsmokers who had no detectable cancer, a positive test (5 ng/ml or greater) was found in 13.6 percent of the 110 smokers but in only 1.8 percent of the 433 nonsmokers. Similar results were obtained by Alexander, et al. (*1*) who determined CEA levels in 276 healthy volunteers, of whom 154 were smokers and 122 were nonsmokers. They found mean CEA levels to be significantly higher in smokers than in nonsmokers, and a significantly higher percentage of smokers had elevated CEA levels. The results (*21*) also indicated that CEA levels of smokers declined to those of nonsmokers in about three months after cessation of smoking.

Hansen, et al. (*10*) in a collaborative study evaluating the clinical usefulness of the CEA assay in more than 10,000 patients and healthy subjects, suggested that the patient's smoking history must be taken into consideration when interpreting the CEA titer. As shown in Table 11, these investigators (*10*) found that 25 of 620 healthy subjects who were smokers had CEA titers above the value used to separate normals from abnormals.

Summary and Conclusions

1. Cigarette smoking is associated with an increase in leukocytes which appears to be dependent on the amount of smoke inhaled.
2. Cigarette smoking may cause increases in red cell mass, hemoglobin, carboxyhemoglobin, hematocrit, and mean corpuscular volume.
3. Cigarette smoking appears to have an effect on serum levels of creatinine, albumin, globulin, and uric acid.
4. Cigarette smoking appears to increase platelet aggregation, plasma viscosity, blood viscosity, and tensile strength of the clot along with a decrease in coagulation time.

5. Cigarette smoking appears to increase the serum carcinoembryonic antigen level in otherwise healthy individuals.

6. The majority of the blood components elevated due to cigarette smoking appear to revert to approximately normal levels after cessation of smoking.

7. The smoking status of an individual should be included in reports of clinical/diagnostic tests performed on that individual.

Smoker and Nonsmoker Responses to Diagnostic Tests: References

(1) ALEXANDER, J.C., JR., SILVERMAN, N.A., CHRETIEN, P.B. Effect of age and cigarette smoking on carcinoembryonic antigen levels. Journal of the American Medical Association 235(18): 1975-1979, May 3, 1976.

(2) ANDERSON, R., RABSON, A.R., SHER, R., KOORNHOF, H.J. The N.B.T. test in cigarette smokers. American Journal of Clinical Pathology 61(6): 879, June 1974.

(3) BANKS, D.C. Smoking and leucocyte-counts. Lancet 2(7728): 815, October 9, 1971.

(4) BILLIMORIA, J.D., POZNER, H., METSELAAR, B., BEST, F.W., JAMES, D.C.O. Effect of cigarette smoking on lipids, lipoproteins, blood coagulation, fibrinolysis and cellular components of human blood. Atherosclerosis 21(1): 61-76, January/February 1975.

(5) CORRE, F., LELLOUCH, J., SCHWARTZ, D. Smoking and leucocyte-counts. Lancet 2(7725): 632-634, September 18, 1971.

(6) DALES, L.G., FRIEDMAN, G.D., SIEGELAUB, A.B., SELTZER, C.C. Cigarette smoking and serum chemistry tests. Journal of Chronic Diseases 27(6): 293-307, August 1974.

(7) DINTENFASS, L. Elevation of blood viscosity, aggregation of red cells, haematocrit values and fibrinogen levels in cigarette smokers. Medical Journal of Australia 1(20): 617-620 May 17, 1975.

(8) FRIEDMAN, G.D., SIEGELAUB, A.B., SELTZER, C.C., FELDMAN, R., COLLEN, M.F. Smoking habits and the leukocyte count. Archives of Environmental Health 26(3): 137-143, March 1973.

(9) GLAUSER, S.C., GLAUSER, E.M., REIDENBERG, M.M., RUSY, B.F., TALLARIDA, R.J. Metabolic changes associated with the cessation of cigarette smoking. Archives of Environmental Health 20(3): 377-381, March 1970.

(10) 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.

(11) HAWKINS, R.I. Smoking, platelets and thrombosis. Nature 236(5348): 450-452, April 28, 1972.

(12) HELMAN, N., RUBENSTEIN, L.S. The effects of age, sex, and smoking on erythrocytes and leukocytes. American Journal of Clinical Pathology 63(1): 35-44, January 1975.

(13) HOWELL, R.W. Smoking habits and laboratory tests. Lancet 2(7664): 152, July 18, 1970.

(14) ISAGER, H., HAGERUP, L. Relationship between cigarette smoking and high packed cell volume and haemoglobin levels. Scandinavian Journal of Haematology 8(4): 241-244, 1971.

(15) LEVINE, P.H. An acute effect of cigarette smoking on platelet function. A possible link between smoking and arterial thrombosis. Circulation 48(3): 619-623, September 1973.

(16) NOBLE, R.C., PENNY, B.B. Comparison of leukocyte count and function in smoking and nonsmoking young men. Infection and Immunity 12(3): 550-555, September 1975.

(17) OKUNO, T. Smoking and blood changes. Journal of the American Medical Association 225(11): 1387-1388, September 10, 1973.

(18) PARULKAR, V.G., BALSUBRAMANIAM, P., BARUA, M.J., BHATT, J.V. Smoking and differential leucocyte (W.B.C.) count. Journal of Postgraduate Medicine 21(2): 75-77, April 1975.

(*19*) SAGONE, A.L., JR., BALCERZAK, S.P. Smoking as a cause of erythrocytosis. Annals of Internal Medicine 82(4): 512-515, April 1975.

(*20*) SAGONE, A.L., JR., LAWRENCE, T., BALCERZAK, S.P. Effect of smoking on tissue oxygen supply. Blood 41(6): 845-851, June 1973.

(*21*) STEVENS, D.P., MACKAY, I.R. Increased carcinoembryonic antigen in heavy cigarette smokers. Lancet 2(7840): 1238-1239, December 1, 1973.

(*22*) 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, DHEW Publication No. (CDC) 78-8357, 1976, 657 pp.

Interactions with Radiation

In studies of humans, radiation exposures to the lungs of uranium miners who smoked cigarettes produced much more lung cancer than did similar exposures to nonsmoking miners (*3*). It is not known whether lung cancer induction by other forms of ionizing and nonionizing radiation is similarly conditioned by smoking nor whether other cancer sites are involved (*5*). Archer, et al. (*2*) also noted some evidence of decreased pulmonary function and excess mortality from chronic respiratory disease among uranium miners who smoked cigarettes compared with nonsmoking miners. However, the authors indicated that other substances in the mining environment, such as silica dust and diesel exhaust, may play a role in the onset of these conditions (*1*).

Experimental studies have shown some synergistic effects between ionizing radiation exposure and chemical carcinogens such as those contained in cigarette smoke (*6*). Results from a study of dogs at Battelle Northwest, sponsored by the Department of Energy, indicate that the effects of exposures to smoking and radiation are similar to those in uranium miners (*4*). It is suggested that when epidemiological studies of bladder and laryngeal cancer are undertaken, the possible synergistic effects of smoking and exposure to radiation be considered by appropriate study design and analysis of data.

Interactions with Radiation: References

(1) ARCHER, V.E., BRINTON, H.P., WAGONER, J.K. Pulmonary function of uranium miners. Health Physics 10(12): 1183-1194, 1964.

(2) ARCHER, V.E., GILLAM, J.D., WAGONER, J.K. Respiratory disease mortality among uranium miners. Annals of the New York Academy of Sciences 271: 280-293, May 28, 1976.

(3) ARCHER, V.E., WAGONER, J.K., LUNDIN, F.E., JR. Uranium mining and cigarette smoking effects on man. Journal of Occupational Medicine 15(3): 204-211, March 1973.

(4) FILIPY, R.E., STUART, B.O., PALMER, R.F., RAGAN, H.A., HACKETT, P.L. The effects of inhaled uranium mine air contaminants in beagle dogs. In: Karbe, E., Park, J. F. (Editors). Experimental Lung Cancer. Carcinogenesis and Bioassays. Berlin, Springer-Verlag, 1974, pp. 403-410.

(5) LUNDIN, F.E., JR. An exposure-time-response model for lung cancer mortality in uranium miners—effects of radiation exposure, age, and cigarette smoking. Presented at the Second Conference on Quantitative Aspects of Environmental Epidemiology, sponsored by the SIAM Institute for Mathematics and Society, June 26-30, 1978, 22 pp.

(6) MCGANDY, R.B., KENNEDY, A.R., TERZAGHI, M., LITTLE, J.B. Experimental respiratory carcinogenesis: Interaction between alpha radiation and benzo(a)pyrene in the hamster. In: Karbe, E., Park, J.F. (Editors). Experimental Lung Cancer. Carcinogenesis and Bioassays. Berlin, Springer-Verlag, 1974, pp. 485-491.