Introduction

The best approach to the medical problems of cigarette smoking can be summarized in two words, "DON'T SMOKE." However, there will always be some who disregard the best of advice and pursue this noxious habit, in spite of the high risk of disease and early death. This paper is directed to this stubborn group in the hope that it will reduce these risks and overcome some of the great losses to our economy resulting from the chronic inhalation of tobacco smoke.

Up to now, the main trends for reducing the health hazards of smoking have been along the lines of obtaining tobaccos which yield less tars and nicotine in the smoke and of improving the efficiency of filters in removing the suspect smoke constituents. Both of these approaches have serious practical limitations; tobaccos will always yield some tar and nicotine and an acceptable filter cannot be made 100 percent efficient to remove all undesirable smoke constituents. The best that can be hoped for is only a partial reduction in the potential hazards.

The various effects of tobacco smoke on the human body and the reduction of their morbidity are essentially medical problems —preventive medical problems. Yet very little medical research has been done for finding a simple means of increasing the resistance of the human organism to the irritating, toxic, and carcinogenic constituents of cigarette smoke and detoxicating these constituents in vivo. This physiological approach to the smoking problem has been virtually completely neglected.

The medical techniques of epidemiological research, which have paid off so handsomely in eliminating diseases such as diphtheria, poliomyelitis, and others, have not been applied to the smoking problem. These techniques involve increasing the resistance of susceptible individuals to attack by the causative agent. The probable reason that similar studies have not been undertaken in connection with smoking has been the lack, until recently, of a satisfactory rationale for the use of any single
antitoxic substance which would detoxify the absorbed smoke constituents and increase the body's resistance to the noxious effects of smoking. Needless to say, such a substance must also be completely harmless, without undesirable side effects, inexpensive, commonly available, and easily administered. Ascorbic acid or sodium ascorbate fills all these requirements, and the rationale for their use has been developed during the last decade through work on the evolutionary history and genetics of scurvy.

In 1966 it was shown that scurvy, which Medicine for over 60 years has regarded as a simple dietary disturbance, a vitamin-deficiency disease (Funk, 1912), is actually a genetic liver-enzyme disease called hypoascorbemia (Stone, 1966). This inherited malady, which afflicts 100 percent of the population, is due to humans carrying a defective gene for the synthesis of the liver-enzyme protein, L-gulonolactone oxidase (Stone, 1966a; Stone, 1967). This defective gene originated in a primate ancestor of Man, when it mutated some 60 million years ago (Stone, 1972). Most mammals possess the intact gene for this enzyme and are thus able to convert blood glucose into ascorbate at the high normal rate of many grams per day (Chatterjee, 1973). The mammals also possess a feedback mechanism for increasing ascorbate synthesis under stress (Subra-manian et al., 1973). During the course of mammalian evolution ascorbate has served as an antistressor and detoxicant required in large daily amounts for survival (Stone, 1965).

The most damaging effect of Medicine's long "love affair" with the vitamin C-deficiency disease hypothesis has been its orientation and insistence toward very low daily intakes of ascorbate and its reluctance to change this thinking. The present recommended daily allowance for ascorbate for an adult is 45 mg (Food and Nutrition Board, 1974), whereas a closely related mammal, a 70 kg goat, is capable of producing 13,300 mg of ascorbate in its liver to supply its daily need for this metabolite.

Another factor which has distorted medical thinking on the present incidence of scurvy is the fact that the classical signs of frank clinical scurvy used for diagnosing the disease are actually the terminal sequelae of the genetic defect. While these terminal signs may be of rare occurrence in the developed countries, the relatively a-symptomatic, less dramatic but nonetheless serious, chronic subclinical scurvy is our most widespread insidious disease (Stone, 1972a). Less than 10 mg of daily ascorbate is sufficient to prevent the appearance of these classical terminal signs, but a great deal more is required to fully correct this genetic defect. Calculations by several different methods indicate the corrective range of daily ascorbate intake to be about 2.5 to 15 g (Stone, 1974), when humans are regarded as mammalian mutants (Stone, 1974a).

Destruction of Ascorbate by Tobacco Smoke

The destructive action of tobacco smoke and smoking stress on the ascorbate levels in the body, both locally and systemically, has long been known and repeatedly demonstrated. In 1939, Strauss and Scheer (Strauss and Scheer, 1939) reported that 25 subjects given 200 mg ascorbic acid showed a constant and marked reduction in the urinary excretion of ascorbate following the smoking of one to three cigarettes. This indicated a destruction of the administered ascorbate by the smoke constituents.

In the period 1950-1959, F. Venulet and coworkers published a series of 15 papers on the effects of smoking on ascorbate metabolism (Andrzejewski, 1966). Venulet was Director of the Institute for General Pathology of the Medical Academy in Lodz, Poland. In 1951, Venulet and Moskwa (Venulet and Moskwa, 1951) confirmed the marked loss of ascorbate in both the blood and urine of animals exposed to cigarette smoke. In their 1952-53 studies (Venulet and Moskwa, 1952), on 60 medical students, the blood ascorbate was lower in the smokers than the nonsmokers.
Nonsmokers who volunteered to smoke only six to eight cigarettes a day had a significant drop in serum ascorbate by the third day. In studies on mice and frogs reported in 1953-54 (Venulet, 1953), Venulet again confirmed that tobacco smoke lowered the blood ascorbate and reduced its urinary excretion; the longer the exposure the greater the reduction. He also determined the ascorbate levels in the various organs and found the greatest loss in the adrenals, the spleen, the heart, and the lungs. He also stated his belief that "the loss of so fundamental a life factor as ascorbic acid plays a large role in the pathogenesis of different smoke damage." In 1955, Venulet and Danysz (Venulet and Danysz, 1955) published their findings on nursing mothers showing that the milk from nonsmoking mothers contained 5.9 mg percent of ascorbate while that from the smokers contained only 2.1 mg percent. In a brief review in English, published in 1966, Andrzejewski (Andrzejewski, 1966) outlined all the papers presented by Venulet and his group on this subject.

McCormick in 1952 (McCormick, 1952), in a paper on the chemotherapeutic properties of large doses of ascorbic acid, discussed its toxin-neutralizing properties and pointed out that there is a simultaneous proportional loss of ascorbate in this detoxicating process. He stated that laboratory and clinical tests showed "that the smoking of one cigarette neutralizes in the body approximately 25 mg of ascorbic acid, or the amount in one medium-sized orange." He suggested that this loss may account for the fact that the incidence of postoperative pneumonia is four times greater in habitual smokers than in non-smokers. He recommended that "the steady smoker, who is usually short on his dietary intake as well, requires much heavier therapeutic dosage of this vitamin than the non-smoker."

Bourquin and Musmanno, in both smoking tests on humans and in vitro tests on human blood, as reported in 1953 (Bourquin and Musmanno, 1953), showed a lowering of blood ascorbate levels by smoking and a destruction of the ascorbate in the blood by addition of nicotine. They also suggested an increased intake of ascorbic acid by habitual smokers.

In a 1955 report, Goyanna (Goyanna, 1955) examined 500 smokers and found that excretion of ascorbate in the urine was stopped by smoking 20 or more cigarettes, indicating destruction of the body's ascorbic acid. Calculations from in vitro tests wherein tobacco was mixed with ascorbic acid indicated that each cigarette was capable of destroying 2 mg of ascorbic acid. In concluding he remarked that smokers should elevate to a maximum the use of ascorbic acid, as "the salvation of the smoker may be in this vitamin."

Dietrich and Buchner in 1960 (Dietrich and Buchner, 1960) concluded as a result of tests on groups of smokers and non-smokers that smokers exhibit a vitamin C deficiency compared to nonsmokers. They advised all smokers to consume an abundance of ascorbic acid in order to be better able to prevent deficiency symptoms.

As a result of tests on 37 nonsmokers and 40 smokers, Durand, Audinot, and Frajdenrajch in 1962 (Durand et al., 1962) presented evidence that there was a pronounced drop in the blood plasma levels of ascorbate in smokers which was dependent upon the number of cigarettes smoked per day. They also found that the plasma ascorbate practically disappeared when the smokers were also alcoholics. They also conducted tests in which the subjects were given 1 g of ascorbic acid per day for periods during the test schedule. The ingestion of this ascorbic acid raised the plasma ascorbic acid levels. They concluded that there was a vitamin C deficiency in heavy smokers, which could be rectified by administration of ascorbic acid. The greater the number of cigarettes smoked the more ascorbic acid was required.

Calder, Curtis, and Fore in 1963 (Calder et al., 1963) reported the blood plasma ascorbate levels of smokers and non-
smokers subjected to short-term examinations. These subjects were not allowed to smoke from midnight to the start of the test and then smoked 12 to 25 cigarettes during the six-hour test period. Hourly tests of their blood plasma up to six hours showed no change in ascorbate levels. However, when they determined the ascorbate content of the blood plasma and leucocytes of 83 habitual moderate smokers (14 cigarettes or less a day) and 31 heavy smokers (15 or more cigarettes a day), they found significantly lower levels in both the blood plasma and leucocytes than in similar samples from a group of 91 nonsmokers.

In tests on 18 nonsmoking healthy soldiers and 22 smokers, Rupniewska in 1964 (Rupniewska, 1964) found significantly lower levels of fasting blood plasma ascorbate in the smokers. Four hours after administration of 500 mg of ascorbic acid this difference was no longer significant. The mean urinary excretion of ascorbate four hours after the 500 mg intake was 35.4 mg for the nonsmokers and 14.5 mg for the smokers, a highly significant difference. In her English summary, the author states that she "feels chronic vitamin C deficiency in smokers may explain at least partially one of the causes of early appearance of atheromatosis in smoking addicts."

In a later paper (1965), Rupniewska conducted tests on older men whose mean age was 73 years and mean duration of smoking 46 years. Urinary ascorbate excretion was measured after fasting and four hours after a 500 mg injection of ascorbic acid. "A decreased urinary excretion of ascorbic acid was found (about 60 percent) in the smokers evidencing a decreased store of this substance in the organism." She was unable to correlate these data with those of younger men in order to establish a quantitative relationship between years of smoking and ascorbic acid levels.

A 1968 study by Brook and Grimshaw (Brook and Grimshaw, 1968) shows that the plasma and leucocyte ascorbate is significantly lower in men than in women. In nonsmokers the plasma levels declined with age, while the leucocyte levels did not. Cigarette smoking was found to significantly lower both the blood plasma and the leucocyte ascorbate concentrations. Heavy smoking had the same effect on the blood plasma ascorbate as increasing the chronological age by some 40 years.

Pelletier, in tests on five smokers and five nonsmokers, as reported in 1968 (Pelletier, 1968), showed that the ascorbate levels of the blood and blood plasma of smokers was 40 percent to 45 percent of that of nonsmokers. On giving his subjects 2 g of ascorbic acid a day, in an attempt to "saturate" them, he found that after continued administration the blood levels stabilized at approximately the same values in both groups, but the urinary excretion of ascorbate in the smokers never reached the levels excreted by the nonsmokers. In tests on guinea pigs fed nicotine for one month in amounts equivalent to that consumed by heavy smokers, the ascorbate in the blood and several organs was lower compared to guinea pigs fed the same diet without the nicotine. The drop in tissue ascorbate was as follows: adrenals 49 percent, kidneys 50 percent, heart 47 percent, liver 34 percent, spleen 22 percent, brain 17 percent.

Guinea pig tests reported in 1967 (Evans et al., 1967), in which the animals were exposed to smoke for two 10-minute periods a day for a month, the smoking group gained weight less rapidly and the adrenal ascorbic acid was 30 percent lower than that of the controls.

**Detoxication with Ascorbate**

An important function of ascorbate in the mammalian organism is the detoxication of poisons, carcinogens, and toxins. The literature covering this is so voluminous that adequate treatment would require much more space than is available in this article.

In rats treated with the carcinogen, benzpyrene, a pathway of detoxication is through hydroxylation by liver microsomes and ascorbate is an activator of this hydroxylation (Degwitz and Staudinger, 1965). The rate is dependent upon the ascorbate levels, and in scorbatic
guinea pigs the detoxication rate is only 10 percent of that in guinea pigs receiving an adequate supply of ascorbate (Degwitz and Staudinger, 1965a). By nonenzymatic hydroxylation with ascorbate, the carcinogens benzpyrene, cho-lanthrene, methylcholanthrene, anthracene, and others are rendered non-carcinogenic (Warren, 1943).

Cyanide, a highly toxic constituent of tobacco smoke, is detoxified by ascorbate (Leibowitz and Guggenheim, 1938-39; Vauthey, 1951). Carbon monoxide, the noxious gas that kills people when automobile engines run without sufficient fresh air, is also present in high levels in tobacco smoke and is detoxified with ascorbate.

The detoxicating action of ascorbate on arsenic compounds, another smoke constituent, has a long history. Many papers were published in the early 1940's, the pre-penicillin days when the arseno-benzenes were popular medication in the therapy of venereal disease. Combination with ascorbic acid was widely used to counteract the toxic effects of these arsenic compounds (Bundesen et al., 1941; Delp, 1941; McChesney, 1945; and Marocco and Rigotti, 1962). Ascorbic acid has been used to combat industrial toxicity (Dainow, 1941), lead (Holmes, 1939; Marchmont-Robinson, 1941; and Gontzea, 1963), mercury (Marin, 1941; Chapman and Shafer, 1947; and Mokran-jac and Petrovic, 1964), and chromates (Samitz et al., 1962). It has also been used to reduce the toxicity of such diverse materials as strychnine (Dey, 1967), ozone (Mittler", 1958), sulfanilamide (Dainow, 1941a), nitrates (Krajesovics, 1964), salicylates (Pelner, 1943), phosphorus (Volynskii, 1960), and an azo dye carcinogen, 3'methyl-4-monomethylaminoazobenzene (Bobb, 1963). While this is only a small segment of the literature, it is clearly evident that ascorbate is a wide-spectrum detoxicant when used at the proper dosage.

In unpublished studies by the author on the toxic effects of massive inhalation of cigarette smoke by guinea pigs, it was found that animals with depleted ascorbate reserves were much more susceptible to these toxic effects than animals fed a normal diet. The smoking of six cigarettes a day proved quite deadly, killing the depleted guinea pigs in about five days while those on a normal diet survived for over 10 days. The smoke from six cigarettes a day for a 200-gram animal contains a massive dose of toxic materials; scaled up to a 70 kg body weight basis of an adult human it would be equivalent to the smoke from 2,100 cigarettes a day. Funds ran out before we could test the survival of guinea pigs treated with daily megadoses of ascorbate under this massive smoke poisoning.

Smoking and Bladder Cancer
Since 1931 tobacco tar inhalation has been suspected of causing bladder tumors (Roffo, 1931). The 1964 Report of the Surgeon General (1968) concluded that "Available data suggest an association between cigarette smoking and urinary bladder cancer in the male." Also in 1964 it was found that intermediate products of tryptophan metabolism induced cancer when placed in the bladder of mice (Boyland et al., 1964). In the next year, Kerr et al. (1965) showed that smokers tended to excrete in their urine more of these potentially carcinogenic intermediates, 3-hydroxyanthranilic acid (3-HOA) and 3-hydroxykynurene (3-HOK), than nonsmokers. Their studies suggested that cigarette smoking changes the normal metabolic pattern of tryptophan, leading to the accumulation of potentially carcinogenic intermediate metabolites in the urine.

In 1968, the group at Tulane University published a series of papers on the induction of bladder cancer by these tryptophan metabolites. They showed (Pipkin et al., 1968) that the spontaneous nonenzymatic oxidation of 3-HOA resulted in the formation of the carcinogenic "Compound IV," which induced bladder tumors in implantation experiments. This spontaneous oxidation and carcinogen formation could be completely prevented with ascorbate (Pipkin et al., 1967). In tests on bladder cancer patients, smokers and nonsmokers
(Schlegel et al., 1968), they reported that the urinary excretion of 3-HOA or 3-HOK was about the same in all groups, but the formation of the carcinogenic "Compound IV" was significantly greater in the urine of the bladder tumor patients than in the nonsmoker's urine, while the smoker's fell in between. Their most consistent observation was that the oral administration of 1 1/2 g of ascorbic acid daily completely prevented formation of carcinogenic "Compound IV" in all cases. They recommended the oral administration of high amounts of ascorbic acid, sufficient to significantly raise urinary levels, to prevent recurrence of bladder cancer. While they only discussed the prevention of recurrence, it would seem implicit from their work that if the smokers had sufficiently high levels of ascorbate in their urine, the bladder cancer would not have appeared in the first place.

Smoker's Scurvy

The chronic destruction of ascorbate in smokers aggravates the chronic subclinical scurvy already present due to inadequate daily ascorbate intakes. This severe chronic subclinical scurvy brought about by the biochemical insults of smoking has been termed "Smoker's Scurvy." In this state the classical terminal symptoms of frank clinical scurvy may not be manifest, but the biochemical scorbatic effects are present. A similar scorbatic state without the clinical signs of scurvy was noted by Thiele in 1964 (Thiele, 1964) in chronic benzene poisoning and by Marchmont-Robinson in chronic lead poisoning (Marchmont-Robinson, 1941).

In this depleted state there is lowered resistance to disease, impaired detox-ication processes, increased capillary fragility, and tendency to hemorrhaging, decreased phagocytosis, abnormal immunity responses, and a marked lowering in the reaction rates of many cellular and blood enzymes. It is not very surprising that there are so many adverse effects of inadequate ascorbate intakes because this ubiquitous metabolite is involved in so many important physiological mechanisms in the living process. Normality can be easily restored by the mere repletion of the ascorbate.

Discussion

The evidence is overwhelming that smoking destroys the ascorbate in the body. Also that ascorbate at high levels is an antistressor, anticarcinogen, and de-toxicant. Further evidence for its use in the prevention and treatment of cancer was given by Burk and coworkers at the National Cancer Institute with the findings that high levels of ascorbate were toxic and lethal to cancer cells and harmless to normal cells (Benade et al., 1969). The work of Pauling and Cameron (Cameron and Pauling, 1973) on ascor-bate's inhibitory action on the cellular enzyme, hyaluronidase, establishes the rationale for its use in inhibiting carcinogenesis and metastasis. Cameron and Pauling (1974) and Cameron and Campbell (1974) have provided both the rationale and clinical tests for this mega-scorbic cancer therapy. Additional data for the megascorbutic therapy of cancer is obtained from the natural history of ascorbate (Stone, 1974b) and also for its use in leukemia (Stone, 1974c). This whole subject of the effect of mega-scorbics in human health has recently been reviewed (Stone, 1972b).

All this evidence can be used to formulate a simple and inexpensive megascorbutic preventive medical regime for the practical use by smokers to inhibit or delay or even possibly prevent the eventual disease consequences of the chronic exposure to high concentrations of the irritating and toxic constituents of tobacco smoke.

The regime would comprise the full correction of the genetic disease, hypo-ascorbemia, by the daily intake of sufficient ascorbate for conditions of little stress. This would be the same intake as used by nonsmokers plus 3 to 5 g additional for each pack of cigarettes smoked. Because of human individual variations, the estimated daily basal intake of ascorbate under conditions of little stress may vary within the range of 5 g to 20 g per day. These are initial
suggested figures, which may be revised with additional test information.

The use of powdered ascorbate dissolved in foods and drink is the most convenient means of ingestion rather than swallowing a myriad of tablets. The strongly sour-tasting ascorbic acid is limited to certain acidic foods and drinks, while the relatively tasteless sodium ascorbate can be added to all foods and drinks in multigram amounts without noticeable change in flavor. The ascorbate is added to the foodstuffs immediately before serving.

Summary
A simple, inexpensive megascorbic prophylactic regime is developed to supply a normal mammalian metabolite at the required daily dosage to increase the smoker's resistance to the stresses of smoking and to delay the onset or possibly prevent the various smoking pathologies. This essential metabolite, ascorbate, is well documented as an antistressor, anticarcinogen detoxicating agent and a means for preventing bladder cancers in smokers. Smoking destroys the ascorbate normally present in the body which causes "Smoker's Scurvy." This regime not only replaces this destroyed ascorbate and corrects the "Smoker's Scurvy," but also corrects the serious human genetic defect, hypoascorbemia. Three to 5 g of ascorbate for each pack of cigarettes smoked is the estimated intake in addition to the basal corrective intake (nonsmokers) in the range of 5 to 20 g ascorbate per day.

2 Ascorbic acid or sodium ascorbate powder should be available in drug or "health food" stores.

REFERENCES


