M. Paul, P. Greenlaw, F. K. Goodwin, P. Skolnick, *Life Sci.* **22**, 1893 (1978); H. Möhler, P. Polc, R. Cumin, L. Pieri, R. Kettler, *Nature (London)* **278**, 563 (1979); M. Nielsen, O. Gredal, C. Braestrup, *Life Sci.* **25**, 679 (1979); G. D. Colello, D. M. Hockenberry, H. B. Bosmann, S. Fuchs, K. Folkers, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 6319 (1978); J. C. Nixon and J. H. Woolf, *Pharmacologist* **21**, 242 (1979).
4. P. J. Marangos, S. M. Paul, A. M. Parma, F. K. Goodwin, P. Skolnick, *Life Sci.* **24**, 851 (1979).
5. P. Kleihues, K. Kobayashi, K. A. Hossman, *J. Neurochem.* **23**, 417 (1974).
6. M. C. Sun, H. McIlwain, I. Pull, *J. Neurobiol.* **7**, 109 (1977); I. Pull and H. McIlwain, *Biochem. J.* **130**, 975 (1972).
7. L. O. Randall and B. Kappel, in *The Benzodiazepines*, S. Garattini, E. Mussini, L. O. Randall, Eds. (Raven, New York, 1973), p. 27.
8. P. Skolnick, P. J. Syapin, B. A. Paugh, V. Moncada, P. J. Marangos, S. M. Paul, *Proc. Natl. Acad. Sci. U.S.A.* **76**, 1515 (1979).
9. J. F. MacDonald, J. L. Barker, S. M. Paul, P. J. Marangos, P. Skolnick, *Science* **205**, 715 (1979).
10. P. Slater and D. A. Longman, *Life Sci.* **25**, 1963 (1979).
11. J. Crawley and F. K. Goodwin, *Pharmacol. Biochem. Behav.* **13**, 167 (1980).
12. Exploratory and locomotor activity was significantly increased by intraperitoneal administration of clonazepam (0.1 to 1.0 mg/kg), diazepam (0.5 to 5.0 mg/kg), and chlordiazepoxide (5.0 to 20.0 mg/kg). These doses were well below the sedative range for these benzodiazepines, and followed the rank-order potency for benzodiazepine receptor binding and for clinical efficacy: clonazepam > diazepam > chlordiazepoxide. No changes in exploratory or locomotor activity were seen with the peripherally binding RO5-4864, nor with clorgyline, butriptyline, or chlorpromazine. Although locomotor activity was correlated significantly with exploratory activity, the increases observed after benzodiazepine treatment were not observed when mice were tested in a bare, undifferentiated cage. This suggests that the locomotor effect is related to the properties of a two-chambered apparatus, rather than being a generalized motor effect.
13. C. Aron, P. Simon, C. Larousse, J. R. Boissier, *Neuropharmacology* **10**, 459 (1971); A. J. Christmas and D. R. Maxwell, *ibid.* **9**, 17 (1970); L. de Angelis and S. E. File, *Psychopharmacology* **64**, 127 (1979); S. E. File and J. R. G. Hyde, *Pharmacol. Biochem. Behav.* **11**, 65 (1979); I. Geller and J. Seifter, *Psychopharmacologia* **1**, 482 (1960); A. S. Lippa, P. A. Nash, E. N. Greenblatt, in *Anxiolytics*, S. Fielding and H. Lal, Eds. (Futura, Mount Kisco, N.Y., 1979), p. 41; J. B. Malick, *Pharmacol. Biochem. Behav.* **8**, 497 (1978); D. L. Margules and L. Stein, *Psychopharmacology* **13**, 74 (1968); L. Valzelli, in *The Benzodiazepines*, S. Garattini, E. Mussini, L. O. Randall, Eds. (Raven, New York, 1973), p. 405; J. R. Vogel, B. Beer, D. E. Clody, *Psychopharmacologia* **21**, 1 (1971).
14. The number of transitions per 10-minute session for diazepam (2 mg/kg) plus various doses of 2-deoxyinosine were: 50 mg/kg, 71.8 ± 9.7; 100 mg/kg, 43.0 ± 9.3 ($P < .05$); and 200 mg/kg, 40.0 ± 12.8 ($P < .05$). For diazepam (2 mg/kg) plus 2-deoxyguanosine, the values were: 50 mg/kg, 46.5 ± 6.1 ($P < .05$); 100 mg/kg, 50.0 ± 6.5 ($P < .05$); and 200 mg/kg, 11.0 ± 6.3 ($P < .01$). P values were determined by comparison with diazepam (2 mg/kg) plus saline.
15. The number of transitions per 10-minute session were: saline, 35.0 ± 5.7; inosine (500 mg/kg), 5.8 ± 1.6 ($P < .005$); and inosine (1000 mg/kg), 7.5 ± 1.5 ($P < .005$).
16. None of the values of transitions per 10-minute session were significantly different from values for saline controls for the following drug doses: inosine 2, 10, 50, 100, 200, and 300 mg/kg; 2-deoxyinosine 50, 100, and 200 mg/kg; 2-deoxyguanosine 50, 100, and 200 mg/kg; and 7-methylinosine 50, 100, and 200 mg/kg.
17. C. Braestrup and R. F. Squires, *Proc. Natl. Acad. Sci. U.S.A.* **74**, 3805 (1977).
18. The number of transitions per 10-minute session for diazepam (2 mg/kg) plus various doses of 7-methylinosine were: 50 mg/kg, 66.3 ± 5.8; 100 mg/kg, 57.6 ± 5.6; 200 mg/kg, 60.6 ± 6.2. None of these were significantly different from the values for diazepam (2 mg/kg) plus saline.
19. M. K. Ticku and T. Burch, *Biochem. Pharmacol.* **29**, 1217 (1980).
20. P. J. Marangos, S. M. Paul, A. M. Parma, P. Skolnick, *Biochem. Pharmacol.*, in press.
21. F. Leeb-Lundburg, C. Napias, R. W. Olsen, *Neurosci. Abstr.* **5**, 563 (1979).

12 August 1980; revised 4 November 1980

Tyrosine Administration Decreases Vulnerability to Ventricular Fibrillation in the Normal Canine Heart

Abstract. *Intravenous infusion of tyrosine (1, 2, or 4 milligrams per kilogram) for 20 to 30 minutes caused dose-dependent increases in the ventricular fibrillation threshold in normal dogs. Administration of valine, a neutral amino acid that competes with tyrosine for uptake at the blood-brain barrier, in a dose equimolar to the most effective dose of tyrosine, slightly decreased the ventricular fibrillation threshold when given alone and significantly blocked elevation of the ventricular fibrillation threshold after tyrosine infusion. Hence, tyrosine, presumably acting in the central nervous system, can protect against certain ventricular arrhythmias.*

The sympathetic nervous system influences cardiac susceptibility to ventricular arrhythmias (*1*). Augmented sympathetic activity, whether elicited by electrical stimulation of the hypothalamus (*2*) or of the stellate ganglia (*3*), predisposes the heart to diverse arrhythmias. Conversely, reduction of sympathetic neural outflow, achieved either surgically (*4*) or pharmacologically (*5*), protects against arrhythmias. Cabot *et al.* (*6*) demonstrated that the raphe nucleus inhibits sympathetic outflow in the pigeon. There is evidence that treatments that increase the release or postsynaptic effects of serotonin, the transmitter of raphe nucleus neurons (*7*), diminish cardiovascular sympathetic outflow (*8*). Blatt *et al.* (*9*) showed that agents that produce an increase in brain serotonin protect the heart against ventricular fibrillation. Rabinowitz and Lown (*10*) found that administration of L-tryptophan, precursor to serotonin, decreases cardiac vulnerability to ventricular fibrillation (VF), probably by increasing brain serotonin release (*11*) and thereby reducing sympathetic neural outflow.

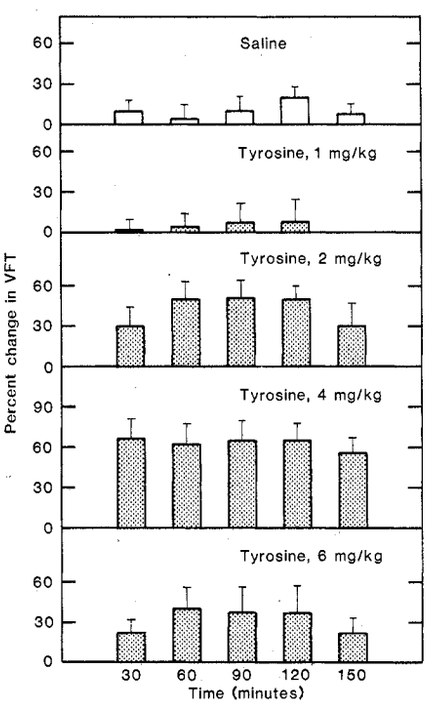

Fig. 1. Effect of tyrosine on ventricular fibrillation threshold (*VFT*). Control VF threshold's were obtained for each dog. The dogs then received intravenous doses of tyrosine (1 mg/kg, $N = 5$; 2 mg/kg, $N = 6$; 4 mg/kg, $N = 6$; or 6 mg/kg, $N = 6$) or vehicle (saline, $N = 8$), and the VF threshold was determined at 30-minute intervals. Percent changes in VF threshold after tyrosine or saline administration are graphed as means and standard errors of the means.

Enhanced central catecholaminergic activity can also diminish sympathetic outflow (*12*). Drugs such as clonidine and α-methyldopa, which presumably act by stimulating α-noradrenergic receptors in the brainstem, decrease blood pressure in hypertensive animals and humans (*13*); moreover, clonidine also decreases vulnerability to VF (*14*) and suppresses digitalis-induced arrhythmias (*15*).

Norepinephrine synthesis (*16*), and probably release (*17*), in the brain can be accelerated by administering its precursor, L-tyrosine, thereby augmenting saturation of the rate-limiting biosynthetic enzyme tyrosine hydroxylase. Tyrosine administration increases brain levels of the norepinephrine metabolite methoxyhydroxyphenylglycol sulfate and decreases blood pressure in spontaneously hypertensive rats (*18*). We hypothesized that administration of tyrosine to healthy dogs, by increasing central catecholaminergic activity and thereby diminishing sympathetic neural outflow to the heart, would raise the threshold of vulnerability and protect against VF.

At least 4 days after arriving from the supplier, healthy mongrel dogs of either sex, weighing 9 to 22 kg, were anesthetized with α-chloralose (100 mg/kg) with additional drug (50 mg/kg) administered as needed to maintain a constant level of anesthesia. Experiments were initiated between 0830 and 0930 hours, at least 30 minutes after induction of anesthesia. The animals were ventilated with a mixture of room air and 40 percent oxygen so that arterial oxygen tension was about 100 mm-Hg. Arterial pH was maintained

0036-8075/81/0213-0727$00.50/0

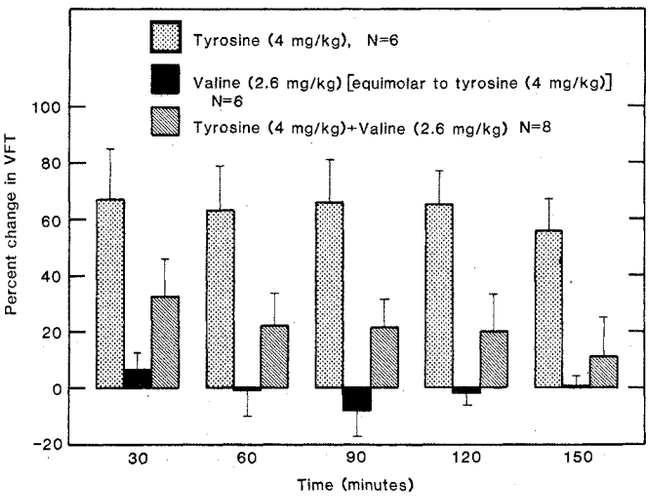

Fig. 2. Effect of amino acid administration on the change in myocardial vulnerability. Dogs received tyrosine (4 mg/kg) by intravenous infusion, an equimolar dose of valine, or both amino acids. The threshold electrical current needed to cause ventricular fibrillation (*VFT*) was measured at 30-minute intervals after infusion. Each dog received one of the three treatments. Vertical lines indicate standard errors of the means. $^*P < .01$, compared to corresponding tyrosine-treated group.

between 7.39 and 7.49 by adjusting the depth and frequency of respiration. A polyethylene catheter was inserted into a femoral vein for administration of anesthetics and amino acids. Blood pressure was monitored with a Statham P23dB pressure transducer connected to a polyethylene catheter that was inserted into a femoral artery. The VF threshold was determined by a method previously described (*19*). Briefly, the heart was paced at 180 beats per minute during threshold testing. The VF threshold was determined by scanning inward in 5-msec decrements from the time of inscription of the apex of the surface electrocardiogram T wave to the border of the refractory period; a single 5-msec stimulus with an initial current of 8 mA was used. If VF was not induced by this stimulus intensity, the current was increased in 2-mA steps, and scanning was continued until VF resulted. The lowest stimulus that elicited VF was taken to be the VF threshold. Termination of VF was achieved with a direct current discharge (50 to 150 W-sec) from a Lown Cardioverter through copper paddles secured across the thorax; termination was usually accomplished within 3 seconds after the onset of arrhythmia.

Each dog served as its own control. At the start of the experiment, at least two VF thresholds were determined, and the control value was defined as the mean of these measurements. Starting one-half hour after the completion of amino acid infusion, we determined VF thresholds at 30-minute intervals for 150 minutes. Tyrosine, dissolved in saline (5 to 10 ml per kilogram of body weight), was administered intravenously for 20 to 30 minutes by means of an infusion pump. Branched-chain amino acids inhibit the uptake of tyrosine into the brain by competition for the large neutral amino acid transport system within the blood-brain barrier (*20*). As a means of determining whether the changes in the VF threshold after tyrosine administration resulted from a central rather than a peripheral action, tyrosine was also administered with valine. Valine, a branched-chain amino acid, when given alone, significantly decreases brain tyrosine (for example, from 13.5 ± 0.6 to 10.7 ± 0.3 μg/g in rats receiving valine at a dose of 130 mg/kg) (*21*). Since VF threshold values vary among animals, changes were expressed as percent deviations from the control values. Statistical analysis included analysis of variance and an unpaired *t*-test.

Tyrosine administration induced a dose-related increase in the VF threshold (Fig. 1). The rise in the fibrillation threshold was dose-dependent in the range 1 to 4 mg/kg; at 6 mg/kg, the effect was smaller. There was a 65 percent average rise in VF threshold after a tyrosine dose of 4 mg/kg. Neither heart rate nor blood pressure was consistently altered by any tyrosine dose. The threshold for repetitive extrasystoles, examined in dogs receiving the amino acid in doses of 4 mg/kg, was increased after tyrosine administration by about the same proportion (65 percent) as the VF threshold. Valine alone, in a dose equimolar to that of tyrosine at 4 mg/kg, did not affect the VF threshold significantly (Fig. 2). However, when given with tyrosine, valine significantly diminished the increase in the VF threshold that follows tyrosine administration.

Although tyrosine is also a precursor for other substances, such as thyroid hormone, melanin, homogentisic acid, and a variety of polypeptides, the only biologically active compounds whose synthesis from tyrosine has been shown to be dependent on plasma or tissue tyrosine concentrations are the catecholamine neurotransmitters. Tyrosine is coverted to L-dopa by tyrosine hydroxylase; L-dopa is then decarboxylated to form dopamine, which is further transformed to norepinephrine by the enzyme dopamine-β-hydroxylase. Treatments that enhance the release or postsynaptic effects of norepinephrine in the brainstem diminish sympathetic neural outflow via alpha receptors and thereby reduce blood pressure (*22*). However, exogenous tyrosine might also be expected to enhance sympathetically mediated mechanisms by accelerating catecholamine synthesis in, and release from, postganglionic sympathetic neurons and adrenal medulla (*23*). The resulting augmentation in peripheral (that is, circulating or synaptic) epinephrine and norepinephrine might lower the VF threshold substantially by direct action on the myocardium (*24*). The opposite effect was observed; tyrosine administration significantly increased the VF threshold, an indication that the amino acid acted primarily on central catecholaminergic neurons in our dogs. This central action of tyrosine would be expected to annul the opposite peripheral effects of the amino acid, since it would probably decrease the firing frequency of postganglionic sympathetic neurons and thus suppress their responsiveness to tyrosine.

Our finding that simultaneously administered valine blocks the effect of tyrosine supports the hypothesis that the action of tyrosine is central rather than peripheral. Valine is not directly involved in catecholamine biosynthesis or metabolism; it impedes the transport of circulating tyrosine across the blood-brain barrier. That valine can reduce the tyrosine-induced rise in the VF threshold supports the thesis that tyrosine must reach catecholaminergic brain neurons to affect cardiac vulnerability to VF. The absence of changes in heart rate and blood pressure during tyrosine administration suggests that distinct brain mechanisms selectively control the sympathetic neural outflow to the heart and also that the cardiac sympathetic nerves have differentiated sites of action.

Our findings, and the earlier reports that tryptophan (*10*) and other serotoninergic compounds (*9*) increase the vulnerability threshold, provide a novel approach to therapy for arrhythmias and specifically for ventricular fibrillation. Precursor therapy (*25*) to modify the

excitable properties of the heart may be of value in preventing sudden cardiac death, which usually results from ventricular fibrillation.

NEAL A. SCOTT, REGIS A. DESILVA
BERNARD LOWN
RICHARD J. WURTMAN
Cardiovascular Research Laboratories, Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts 02115 and *Laboratory of Neuroendocrine Regulation, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge 02139*

References and Notes

1. R. Hunt, *Am. J. Physiol.* **2**, 395 (1899); D. L. Pearle and R. A. Gillis, *Am. J. Cardiol.* **34**, 704 (1974); B. Lown *et al.*, *ibid.* **39**, 890 (1977).
2. R. L. Verrier, A. Calvert, B. Lown, *Am. J. Physiol.* **228**, 923 (1975).
3. B. R. Kliks, M. J. Burgess, J. A. Abildskov, *Am. J. Cardiol.* **36**, 45 (1975); B. S. Kolman, R. L. Verrier, B. Lown, *Circulation* **52**, 578 (1975).
4. A. S. Harris, A. Estandia, R. F. Tillotson, *Am. J. Physiol.* **165**, 505 (1951).
5. S. H. Rabinowitz, R. L. Verrier, B. Lown, *Circulation* **53**, 622 (1976); G. J. Kelliher and J. Roberts, *Am. Heart J.* **87**, 458 (1974).
6. J. B. Cabot, J. M. Wild, D. H. Cohen, *Science* **203**, 184 (1979).
7. A. Dahlstrom and K. Fuxe, *Acta Physiol. Scand. Suppl.* **232**, 1 (1964).
8. T. Baum and A. T. Shropshire, *Neuropharmacology* **14**, 227 (1975).
9. C. M. Blatt, S. H. Rabinowitz, B. Lown, *Circ. Res.* **44**, 723 (1979).
10. S. H. Rabinowitz and B. Lown, *Am. J. Cardiol.* **41**, 516 (1978).
11. J. D. Fernstrom and R. J. Wurtman, *Science* **173**, 149 (1971).
12. J. H. Coote and V. H. Macleod, *J. Physiol. (London)* **241**, 453 (1974).
13. P. A. Van Zwieten, *Prog. Pharmacol.* **1**, 1 (1975); H. Schmitt and H. Schmitt, *Eur. J. Pharmacol.* **6**, 8 (1969).
14. F. A. Rotenberg, R. L. Verrier, B. Lown, M. J. Sole, *Eur. J. Pharmacol.* **47**, 71 (1978).
15. R. A. Gillis, R. A. Dionne, F. G. Standgert, *J. Pharmacol. Exp. Ther.* **182**, 218 (1972).
16. C. J. Gibson and R. J. Wurtman, *Biochem. Pharmacol.* **26**, 1137 (1977).
17. ———, *Life Sci.* **22**, 1399 (1978).
18. A. F. Sved, J. D. Fernstrom, R. J. Wurtman, *Proc. Natl. Acad. Sci. U.S.A.* **76**, 3511 (1979).
19. R. J. Matta, R. L. Verrier, B. Lown, *Am. J. Physiol.* **230**, 1469 (1976).
20. W. M. Pardridge and W. H. Oldendorf, *J. Neural Transm. Suppl.* **15**, 43 (1979); *Biochim. Biophys. Acta* **401**, 128 (1975); *J. Neurochem.* **28**, 5 (1977); W. M. Pardridge, in *Nutrition and the Brain*, R. J. Wurtman and J. J. Wurtman, Eds. (Raven, New York, 1977), vol. 1, p. 141.
21. J. Agharanya, personal communication.
22. J. J. Buccafusco and H. E. Brezenoff, *Neuropharmacology* **16**, 775 (1977).
23. J. C. Agharanya and R. J. Wurtman, *Neurosci. Abstr.* **5**, 85 (1979).
24. S. Han, P. Garcia de Jalon, G. K. Moe, *Circ. Res.* **14**, 516 (1964).
25. J. H. Growdon, E. L. Cohen, R. J. Wurtman, *Ann. Intern. Med.* **86**, 337 (1977).
26. We thank our technical assistants, S. Carr and J. Young, and our engineer, J. Kiely. We also thank R. Verrier for his technical advice, W. Rand for his advice on statistical analysis of the data, and M. Cashman for secretarial assistance. Supported in part by NIH grants AM-14228 and 21384-08 and by grants (to N.A.S.) from the Sandoz Foundation, the Whitaker Health Sciences Fund, and the Lown Cardiovascular Research Foundation.

7 July 1980; revised 6 October 1980

Cigarette Smoking in the 1970's: The Impact of the Antismoking Campaign on Consumption

Abstract. *Per capita cigarette consumption has declined annually since 1973. This downturn represents a new nonsmoking ethos, which is also reflected in the legislative successes of the nonsmokers' rights movement. Time series regression analysis of cigarette demand suggests that, in the absence of the antismoking campaign, consumption would have exceeded its 1978 level by more than a third.*

Adult per capita cigarette consumption in the United States rose throughout the century until 1964, the year of the Surgeon General's report on smoking and health (*1-3*) (Fig. 1). Continued increases would have been expected in the absence of an antismoking campaign, especially with more women smoking (*4*) and decreases in the nicotine content of cigarettes. According to the nicotine regulation hypothesis, the latter should have increased the typical smoker's cigarette consumption (*5*). Yet per capita consumption fell in 1968 through 1970; this was the first time that it had dropped for more than two consecutive years. Although causality has not been conclusively established, numerous investigators have attributed the decreases to antismoking messages carried on television and radio as a result of the Federal Communication Commission's Fairness Doctrine. Several downturns occurred earlier in years with specific major antismoking "events" such as the first attention in the popular press in 1953 and 1954 to the link between smoking and illness and the Surgeon General's 1964 report (*3, 6*).

Since 1973 per capita cigarette consumption has fallen approximately 1 percent per year. This downturn cannot be associated with discrete antismoking events, but it has occurred during a decade in which an active nonsmokers' rights movement has developed.

To assess the effect of the antismoking campaign on cigarette consumption and explore the relation between the nonsmokers' rights movement and the decreases in consumption, I have revised my earlier time series analysis of adult per capita demand for cigarettes (*7*). As in other studies (*6*), I account for the effects of smoking-and-health publicity by inclusion in a demand regression equation of binary (dummy) variables with a value of 1 in years of adverse publicity and 0 in other years. In order to examine the decline in consumption since 1973, I include a measure of the effectiveness of the nonsmokers' rights movement, namely, the percentage in a given year of the adult population residing in states with laws that restrict smoking in public places.

A least-squares regression for the years 1947 to 1978 yields the demand equation (*8*)

$$C_t = -4621.2 - 16.36{*}P_t + 0.6896{*}C_{t-1} + 1824.7{*}Y_t - 131.39{**}D53_t - 305.41{*}D54_t - 195.25{*}D64_t - 110.05{***}D68_t - 226.72{*}D69_t - 79.3D70_t - 837.81{*}L_t$$

$$[{*}P < .01, \ {**}P < .05, \ {***}P < .10;$$

$$F(10, 21) = 76.56; \ R^2 = .9733]$$

where C_t is adult per capita cigarette consumption in year t (mean = 4055.8); C_{t-1} is lagged consumption, which captures the effect of habit; P_t is relative real cigarette price in year t (index with $P_{1967} = 100$) and assesses price responsiveness of consumption; Y_t is the natural logarithm of the last two digits of year t and reflects increases in the smoking population due to the diffusion of the behavior, particularly among women, and increases in smokers' consumption levels (*9*); $D53_t$ and so forth are the dummy variables for 1953, 1964, 1968, 1969, and 1970, which provide estimates of the impact on consumption of antismoking activities during these years; $D54_t$ is 0 before 1954 and $0.5^{(t-1954)}$ in 1954 and on, a dummy for the second year of smoking and health publicity, which equals 1 in 1954 and has a continuing, though rapidly diminishing, additional effect that reflects additional publicity through the mid-1950's; and L_t is the state law population measure in year t.

The habit factor C_{t-1} indicates the persistence of close to 70 percent of the preceding year's per capita consumption, with other factors held constant. The P_t coefficient implies a price elasticity of demand of -0.37 at the means of dependent and independent variables. Estimates of elasticity range from close to 0 to -1, with a consensus estimate of -0.45 to -0.5 (*10*). However, some investigators suggest that either elasticity has been falling or it has been systematically overestimated (*11, 12*).

0036-8075/81/0213-0729$00.50/0