developed. Both methods yielded essentially the same results as shown in Table 1.

Secondary amines all have been found to be inactive or almost inactive by contrast to the above pyridine derivatives, which are tertiary amines.

Doses of from 0.001 to 0.01 γ/ml of Compound 63 were active; 0.02 γ/ml prevented any response of the intestinal strip to histamine diphosphate in doses of from 0.2 to 1.0 γ/ml, or restored normal tonus when given after histamine. To abolish or prevent an acetylcholine contraction with Compound 63 a dose one hundred times greater is necessary in contrast to an antispasmodic like Trasentine, which is one hundred times more active against acetylcholine than against histamine.

The activity *in vivo* was tested in guinea pigs exposed for 5 minutes to a histamine-aerosol-air-stream (0.139 γ/ml) of about 18.6 l.p.m., according to the method of Kallós and Pagel,[13] Halpern (*l.c.*). Our animals developed severe asthma 35 to 90 seconds after exposure and went into a convulsive shock-like condition in 1½ to 3½ minutes. As criteria of activity, both the duration of protection and the doses necessary to confer protection were chosen.

In this test, repeated at hourly intervals, appearance of convulsions could be delayed in most animals from 2 to 6 hours if the animals were treated 15 minutes before the first exposure by 0.1 mg/kg of Compound 63.

Compound 63 was about twice as active as Compound *IV* and ten times more active than Compound 106, and one hundred times more active than Compound 74. 0.1 mg/kg of Compound 63 administered subcutaneously fifteen minutes before exposure protected the majority of animals for two to six hours from developing convulsions. The activity by mouth of the same compound was only slightly less pronounced than by subcutaneous injection. A group of typical experiments is shown in Table 2.

TABLE 2

HISTAMINE SHOCK—NUMBER OF ANIMALS PROTECTED BY DIFFERENT DOSES OF N,N-DIMETHYL-N¹-BENZYL-N¹-(α PYRIDYL) ETHYLENEDIAMINE HCL FOR 0 TO OVER 6 HOURS

Mg/kg	Hours of protection								Total number animals used
	0	0–1	1–2	2–3	3–4	4–5	5–6	over 6	
0.1	2	3	5	5	2		1	4	22
0.2		1	1		1	4	3		10
0.5	1	4	2	3	3	7	4		24
1.0		1		1	1	7	6	7	23
5.0					3	9	10	15	37
10.0							8	2	10
									(126)

Guinea pigs sensitized with horse serum in the customary way were treated subcutaneously with antihistaminic substances 21 days later, and 10 minutes before they received an intracardial injection of 0.5 ml horse serum. The smallest dose of Compound 63 which protected guinea pigs from acute anaphylactic shock was 0.1 mg/kg. Table 3 shows the effect of various dosages, and demonstrates that with 1.0 mg/kg complete protection is obtained. In these experiments also, Compound 63 was about twice as active as the corresponding phenyl compound *IV*.

TABLE 3

ANAPHYLACTIC SERUM SHOCK IN GUINEA PIGS—PROTECTION WITH 63

#	Dose 63 mg/kg	Serum re-injection	Death
1	None	Shock in 1 min.	In 2 mins.
2	None	" " " "	" " "
3	0.1	" " " "	" 24 hours
4	0.1	No shock, weak after 10 min.	Survived
5	0.5	" "	"
6	0.5	" " , convulsions after 15 mins.	In 24 hours
7	0.5	" "	Survived
8	1.0	" " , weak after 25 mins.	"
9	1.0	" "	"
10	1.0	" "	"
11	1.0	" "	"
12	1.0	" "	"

The conclusion is reached that a close relationship exists between the antihistaminic activity demonstrated *in vitro* and *in vivo* and the antianaphylactic property of Compound 63. Reports on other pharmacological activities of Compound 63 are in press, and a study on the tolerance and therapeutic activity in patients suffering from allergic diseases is under way.

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[13] P. Kallós and W. Pagel, *Act. Med. Scandiv.*, 91: 292, 1937.

THE ROLE OF NICOTINE IN THE CIGARETTE HABIT

THE physiological and psychological basis for the tobacco habit has been the subject of considerable speculation. Variously suggested factors include the following: nicotine; optical perception of the smoke; fire worship; agreeable smell and taste; mechanical manipulation of cigar or cigarette somewhat resembling the influence of the nipple on the infant; pleasurable irritation of the laryngeal and tracheal sensory branches of the pneumogastric nerve; relief of tension; stimulation; sociability; gives people something to do; permits one to do nothing, gracefully; produces a rise in blood sugar; satisfies a desire or craving; one becomes used to combatting with nicotine hunger and thirst, joy and pain, heat and cold, irritation and languidness.

To prove or disprove or even to debate the merits of each of these suggestions individually is quite beyond the scope of our intentions, and we simply wish to record some observations that we have made on the role of nicotine in the cigarette habit.

Of particular interest in this connection are the recent observations of Johnston[1] on the comparison of the effects of smoking with those of hypodermically injected nicotine. Whereas smokers almost invariably thought the sensation (following nicotine injection) pleasant and, given an adequate dose, were disinclined for a smoke for some time thereafter, non-smokers usually termed it "queer." Johnston gave himself 80 hypodermic doses of nicotine at the rate of 3 to 4 a day with some smoking; after this course he preferred a hypodermic injection of 1.3 mg of nicotine to inhaling a cigarette, and feelings of deprivation were experienced when the injections were discontinued.

Recently we have had the opportunity to make observations on the role of nicotine in the tobacco smoking habit, using a somewhat different approach. Having been furnished with an adequate amount of tobacco naturally low in nicotine,[2] the tobacco was divided into two lots. One lot was treated with sufficient nicotine in the form of nicotine malate to give a final nicotine content of about 2 per cent. A casing solution consisting of 3.5 pounds of glycerine and 2.4 pounds of invert sugar per 100 pounds of tobacco was then sprayed on each lot following which each lot was made into cigarettes. Subsequent analysis for nicotine with silicotungstic acid according to the A.O.A.C.[3] showed that the low nicotine cigarettes contained 0.23 per cent. nicotine, the cigarettes to which nicotine had been added 2.08 per cent. nicotine. Smoke from these cigarettes collected by the procedure described by Bradford, Harlan and Hanmer[4] and analyzed for nicotine by the silicotungstic acid method assayed 0.34 mg nicotine per cigarette for the low nicotine cigarettes and 1.96 mg per cigarette for the ones to which nicotine had been added.

Twenty-four habitual cigarette smokers (all inhalers) ranging in age from 22 to 50 years were selected, each of whom felt that he could not easily forego the habit. Throughout the experiment each subject kept a daily record of the number of cigarettes smoked. For the first month, the subjects smoked their accustomed brands in order that a record of their normal smoking habits might be obtained. Following this each was given to smoke at least 2 cartons of the cigarettes to which nicotine had been added, followed by at least 4 cartons of low nicotine cigarettes, and these in turn were followed by 2 cartons of the cigarettes containing added nicotine. This use of the experimental cigarettes to which nicotine had been added was made necessary by the fact that the smoking quality of the low nicotine tobacco was decidedly inferior to that of standard cigarettes. By this means it was felt that a control on the taste and aroma factors was obtained. In other words, by the time the subject was suddenly virtually deprived of nicotine, he was fairly well accustomed to the inherently different taste and aroma of the low nicotine tobacco. The subjects were asked to keep a personal account, and in addition were repeatedly questioned as to their reactions to each carton smoked. In no instance did they know in advance when switches in nicotine content were made. The results are expressed in Table 1.

TABLE 1

ROLE OF NICOTINE IN THE SMOKING HABITS OF 24 INVETERATE CIGARETTE SMOKERS

Subject	Average daily consumption: Standard brands	Experimental cigarettes: Nicotine added (first period)	Low nicotine	Nicotine added (second period)	Degree to which nicotine was missed
L.H.	21.8	21.4	21.9	22.5	0
R.M.	20.7	24.2	31.5	20.3	0
S.N.	20.4	20.6	19.8	20.5	0
H.S.	*ca.* 60	*ca.* 60	*ca.* 75	*ca.* 60	0
J.B.	19.2	14.8	17.4	16.1	0
N.C.	19.4	18.9	20.1	21.3	0
(Means)	26.9	26.6	30.9	26.8	(Total) 6
A.F.	24.0	23.8	22.3	18.9	+
S.H.	21.3	20.8	24.5	25.6	+
J.M.	19.3	19.1	36.2	23.9	+
G.O.	20.8	20.3	23.4	19.7	+
F.W.	25.4	19.1	30.2	28.5	+
H.W.	23.4	28.9	22.7	26.6	+
(Means)	22.4	22.0	26.5	23.9	(Total) 6
J.F.	28.2	38.2	32.4	37.5	++
P.L.	24.5	27.2	28.5	23.1	++
F.P.	18.2	19.5	25.0	22.2	++
(Means)	23.6	28.3	28.6	27.6	(Total) 3
G.B.	25.5	17.0	27.7	20.7	+++
E.H.	22.1	25.5	28.5	30.3	+++
K.K.	25.1	27.3	26.4	27.4	+++
H.B.	25.3	28.4	25.8	24.2	+++
M.F.	21.4	25.8	24.8	28.6	+++
D.G.	34.4	27.6	27.0	26.7	+++
F.H.	28.8	24.4	26.7	25.4	+++
W.P.	21.0	21.6	16.1	19.3	+++
C.Z.	21.2	24.8	18.6	21.3	+++
(Means)	25.0	24.7	24.6	24.9	(Total) 9

0 Did not miss the nicotine.
+ Mild initial dissatisfaction with low nicotine cigarettes.
++ Definite temporary lack of satisfaction with low nicotine cigarettes.
+++ Definite and prolonged lack of satisfaction with low nicotine cigarettes.

Six of the 24 subjects experienced no change in physical or mental tranquility during their period on low nicotine cigarettes; 6 experienced an initial vague lack in the satisfaction that they normally derived

[1] L. M. Johnston, *Lancet*, 2: 742, 1942.
[2] Through the courtesy of Dr. W. D. Valleau, Kentucky Agricultural Station, Lexington, Ky.
[3] Assoc. Official Agr. Chem., "Official and Tentative Methods of Analysis," 5th ed., p. 64, 1940.
[4] J. Bradford, W. Harlan and H. R. Hanmer, *Indust. and Eng. Chem.*, 28: 836, 1936.

from smoking; 3 definitely missed the nicotine but became adapted to the change in one to two weeks; 9 definitely missed the nicotine and continued to do so throughout the period (approximately 1 month). The symptoms experienced by the latter 2 groups for the most part took the form of varying degrees of heightened irritableness, decreased ability to concentrate on mental tasks, feeling of inner hunger or emptiness, hypoesthesia (1 case), in short, virtually the same symptoms experienced by many individuals on stopping smoking. Some of the individuals in the last group "just could not take it" and admitted to interspersing a few cigarettes of ordinary nicotine content during their period on low nicotine cigarettes.

CONCLUSIONS

It would seem clear from these results that with many individuals nicotine becomes a major factor in their cigarette habit. Equally certain, with many individuals nicotine is not a factor in their cigarette habit. Even in those individuals in whom nicotine has become a major factor we feel that a cigarette containing no nicotine would be grudgingly accepted as better than no cigarette at all.

There is seemingly no correlation between the number of cigarettes smoked daily and the degree to which nicotine becomes a factor. Indicative of this is the heaviest smoker in the series, a man who for many years has smoked 3 packages daily. This individual made the switch to low nicotine cigarettes without the slightest difficulty.

Groupings on the basis of subject age or duration of the habit showed no correlation with the degree to which nicotine was missed. However, the number of subjects involved was too small to arrive at any definite conclusions in these respects.

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PENICILLIN IN EXPERIMENTAL SPOTTED FEVER

UNTIL relatively recently the treatment of spotted fever (Rocky Mountain spotted fever) has been purely supportive and symptomatic. Published reports on chemotherapeutic treatment are scant. In 1938 Baker reported that the intravenous administration of neoarsphenamine in metaphen solution was beneficial in relieving symptoms and, in a later publication, that all treated cases had survived.[1, 2] The number of cases was not stated. No doubt the sulfonamides have been given in many instances not reported in the literature. In infected guinea pigs the use of sulfapyridine and prontosil resulted in no improvement,[3] and Topping concluded that there was evidence of their being harmful and that they should not be used. We have confirmed and extended these observations, studying the effect of sulfamerizine, sulfadiazine, sulfapyridine and sulfathiazole.[4] In our hands, the latter two drugs were very definitely contraindicated, deaths occurring in the treated animals sooner than in the controls. The first two drugs were without effect. Steinhaus and Parker,[5] in addition to testing some of the sulfonamides, treated guinea pigs with atabrine and tyrothricin and concluded that none of the substances used was of any value. Serotherapy (rabbit immune globulin) is coming into wider use,[6] but it will take some years to evaluate the benefit of this form of treatment in human spotted fever where the mortality with supportive treatment alone is only about 20 per cent. Its striking effects in guinea pigs, however, even when very small quantities are employed,[4] tend to make one exceedingly enthusiastic about its use in the human disease.

In view of the extraordinary effectiveness of penicillin in many other infectious diseases, it seemed pertinent to study its effects on experimental spotted fever. Its use in man has been reported in one case diagnosed as spotted fever; the patient recovered.[7]

Male guinea pigs weighing from 450 to 600 grams were infected by the intraperitoneal route with 1 cc of a 10 per cent. suspension of spleens obtained from guinea pigs infected with the Bitter Root strain of spotted fever. Temperatures were taken twice daily to determine exactly the time of onset of fever. In the first experiment, groups of 4 guinea pigs were selected for treatment 24, 48, 72 and 96 hours after the temperatures rose above 103.5° F. All guinea pigs, except the 96-hour group, received intramuscularly 200 Oxford units of penicillin contained in a volume of 0.2 cc every 4 hours for 36 hours, or a total of 1,800 units per animal. The disease in the guinea pigs selected for treatment 96 hours after the onset of fever had progressed so far that it was deemed advisable to give them larger doses. Five hundred units at 4-hour intervals were administered for 36 hours, or a total of 4,500 units per guinea pig. No beneficial effect could be observed in any of the treated animals.

A second experiment was undertaken to see if the larger dose of penicillin given earlier in the disease

[1] G. E. Baker, *Rocky Mt. Med. Jour.*, 35: 36, 1938.
[2] *Idem, Ann. Intern. Med.*, 17: 247, 1942.
[3] N. H. Topping, *U. S. Pub. Health Rep.*, 54: 1163, 1939.
[4] Unpublished experiments.
[5] E. A. Steinhaus and R. R. Parker, *U. S. Pub. Health Rep.*, 58: 351, 1943.
[6] N. H. Topping, *U. S. Pub. Health Rep.*, 58: 757, 1943.
[7] P. K. Edmunds, *Rocky Mt. Med. Jour.*, 41: 910, 1944.