group of urban women, there was no social or economic group (except the relief families) that had a birth rate high enough to maintain itself and as a whole they would decline in numbers by 30 per cent. in a generation.

The small sample of the rural population studied like the urban showed in general an increase in the marital birth rate as social status declined and also as the amount of education decreased. But it had a significantly higher birth rate than the urban group, enough higher to insure the maintenance of its numbers with some to spare for increase.

This study is significant for the factual information it contains rather than for any changes found in the usual class, race and nativity differentials. To the reviewer the most interesting point in the study is that it adds to the accumulating evidence that differentials between the birth rates of social and economic classes are diminishing. This is probably taking place not through a rise in the birth rate of the more fortunate groups but through the further decline of that of the less fortunate groups. It is a sad commentary on our civilization that the people who have got most out of it economically, and in position, have less than half enough children to take their places in the next generation. Even if the birth rate in 1935 was somewhat below what might be considered normal it is still of great significance that those to whom our civilization has been kindest do not consider it a fit environment in which to bring up children; or is it that they are so absorbed in their own success that they have no time to consider the need for their participation in the future of our national life by taking part in reproduction? Such facts as are here adduced can not but arouse thoughts on the meaning of a civilization which sterilizes or nearly sterilizes those who generally believe themselves to be its most perfect fruit.

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SPECIAL ARTICLES

PURIFICATION AND PROPERTIES OF THE SECOND ANTIBACTERIAL SUBSTANCE PRODUCED BY PENICILLIUM NOTATUM[1,2]

IN an investigation begun in the laboratories of Dr. S. A. Waksman, New Jersey Agricultural Experiment Station, in the winter of 1940 and continued at the University of Pennsylvania, the observation was made that strains of *Penicillium notatum* produce an antibiotic substance different from penicillin. The properties of this second antibacterial substance, for which the name penatin has been proposed, have been discussed[3] and the cultural conditions for the production established.[4] Progress has been made in the purification of penatin, which, in its bacteriostatic power, not only surpasses the purest preparations of penicillin, but is also effective against bacteria which are not susceptible to any appreciable degree to the action of penicillin, notably some gram-negative organisms. Of 50 pathogenic and non-pathogenic organisms tested, none have been found which would resist the bacteriostatic action of penatin in dilutions of not less than 1:10 millions. The purest preparations obtained were bacteriostatic to certain organisms in even higher dilutions, for instance, 1:400 millions. Penatin is also bactericidal, but to a lesser degree. Table 1 shows the bacteriostatic action of penatin, which contrasts sharply with the range of action of penicillin.

TABLE 1

BACTERIOSTATIC ACTION OF PENATIN AGAINST VARIOUS PATHOGENIC AND NON-PATHOGENIC ORGANISMS

Test organism	Dilution 1: millions						
	12.5	25	42	125	250	420	1250
Sarcina lutea	–	–	–	–	–	Tr	N
Gaffkya tetragena	–	–	–	–	–	I	N
N. catarrhalis	–	–	–	–	–	I	N
Staph. aureus	–	–	–	–	Tr	N	N
C. diphtheriae	–	–	–	I	N	N	N
Cl. histolyticum	–	–	–	I	N	N	N
Ps. aeruginosa	–	–	–	N	N	N	N
Eb. typhosa	–	–	–	N	N	N	N
B. anthracis	–	–	Tr	N	N	N	N
Br. melitensis	–	–	Tr	N	N	N	N
Br. abortus	–	–	Tr	N	N	N	N
S. paratyphi	–	–	I	N	N	N	N
D. pneumoniae, Type I	–	Tr	I	N	N	N	N
S. pyogenes (C203M)	–	Tr	N	N	N	N	N
Es. coli	–	I	N	N	N	N	N
Trichophyton interdigitale[5]	–	I	N	N	N	N	N

Conduct of the test: Penatin was incorporated in tryptose agar and the test organism streaked out. Readings after 48 hours at 28° or 37° respectively. – = no growth, Tr = trace of growth, I = inhibited growth, N = normal growth, similar to control.

While the addition of growth-stimulating substances, such as corn-steep liquor, yeast or malt extract, to the Czapek-Dox medium were found to be beneficial for the formation of penicillin, their presence will prevent the formation of penatin. It is further noteworthy that the particular strain of *Penicillium notatum* (PEN 2) found most active in the production of penatin was discovered years before

[1] From the Schools of Medicine and Veterinary Medicine, University of Pennsylvania.

[2] This investigation has been supported by the Thos. H. Dougherty, Jr., Fund, and by grants from the Department of Agriculture, Commonwealth of Pennsylvania.

[3] W. Kocholaty, *Jour. Bact.*, 44: 143, 1942.

[4] *Ibid.*, 44: 469, 1942.

[5] Krainsky's agar was used. Readings after 10 days at room temperature.

Fleming's discovery of the strain of *Penicillium notatum* which produces penicillin.

In contrast to penicillin, penatin is not extractable from the crude culture by the common organic solvents. Two ways of purification have been found. One is the precipitation of penatin with phosphotungstic acid (penicillin is not precipitated by this agent) which will form an acid-insoluble penatin-phosphotungstate. Because of losses in free penatin encountered in the decomposition of this compound, another method of purification was used. It consists in the adsorption of penatin on kaolin at pH 4, elution of the washed kaolin with pyridin or sodium phosphate at pH 6.3, and precipitation of the penatin by dioxane. The dioxane precipitate is dissolved in water and dried by the lyophilic method. Concentrated solutions of penatin in this state of purification are yellow. In dry preparation, penatin is a yellowish hygroscopic powder, completely soluble in water and stable for months. Penatin is sensitive to the action of alkalis, but more resistant to acids.

A single intravenous injection of 16.5 mg of penatin into a rabbit and a single intramuscular injection of 250 mg of penatin into a guinea pig were made without obvious ill effects. Furthermore, its action is not impeded in 90 per cent. serum. Further experiments on toxicity and antibacterial action *in vivo*, as well as some peculiarities of penatin, will be reported elsewhere.

WALTER KOCHOLATY

SOME CHEMICAL AND PHARMACOLOGICAL OBSERVATIONS ON "LOW NICOTINE" TOBACCO

THROUGH the kindness of Dr. W. D. Valleau, of the Kentucky Agricultural Station, we were supplied with sufficient "low nicotine" Kentucky burley tobacco to make certain chemical and pharmacological observations which appear of interest. The only previous report of similar studies is that of Wenusch and Maier[1] whose observations our present work confirms in general.

On chemical analysis, the leaf web of this tobacco was found to contain 0.13 per cent. nicotine and 0.27 per cent. nornicotine.[2] Cigarettes weighing one gram each were made of the granulated leaf web and the main stream smoke analyzed (excepting for nornicotine) by the methods described by Bradford, Harlow, Harlan and Hanmer.[3] The smoke from each cigarette contained 0.42 mg total volatile bases (calculated as ammonia) including 0.23 mg nicotine and 0.058 mg nornicotine.

[1] Adolph Wenusch and Gerda Maier, *Munchen. Med. Wchnschr.*, 87: 1263, 1940.

[2] Methods of analysis to be published.

[3] J. A. Bradford, E. S. Harlow, W. R. Harlan and H. R. Hanmer, *Ind. and Eng. Chem.*, 29: 45, 1937.

The amount of nicotine is less than 10 per cent. of that found in the smoke of the average standard cigarette. The presence of nornicotine in the tobacco adds an unusual feature to these cigarettes, since this substance is not normally reported present in cigarette tobaccos. Wenusch[4] has stated that only a small amount of nornicotine is transferred into the smoke from material containing it. The data presented here indicate that the transfer is less than 4 per cent. compared to 29 per cent. for nicotine. The percentage transfer of nicotine from average standard cigarettes is about 22 per cent., the higher value obtained here representing a recognized tendency for low nicotine tobaccos to transfer a higher percentage of their nicotine content into the smoke.[3]

Solutions were prepared from the smoke of these cigarettes as well as from that of a standard brand of cigarettes by a method previously described[5] and studied pharmacologically. These solutions were so made that, calculated on the nicotine content of smoke, each ml contained 0.5 mg nicotine. When tested for their toxicity by intraperitoneal injection into white mice, the L. $D._{50}$ for the two solutions was identical and in accord with their calculated nicotine content. The failure of nornicotine to materially affect the result is due to its low percentage transfer in the smoke and to its toxicity being only half that of nicotine by the intraperitoneal mode of administration.[6] When these solutions were injected intraveneously into an anesthetized dog arranged for the recording of blood pressure, the blood pressure response was identical to that produced by a control solution of pure nicotine of similar nicotine content. The pressor potency of nornicotine is only one twelfth that of nicotine.[6]

A limited number of studies were made on the effect of smoking these low nicotine cigarettes on the blood pressure and pulse rate in man, using the method of standardized smoking described by Main.[7] The results of these preliminary tests showed that the smoke from the low nicotine cigarettes on an average produced effects comparable to those observed after the smoking of nicotine-free cigarettes,[7, 8] both types of cigarettes evoking circulatory responses, markedly less than those effected by ordinary cigarettes.

SUMMARY

Chemical and pharmacological tests have been carried out on a sample of "low nicotine" tobacco. Laboratory tests involving toxicological studies on mice

[4] Adolph Wenusch, *Pharm. Zentralhalle*, 77: 141, 1936.

[5] H. B. Haag, *Jour. Lab. and Clin. Med.*, 25: 610, 1940.

[6] P. S. Larson and H. B. Haag, *J. Pharmacol. and Exper. Therap.*, in press.

[7] R. J. Main, *Proc. Soc. Exper. Biol. and Med.*, 48: 495, 1941.

[8] J. H. Weatherby, *Am. Heart Jour.*, 24: 17, 1942.