TABLE I. Effects of DNP on Oxygen Consumption and Rate of Ciliary Activity of *Mytilus* Gill.

Final conc. DNP, mols • l^{-1}	Oxygen consumption, normal = 1		Ciliary activity, normal = 1	
	n	Mean and std error	n	Mean and std error
1.1 × 10^{-6}	4	.95 ± .03		
2.3 × 10^{-6}	4	.95 ± .01		
4.5 × 10^{-6}	4	.94 ± .02		
9 × 10^{-6}	4	.89 ± .05		
1.8 × 10^{-5}	4	1.08 ± .03	3	.91 ± .02
3.6 × 10^{-5}	4	.97 ± .05	3	.91 ± .06
7.2 × 10^{-5}	5	1.39 ± .02	3	.74 ± .21
1.4 × 10^{-4}	11	1.48 ± .05	3	.68 ± .15
2.9 × 10^{-4}	19	1.75 ± .07	3	.74 ± .02
5.8 × 10^{-4}	23	1.88 ± .02	3	.41 ± .07
1.2 × 10^{-3}	10	1.49 ± .05	3	.16 ± .04
2.3 × 10^{-3}	6	1.35 ± .06	3	.06 ± .03
4.6 × 10^{-3}	6	1.11 ± .02	3	.14 ± .05
7.7 × 10^{-3}			3	No activity

that the augmentation of respiration and the uncoupling of endergonic processes may be closely linked. Further studies of metabolism in ciliated cells may clarify the site of action of DNP.

Summary. 1. The effects of 2,4-dinitrophenol (DNP) upon oxygen consumption and ciliary activity in the excised ctenidia of *Mytilus edulis* were investigated. 2. The maximal stimulation of oxygen uptake was estimated to occur when the DNP was 5 x 10^{-4} M. 3. Ciliary beat was increasingly inhibited as the concentration of DNP was raised. 50% inhibition was estimated at 4 x 10^{-4} M DNP, and inhibition was complete in the presence of 7.7 x 10^{-3} M DNP. 4. The possible role of DNP in uncoupling exergonic from endergonic processes receives support from the close coincidence of these effective concentrations. The close correspondence also suggests a single site of action for DNP.

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Received June 23, 1952. P.S.E.B.M., 1952, v81.

Chemotherapy of Experimental Tuberculosis with Quinoline Derivatives. (19779)

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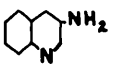
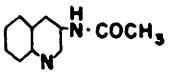
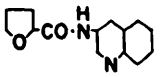
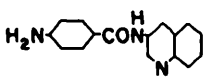
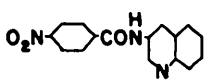
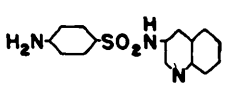
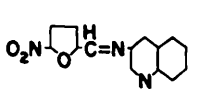
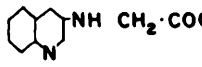
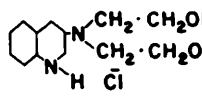
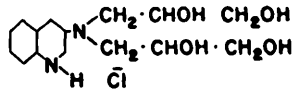
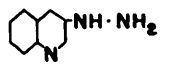
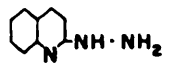
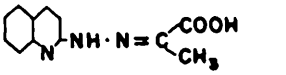
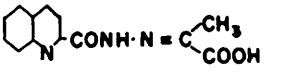
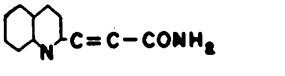
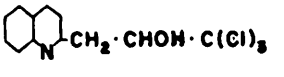
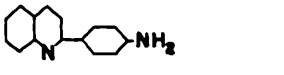
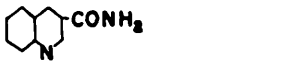
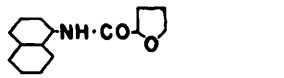
New derivatives of aminoquinolines were investigated for tuberculostatic action and for therapeutic effect on tuberculosis in guinea pigs. Derivatives of 3-aminoquinoline were emphasized, as this compound is highly bacteriostatic. In the present experiments a number of allied compounds were also tested, including hydrazine derivatives of quinoline and naphthylene as well as some 2-substituted quinolines. A few previously reported compounds were included for comparison.

Methods. The bacteriostatic studies were performed on virulent tubercle bacilli, strain No. H37Rv in Kirshner's synthetic asparagin

TABLE I. Tuberculostatic Action on Strain H37Rv.*

No.	Compound	Min. Inhib. Conc. mg.%
1		0.05
2		5.
3		0.05
4		1.25
5		5.
6		0.5
7		0.05
8		0.5
9		10
10		0.5
11		>5.
12		1.25
13		5.
14		5.
15		5.
16		10.
17		>5.
18		1.
19		5.
20		0.5
21		2.5
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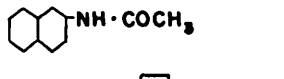
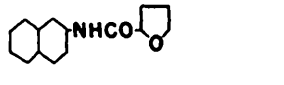
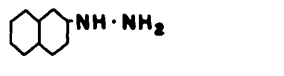
23		0.05
24		0.05
25		0.5

* Above compounds were prepared in this laboratory excepting No. 1, 12, 20, 22, and 25, which were obtained from Eastman Kodak Co. (highest purity).

and glycerine media at a pH of 7.2. The chemicals were dissolved with a minimum of heating in acetone or in 0.8% sodium hydroxide to make 0.5% solutions. Subsequent dilutions were made directly into the media without further heating. Each flask was inoculated with one loopful (4 mm in diameter) of a 14-day-old surface culture of tubercle bacilli. The surface cultures were read at 13 days, using the highest dilution in which there was less than 50% of control growth as an end point.

Animal experiments. Twelve guinea pigs weighing an average of 400 g were used to evaluate each compound. The animals were inoculated in the left groin with 0.1 mg wet weight of H37Rv tubercle bacilli. The drugs were administered daily, orally by pipette, in

TABLE II. Summary of *In Vivo* Experimental Data.

No.	Compound	Avg daily dosage, mg/animal	Path. ratio*	Wt change deviation from control, g	Hemoblob. deviation from control, %
4.	N-(3-quinolyl) *p*-aminobenzamide	200	1.4	—26	+6
5.	*p*-nitrobenzamide	80	1.1	+60	0
6.	*p*-aminobenzene sulfonamide	130	1.7	—46	0
3.	furoylamide	50	.81	—22	+6
10.	N,N-dipropyleneglycol-3-aminoquinoline	100	.87	—45	+5
14.	Quinaldinic acid hydrazide	10	1	—27	—12
15.	Pyruvic acid hydrazone of #14	12	.27	—38	+2
26.	*p*-aminosalicylic acid (sodium salt)	250	2	+30	0
27.	Streptomycin	†	4	+58	0

* Pathological ratio is the quotient of the average numerical pathological rating of control animals divided by that of treated animals.

† Streptomycin given by hypo 40 mg 3 times weekly. Both streptomycin and *p*-aminosalicylic acid were included for comparison.

aqueous suspension. Therapy was started on the day of infection. The dosage of all drugs was increased gradually for the first 2 weeks to the approximate chronic maximum tolerated dose. The experiments were terminated at the end of 7 weeks. Pathology was evaluated numerically, based on a maximum of 4 for each organ (glands, spleen, liver, and lungs). Hemoglobin and weight determinations were made at the end of the experiment.

Results and discussion. The *in vitro* bacteriostatic results are recorded in Table I. Derivatives of 3-aminoquinoline (Nos. 1-11) inhibited growth in varying degrees. The parent compound (No. 1) and its furoyl (No. 3) and 5-nitrofuranil (No. 7) derivatives were all highly bacteriostatic. This may be due to the ease of hydrolysis of the derivatives. Quinoline-3-hydrazine (No. 11), wherein there is a substitution of a hydrazine for the amino group of 3-aminoquinoline, negated the inhibiting effect of the latter compound. Quinoline-2-hydrazine was slightly more bacteriostatic than the 3 isomer, but its corresponding pyruvic acid hydrazone (No. 13) was less active. The hydrazide of quinaldinic acid (No. 14) was a poor inhibitor. The naphthylamine derivatives (Nos. 20-25) were included mainly for comparison, and in general these compounds were more consistently bacteriostatic than the corresponding quinoline analogues. The most active derivatives of 3-aminoquinoline and β-naphthylamine were those most easily hydrolyzed. There was no correlation between activity and solubility, Ka values, or partition coefficients.

The *in vivo* results are summarized in Table II. These compounds were not chosen because of high bacteriostatic activity but rather for their diverse physico-chemical properties such as solubilities, degree of basicity, and for their structural relationship to known biologically active compounds. Of the 7 new compounds evaluated, one showed some therapeutic effect, namely the sulfonamide derivative (No. 6). This compound was toxic as evidenced by weight loss of the animals. The therapeutic results compared unfavorably with those of streptomycin and p-aminosalicylic acid. The sulfonamide derivative described above has been prepared by others(1) but has not been evaluated on many organisms, possibly because of its relatively high dissociation constant.

Summary. 1. Nineteen quinoline derivatives, including eleven 3-aminoquinoline derivatives, were evaluated for tuberculostatic action upon *M. tuberculosis* H37Rv. 2. Seven quinoline derivatives were tested *in vivo* in experimentally induced tuberculosis in guinea pigs. 3. The relationship between chemical structure and tuberculostatic action was discussed.

1. Northey, E. H., *The Sulfonamides and Allied Compounds.* Reinhold Publishing Corp., New York, 1948, p. 71.

The technical assistance of Miss Elizabeth Girdish is acknowledged.

Received June 23, 1952. P.S.E.B.M., 1952, v81.