will be seen that all 7 of the controls died in less than 8 hours, with an average survival time of 6.7 hours. At autopsy, 6 of the 7 control rats showed perforation of the stomach. Of the 9 rats receiving Etamon chloride only 4 died; the shortest survival time was 7.1 hours, and only one of these 4 showed perforation. The remaining 5 experimental rats were sacrificed no sooner than 9.7 hours postoperatively, so that the shortest postpyloric ligation time was 1 hour longer than the longest control survival.

The stomachs were examined microscopically for ulceration. The results of this examination have been tabulated on the basis of an arbitrary division into two groups: (a) stomachs having ulcers in which one axis was at least 3 mm. long, and (b) stomachs having ulcers in which the longest axis was less than 3 mm. It will be seen that 6 of the 7 control rats were in

TABLE 1

Rat No.	Weight (gram)	TEAC* (mg.)	Survival (hr.)	Perforation	No. of ulcers					
					3 mm. or greater			Less than 3 mm.		
					Rumen	Body	Antrum	Rumen	Body	Antrum
Control series										
3	90	0	4.8	+	1	0	0	5	0	0
5	95	0	4.6	+	5	0	0	0	1	0
7	90	0	6.8	0	1	0	0	1	0	0
11	82	0	8.7	+	0	0	0	11	0	0
13	90	0	6.7	+	1	0	0	1	0	0
15	100	0	7.4	+	3	0	0	17	0	1
17	100	0	7.8	+	2	0	0	9	0	0
Total			46.8		13			44	1	1
Average			6.7		1.9			6.3		
Experimental series										
2	95	13	12.8†	0	1	0	0	0	0	0
4	90	10	9.8	0	0	0	0	0	0	0
6	90	11	9.9	+	1	0	0	9	0	0
8	95	12	11.5†	0	0	0	0	8	0	0
10	90	11	11.2†	0	1	0	0	1	0	0
12	80	8	7.1	0	0	0	0	0	0	0
14	100	10	10.4†	0	0	0	0	0	0	0
16	88	8	7.8	0	1	0	0	0	0	0
18	95	10	9.7†	0	1	0	0	4	0	0
Total					5			22		
Average					0.6			2.4		

* Tetraethylammonium chloride.

† Rats were sacrificed after this survival time.

the group having large ulcers in the rumen, while this was true of only 5 of 9 experimental rats. Furthermore, 3 of the 6 control rats had more than one large ulcer. Six of the 7 control rats were in the group having small ulcers in the rumen, and in 4 of these the ulcers were multiple. Four of the 9 experimental rats had small ulcers in the rumen, and in 3 of these the ulcers were multiple. One control rat each had a small ulcer in the body and in the antrum of the stomach. Three of the experimental rats showed no gastric ulceration, while all of the control rats showed ulceration.

A comparison of the effect of Etamon chloride on gastric fluid volume and acidity was impossible due to the high incidence of perforation in the control series.

Although Etamon chloride did not completely prevent gastric ulceration in this series, on the basis of survival time, perforation, and incidence of ulceration it appears that it was definitely beneficial. When one considers the possibility that the difference between the two series might have been more striking had all remaining animals been sacrificed and examined after 7 hours (approximately the average survival time of the control rats), the probable clinical usefulness of Etamon chloride is enhanced.

Lyons, *et al.* (*3*) reported that in one hypertensive patient, who also had a duodenal ulcer, a single intramuscular injection of 1.2 gram of Etamon chloride resulted in the cessation of gastrointestinal motility, relief of the ulcer pain, and a decrease in the acidity and volume of the gastric juice. As the effects of the drug diminished, pain returned, at about 7 hours, and peristalsis was believed to be more rapid. We have studied the effect of Etamon chloride in two human patients who had active duodenal ulcers as well as in patients with other gastrointestinal disorders, with suggestive beneficial results. The clinical studies are being continued and will be reported elsewhere.

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A Method for Screening Antimalarial Compounds in the Mosquito Host

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Although methods of antimalarial drug screening have been improved and refined during the past several years, there has, nevertheless, been need for new screening technics, principally because it has not been possible to establish consistent or predictable relations between drug activity in experimental animal malarias and that in human malaria. For example, whereas sodium sulfadiazine and other sulfonamide derivatives have a kind of prophylactic effect against sporozoite-induced *Plasmodium gallinaceum* infections in chicks, these drugs are ineffective as prophylactic agents against human malarial infections. The present study was undertaken to devise a method of drug screening which would permit of more direct screening for certain drug qualities against a specific malarial parasite, or which would permit of screening of compounds for prophylactic effect against the human malarial parasite without the need for infecting undue numbers of human hosts.

In these experiments, laboratory strains of *Aëdes aegypti* were infected with a strain of *P. gallinaceum* designated as the 8A strain. Quinine hydrochloride, quinacrine hydrochloride,

plasmochin citrate, 7-chloro-4-(4-diethyl-amino-1-methyl butyl amino)-3-methyl quinoline bisulfate (SN6911), and sodium sulfadiazine were prepared in solutions calculated in terms of the salt. These drugs were added in various concentrations to a 4 per cent sugar nutrient solution used as the standard maintenance diet for infected mosquitoes in this laboratory. Mosquitoes fed readily on these drug mixtures, and, as in animal drug testing, mortality or survival was directly related to drug levels. It is evident that mosquitoes on these diets took up the drug, since they survive for as long as 20 days following their infective meals, whereas mosquitoes will not survive beyond 48 hours when deprived of food and water. Generally, in infected mosquitoes maintained on sugar solutions there is an average mortality of 30–35 per cent during the period of the experiment, and in these studies the maximum tolerated dose was considered to be that dosage in which mortality was approximately 60–70 per cent, or double that of the normal attrition. Usually, drug administration was begun 72 hours before the mosquitoes were given their infective blood meals and continued throughout the course of the infection. Later, drug schedules were varied according to the needs of an experiment.

TABLE 1

COMPARISON OF THE EFFECTS OF VARIOUS DRUGS ON THE SPOROGONOUS CYCLE OF *P. gallinaceum* IN *A. aegypti* AS DETERMINED BY SUBSEQUENT INOCULATION INTO CHICKS*

Drug	Drug conc. (grams/ 100 ml.)	Average per cent red cells parasitized (days after inoculation)						No. survivors
		8	10	12	14	16	18	
Quinine	.08	4.2	29.1	28.0				0/8
Quinacrine	.03	3.7	26.8	32.0	22.0			1/8
Plasmochin	.02	3.1	25.9	36.2				0/8
SN6911	.075	4.0	32.1	58	39.1			0/9
Sodium sulfadiazine	.1	0	0	0	0	0	0	8/8
Controls		2.8	31.7	30.9				1/8

* Inoculum contained one mosquito equivalent.

With this drug-diet method it has been possible to administer drugs to mosquitoes infected with *P. gallinaceum* and to test the effects of these compounds on the sporogonous cycle of the parasite. It has been found that quinine, quinacrine, plasmochin, and SN6911 administered in maximum tolerated doses have no effect on sporozoite production or sporozoite viability, and sporozoites from mosquitoes treated with these drugs, inoculated into normal chicks, produce infections indistinguishable from those produced by the inoculation of sporozoites from control mosquitoes maintained on sugar solutions alone. On the other hand, in infected mosquitoes treated with adequate concentrations of sodium sulfadiazine, oocysts fail to develop properly and sporozoites are produced only rarely, and those that are produced appear to be incapable of inducing infection when inoculated into normal chicks (Table 1).

Suspensions of mosquitoes prepared from those maintained on sugar solutions and on quinine, quinacrine, plasmochin, and SN6911 ordinarily contain two to three sporozoites per oil immersion field, whereas it may require 10 minutes examination to find a single sporozoite in suspensions prepared from mosquitoes maintained on 0.1 per cent sodium sulfadiazine. With higher concentrations of sodium sulfadiazine it becomes even more difficult to find sporozoites. Thus, drug effect can be readily discerned from microscopic examination of suspensions prepared from drug-treated mosquitoes, and one can predict with accuracy the outcome of subsequent inoculations from suspensions prepared from drug-treated or control mosquitoes.

During the course of several experiments, inoculation of whole mosquitoes or of several mosquito equivalents of those maintained on sulfadiazine levels above 0.1 per cent has failed to produce infection. Reinoculation of these negative chicks has resulted in characteristic infections with high parasitemias. At a 0.1 per cent level oocysts are formed in large numbers but rarely grow beyond the medial point of development. With concentration of sulfadiazine increased to 0.3 per cent, there is more complete inhibition of oocyst development, and at maximum tolerated levels oocyst development appears to be more completely arrested. However, below 0.1 per cent, which appears to be the critical concentration of the drug, sporozoite production and viability are not too seriously affected, and sporozoites from mosquitoes treated with lower concentrations produce characteristic infections when inoculated into normal birds (Table 2).

TABLE 2

COMPARISON OF THE RELATION OF DRUG CONCENTRATION TO DRUG ACTIVITY IN *A. aegypti* INFECTED WITH *P. gallinaceum* AS DETERMINED BY SUBSEQUENT INOCULATION INTO CHICKS*

Drug	Drug conc. (grams/ 100 ml.)	Average per cent red cells parasitized (days after inoculation)				No. survivors
		8	10	12	14	
Sodium sulfadiazine	.01	1.0	30.0	8.0		2/6
"	.05	0	1.0	8.2	23.0	2/6*
"	.1	0	0	0	0	6/6
"	.3	0	0	0	0	6/6
"	.4	0	0	0	0	6/6

* One chick remained negative.

From the known drug effects of sulfadiazine and the other drugs cited on sporozoite-induced infections of *P. gallinaceum* it would appear, therefore, that there is a definite relation between drug activity and effect in the sporozoite-infected vertebrate host and drug activity in the infected invertebrate host. The analogy extends further, in that sulfadiazine has little or no effect if drug administration is delayed until sporozoites have developed. High concentrations of drug administered over a period of several days after sporozoites have developed do not affect sporozoite viability, and sporozoites from mosquitoes so treated give rise to typical infections when inoculated into normal chicks. Furthermore, if drug administration is terminated too quickly following the infective meal, infective sporozoites are produced even though development is delayed.

With this method it may become possible to evaluate drugs directly in the mosquito host for their prophylactic activity against the human malarial parasite and thus to eliminate the necessity, according to present-day screening methods, of infecting large numbers of human subjects. The method may possibly offer further promise as another means for studies on parasite metabolism and for studies on the mechanisms of drug action.