India ink, etc., it nevertheless was very definite. In some experiments a small amount of overlapping was obtained. At no time, however, has a treated animal been found with definitely greater liver damage than the best control.

Discussion. The mechanism for the protective action of orally administered sulfonamide drugs is unknown. It appears to be in some way related directly to the sulfonamide group since sulfanilic acid exerts very little, if any, protective action.

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Prophylactic Effect of Sulfaguanidine Against Ulcerative Cecitis in Rats.

ARTHUR L. BLOOMFIELD AND WILLIAM LEW.

From the Department of Medicine, Stanford University School of Medicine, San Francisco, California.

In the course of nutrition experiments carried out during the past year our results were badly confused by the development in the rat colony of a disorder which we have come to speak of as "cecal disease." Briefly, rats which at birth appear perfectly well begin unaccountably to lose weight. After several weeks one may feel a mass in the abdomen and finally after a further period the animals die. There has been no clinical diarrhea although the feces may be softer than the usual hard pellets. Most of our rats with this disease have been sacrificed when the illness was obvious. The earliest lesion appears on the mesenteric border of the mucosa of the cecum as a tiny, barely visible grey superficial erosion. Later there are clearly evident shallow ulcers covered by adherent filmy greenish yellow membrane. In further stages the ulcers are deeper and there is thickening of the cecal wall so that finally a mass several millimeters thick with deep ragged excavations one to 2 cm in diameter is found. After the earliest stages the cecal contents are usually abnormal; they consist of a thin yellow material which has a characteristic foul odor. A reaction around the cecum soon takes place so that coils of intestine and enlarged lymph nodes become adherent. In association with these masses there are cyst-like pockets of clear fluid. The other viscera as a rule show nothing remarkable except that the spleen may be enlarged. This "cecal disease" has been described by

Buchbinder, Hall, Wilens and Slanetz[1] and more recently, under the title of "Chronic Ulcerative Cecitis," by Stewart and Jones.[2] Their excellent accounts, which include histological and bacteriological studies, agree in all details with our own observations. Buchbinder, Hall, Wilens and Slanetz give evidence that "cecal disease" is caused by strains of paratyphoid bacilli; Stewart and Jones question this position although they agree that paratyphoid bacilli are commonly obtained from the stools of rats with "cecitis." They raise the question of some other primary agent with salmonella as a commensal or secondary invader.

In another paper we shall report on bacteriological studies. Suffice it to say now that *Salmonella enteritidis* may readily be recovered from the stools of rats with "cecitis." Ingestion of one strain caused a violent acute dysentery but so far we have not produced "chronic cecitis," although it seems clear that this disease is an infection of some sort.

The present experiments were carried out for two reasons. First of all there was the purely practical problem of eliminating from our rat colony an epidemic (or endemic) which vitiated all observations connected with the regular work of the laboratory. Secondly we were struck by the fact that chronic cecitis of rats furnishes an admirable disease for chemotherapeutic studies. Unlike acute infections in mice which the animal survives or to which it promptly succumbs, rat cecitis runs a gradual course over months, stool cultures are readily made and in general conditions approximate closely those which obtain in many diseases of man. Finally it was hoped that information as to the value of chemotherapy in the prophylaxis of bowel infection which might be of use in connection with military problems could be obtained.*

Experiments. The general technic of caging, feeding and observing rats in use for many years in this laboratory was followed.[3] Two sets of 21 rats, littermates, taken from "normal" stock were housed in groups of 5 or 6 in adjacent cages. Individual weights varied from 110 to 170 g but the average weights of the animals in the two groups were nearly the same. One group, the control, were placed on the stock laboratory diet consisting of cornmeal, casein,

[1] Buchbinder, L., Hall, L., Wilens, S. L., and Slanetz, C. A., *Am. J. Hyg.*, 1935, **22**, 199.

[2] Stewart, H. L., and Jones, B. F., *Arch. Path.*, 1941, **31**, 37.

* We are indebted to E. R. Squibb and Sons for generous supplies of sulfaguanidine.

[3] MacKay, L. L., and MacKay, E. M., *Am. J. Physiol.*, 1927, **83**, 179.

linseed oil cake meal, sardine oil, bone ash and sodium chloride. The other group received the same diet with the addition of sulfaguanidine 0.5%. As rats eat approximately 10-15 g of this stock diet daily each animal ingested about 50-75 mg of the drug daily, a dose on the basis of weight comparable to that tolerated by man. Both sets of animals were weighed at frequent intervals and were observed for signs of diarrhea, abdominal tumor or other disability.

Inasmuch as over 50% of the stock rats in the laboratory had been developing "cecitis," our purpose was to find out whether sulfaguanidine rations had any prophylactic effect. The experiment extended from Feb. 21, 1941, to May 13, 1941, a total of 82 days. During this time 4 animals of the control group became clinically ill and were sacrificed. Three of them had miscellaneous lesions but no cecitis; these animals were therefore thrown out of the series. The fourth, examined on the 38th day of the experiment, had advanced cecal disease. None of the animals on sulfaguanidine became clinically ill or lost weight. On May 13th both controls and experimental groups were sacrificed under ether anesthesia. At this time all the rats appeared healthy although some of the controls had lost weight and in a few an abdominal mass was palpable.

Results. 1. Effect of Sulfaguanidine on Weight. Fig. 1 shows

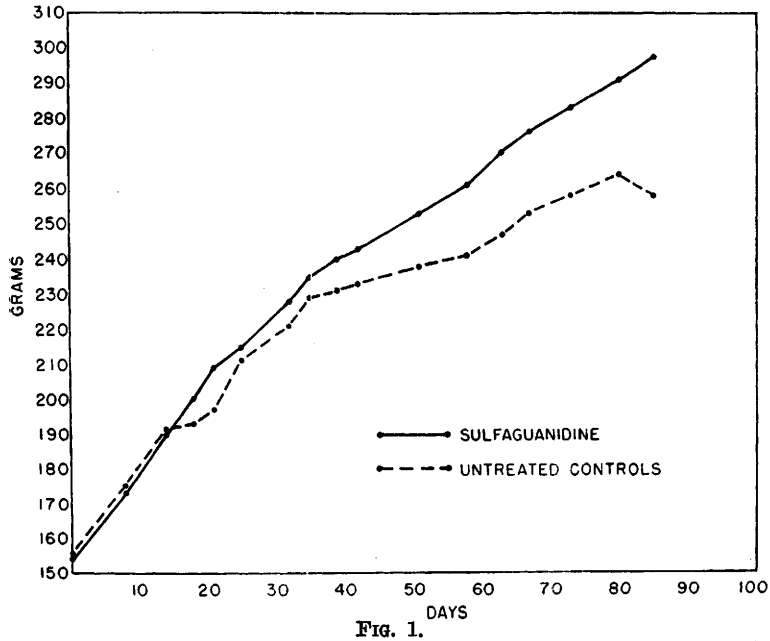

FIG. 1.
Comparison of Weight of Rats with and without Sulfaguanidine in the Diet.

the average weight of the rats with and without sulfaguanidine. It is seen that for the first 3 weeks the curves are almost identical. Thereafter the sulfaguanidine rats gained much faster than the controls which eventually actually lost weight. The lag in the controls seems well explained by the high incidence of "cecitis" as will be shown presently. It is also to be noted that sulfaguanidine did not seem to interfere with the rats' appetite and in general produced no recognizable toxic symptoms. Furthermore, although loss of weight in general was associated with "cecitis" in individual rats there were many discrepancies. Rat No. 32 for example, which at autopsy had a maximal lesion gained 26 g during its last week of life; whereas No. 144 which showed no lesion of any sort gained only 6 g during the same period.

By weighing the feeding boxes each day the approximate amount of food ingested was estimated although there was some error from scattering. The average of a fairly large series of measurements suggests that the controls ate approximately 0.5 g less a day than the sulfaguanidine rats.

2. Incidence and Severity of "Cecitis" in the Two Groups. The cecal lesions at autopsy were graded as follows: 0 = no cecitis, + = superficial erosion not over 0.5 cm in diameter, ++ = shallow ulcer 0.5 to 1 cm in diameter with greenish slough and pericecal adenitis, +++ = ulcer over 1 cm in diameter with thickening of cecal wall and marked pericecitis, ++++ = extreme lesions with huge ulcer and matted adherent coils of intestine.

Table I shows the results. Among the 18 controls 13, or 72%, developed cecitis; in the test group of 21 only 7, or 33.3%, were affected. But the difference in severity of the disease in the two groups is even more impressive. In the test rats such lesions as developed were minimal in all but one case.

Blood Level of Sulfaguanidine. The rats of the test group were exsanguinated at 3 p. m. under ether anesthesia by cutting the aorta, and blood from the entire group was pooled. The blood levels of sulfaguanidine were as follows:†

Duplicate sample No. 1—Free 0.9 mg%; Total 1.1 mg%
" " No. 2— " 1.2 " ; " 1.3 "

Discussion and Summary. Chronic ulcerative cecitis, as it developed spontaneously in a rat colony, presented itself as an ideal experimental disease in which to study the effect of chemotherapy. At the time of the present observations the majority of the animals in

† We are indebted to Dr. A. P. Richardson for the estimation of blood sulfaguanidine.

TABLE I.
Incidence and Degree of "Cecitis" in Experimental and Control Groups.

Control group		Experimental group	
Rat No.	"Cecitis"	Rat No.	"Cecitis"
144	0	71	0
158	0	81	0
94	0	89	0
32	0	91	0
52	0	93	0
142	+	95	0
30	+	26	0
60	+	31	0
14	++	43	0
50	++	55	0
42	++	61	0
40	+++	41	0
48	+++	49	0
09	+++	51	0
593	+++	04	+
29	+++	47	+
44	++++	79	+
58	++++	06	+
		15	+
		62	+
		83	++

our colony developed lesions of "cecitis" by the time they had reached 300+ g in weight. The addition of 0.5% of sulfaguanidine to the diet produced no deleterious clinical effect nor any visible gross lesions. On the contrary rats on sulfaguanidine gained weight rapidly. The drug even in the small doses used had a striking prophylactic effect against the development of cecitis; not only was the incidence very much lower than in the control group but, even more impressive, such lesions as occurred were minimal in contrast to the advanced disease found in most of the untreated rats. The protective effect of sulfaguanidine is demonstrated further by the failure of the treated animals to lose weight as did the controls with progressive lesions.

The concentration of the drug in the stools was not measured but the relatively low blood levels suggest, as pointed out by Marshall[4] that sulfaguanidine is less readily absorbed than some of the other sulfonamides.

In clinical work on ulcerative colitis, dysentery and other bowel infections in man we have not always been impressed with the therapeutic effects of sulfaguanidine. It is possible, however, that the drug may be of greater value as a prophylactic, and the present ex-

[4] Marshall, E. K., Jr., Bratton, A. Calvin, White, H. J., and Litchfield, J. T., Jr., *Bull. Johns Hopkins Hosp.*, 1940, **67**, 163.

periments suggest that such is the case. Trials in man under proper conditions would seem worth while in connection with military establishments.

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Control of Malaria Infection (*P. lophurae*) in Ducks by Sulfonamides.

H. A. WALKER AND H. B. VAN DYKE.

From the Division of Pharmacology, the Squibb Institute for Medical Research, New Brunswick, N.J.

The effect of a number of sulfonamides has been studied in various species of birds infected with different parasites. The course of infection by *Plasmodium cathemerium, P. relictum,* and *P. nucleophilum* in canaries apparently is not significantly altered by sulfonamides.[1, 2] However, sulfapyridine can prevent patent infection by *P. circumflexum* or cause the rapid disappearance of parasites if administered after the infection is patent.[2] No beneficial effects of sulfonamides could be demonstrated in *Hemoproteus columbae* infections in the pigeon.[3] In the Java sparrow infected by *P. praecox,* prontosil was believed effectively to reduce the number of circulating parasites.[4] The action of sulfonamides in infections by *P. lophurae* in the chicken[1] or duck[5] has been reported to be of little or no benefit.

The course of infection by the Coggeshall strain of *P. lophurae* in the duck is particularly suitable for chemotherapeutic study because the number of parasites in the blood usually grows rapidly until death occurs.* In our experiments, Peking ducks 4 or 7 days old were inoculated intravenously with citrated blood from infected

1 Coggeshall, L. T., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 768.

2 Manwell, R. D., Counts, E., and Coulston, F., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 523.

3 Durand, P., and Villain, *Arch. Inst. Pasteur de Tunis,* 1939, **28**, 94.

4 Africa, C. M., Dy, F. J., and Soriano, L. J., cited in *Biol. Abstr.*, 1941, **15**, 1455.

5 Hegner, R., West, E., and Dobler, M., *Am. J. Hyg.*, 1941, **34**, Sec. C, 132.

* We are indebted to Professor Robert Hegner and Miss Evaline West not only for infected ducks carrying the Coggeshall strain of *P. lophurœ* but also for information concerning the transmission and preservation of the parasite in the laboratory.