TABLE I.
Plasma Lipid Concentration in Nephrotoxic Rats.

Rat No.	Day of disease	Total lipid carbon, mg per 100 cc	Total cholesterol, mg per 100 cc	Total lipid phosphorous, mg per 100 cc	Blood urea nitrogen, mg per 100 cc
1	18	2410	253	23.0	13
2	6	1988	387	5.3	11
3	9	2768	473	29.8	34
4	7	1118	208	5.0	34
5	6	1552	218	—	73
6	7	2385	248	—	25
7	12	6413	856	—	40
8	11	8660	713	—	41
9	7	2384	871	—	64
10	5	4325	779	—	46
11	4	916	223	—	—
12	4	1155	378	—	—

or otherwise, and that it is unlikely to be a compensatory osmotic mechanism for the lowered oncotic pressure due to hypoproteinemia.

Summary. Significant hyperlipemia was regularly encountered in rats with severe acute nephritis induced by anti-kidney serum.

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Significance of Salmonella in Ulcerative Cecitis of Rats.*

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Chronic ulcerative cecitis of rats is an ideal disease for chemotherapeutic and prophylactic tests. Unlike most acute experimental infections of small laboratory animals cecitis progresses gradually over a period of months and affords an opportunity to study the effect of drugs on a chronic low grade infection. It seems important therefore to determine definitely the nature of the agent which causes this disorder. Buchbinder and his associates[1] concluded that cecitis of rats was an enzoötic form of paratyphoid infection. Their view was based on the isolation of *S. enteritidis* from the stools and from the spleen as well as on the presence of agglutinins. They give no details of the cultural reactions of their strains of salmonella, of the agglutinin titers, or of the exact relation of salmonella to the lesions. Nor is it clear whether they dealt with a single specific strain.

While these observations are striking they do not actually prove that salmonella is the primary etiological agent of rat cecitis. Stewart and Jones[2] pointed out, for example, that paratyphoid infection or infestation of both laboratory and wild rats is common and that various strains are encountered. Furthermore, Buchbinder and his group report no observations on the experimental production of cecitis with strains of salmonella, and finally the exquisitely chronic and localized lesions so well described and pictured by Stewart and Jones bear no clinical resemblance to any known paratyphoid infection.

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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.

Our experiments were done in the attempt to find out more about the relation of salmonella to rat cecitis.

1. *Isolation of Salmonella from Rat Cecitis.* Cultures were made of cecal contents obtained at autopsy at various times from 12 rats with advanced cecal disease. The material was plated on McConkey agar plates (Difco). Suspicious colonies were fished, subcultured in various carbohydrates and tested for agglutination by stock sera. An attempt was made to estimate the proportion of salmonella in relation to "colon" bacilli. Salmonella were isolated in every case, usually as the predominating organism. Furthermore, the carbohydrate reactions were always the same and every strain was agglutinated in high titer (1:300 up to 1:1280) by a single specific anti-serum. It seems established then that in this epizoötic at least a specific strain of salmonella is intimately associated with the lesions.

In 4 cases of advanced "cecitis" cultures were also made of fluids aspirated from the cyst-like collections which are found between the coils of intestine adherent to the diseased cecum. No salmonella or other organisms were obtained from these fluids. In three rats enlarged glands lying adjacent to the cecum were carefully dissected away with sterile precautions under ether anesthesia. Cultures were made by grinding the glands with sand and broth and planting on a variety of liquid and solid media. In contrast to the cyst fluid all yielded the same type of salmonella as that obtained from the stool cultures, and the organisms were agglutinated by the same specific serum.

Having established, then, the invariable association of a specific organism with the

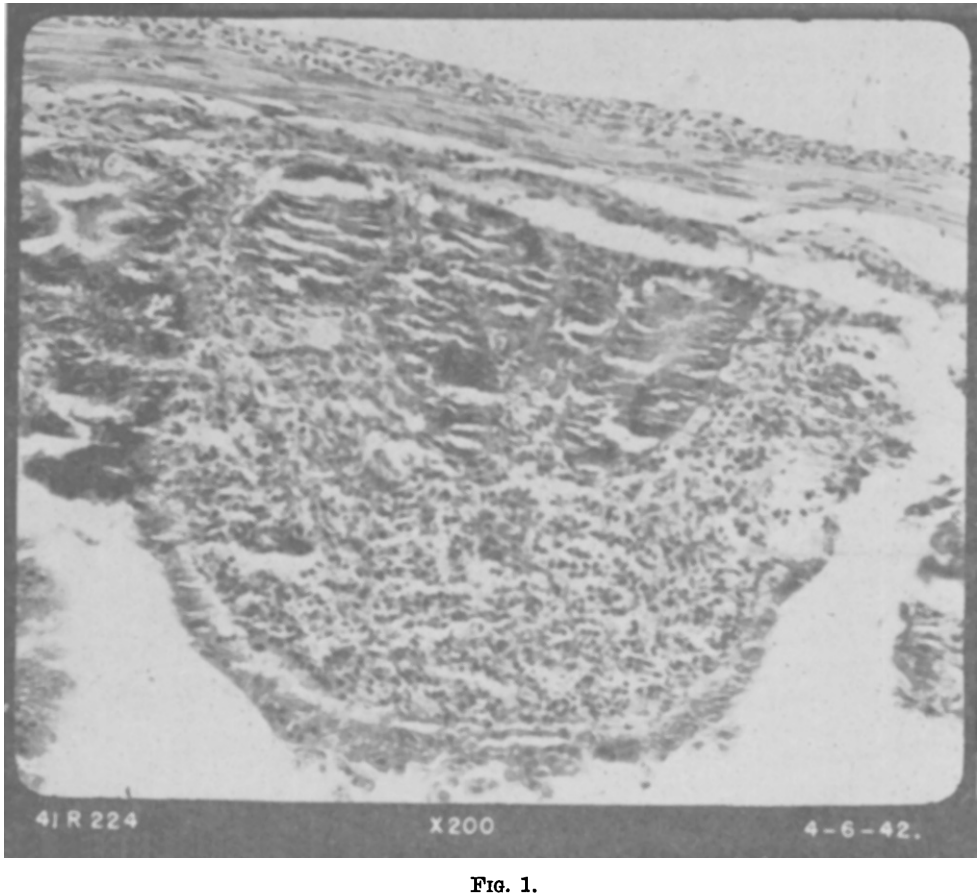

FIG. 1.
Sections of intestine from Rat No. 32 with fulminating enteritis.

TABLE I.
Results of Feeding Salmonella.

Rat No.	Wt at start of exper., g	Wt at end of exper., g	Gain, g	Cecitis
		Experimental Animals.		
43	66	166	100	0
45	66	206	140	0
97	52	192	140	0
55	66	174	108	+
57	70	204	134	+
01	52	178	126	+
59	70	204	134	++
87	72	218	140	++
07	52	218	166	++
61	64	190	126	+++
		Controls.		
44	56	144	88	0
46	62	154	92	0
56	62	166	104	0
72	56	174	118	0
96	52	206	154	0
88	60	200	140	0
70	62	194	132	+
86	52	150	98	+
02	62	168	106	++
04	58	170	112	++
08	52	148	96	++
98	50	190	140	+++

0 = No cecitis.
+ = Superficial erosion not over 0.5 cm in diameter.
++ = Shallow ulcer 0.5 to 1.0 cm with pericecal adenitis.
+++ = Ulcer over 1 cm in diameter with marked pericecitis.

lesion of "cecal disease," it became of importance to know whether this organism was also present in contacts without clinical lesions. At odd times cultures had been made from cecal contents of rats showing no cecitis; in no case was salmonella isolated, and for the most part there appeared a normal growth of *B. coli*. However, a more conclusive experiment was done. A group of normal rats, 5 to 6 months old, which had been housed in the same cages since birth were sacrificed under ether anesthesia. In this group advanced cecitis was found in 5 rats; hence the other 8 in whom no lesions could be discovered had been in intimate contact with the infected animals. Cultures from the cecal contents of these normal rats yielded no salmonella at all in 6 instances. In a seventh normal rat one colony of *S. enteritidis*, agglutinated 1:320, was isolated, and in the eighth animal 2 colonies were recovered which were agglutinated up to 1:640. However, inasmuch as the entire environment was contaminated these occasional colonies can hardly be considered very significant, and it may be concluded for all practical purposes that animals without cecitis even when in contact with others with advanced disease were not infected with the specific organism.

Intimacy of the association of the specific salmonella with the *lesions* of cecitis is further shown by a comparison of cultures of stool and cecal material. A whiff of ether given to a diseased rat led to the expulsion of a pellet of stool which was caught in a test tube for culture. The animal was immediately anesthetized and cultures were also made from the cecal contents. In the case of four animals which had cecitis salmonella was isolated in each instance from the cecal contents; in three of these no salmonella could be recovered from the stool, and in the fourth only a very few colonies, although the cecal contents yielded nearly a pure growth.

The above experiments suggest strongly that a specific strain of salmonella was the cause of cecitis in this epizoötic. It seemed important, however, to study the effects of

introduction of the organism into healthy rats. The obvious difficulty here was the knowledge that the "spontaneous" incidence of cecitis in the colony was nearly 100%. The problem of control was therefore paramount.

2. *Attempts to Produce Cecitis by Ingestion of Strains of Salmonella Isolated from Cecal Contents.* In a first group of experiments huge amounts of culture were placed in the water bottles of healthy rats. Within 48 hr all come down with a violent diarrhœa and approximately half the animals died. Autopsy showed an extreme diffuse acute enteritis with watery bowel contents from which the specific salmonella was recovered in pure culture. An example of the lesion is shown in Fig. 1. Five out of a group of 12 rats recovered from the acute infection and remained apparently well. However, when they were sacrificed 10 weeks later 3 of the 5 showed typical advanced ulcerative cecitis.

In a second group of experiments small amounts of 24-hr agar culture of the salmonella (one or two loops) were placed in the water bottles nearly every day over a period of approximately 2 months. The animals remained well with the exception of 2 who had transient diarrhœa. There were 12 animals in the experimental group and 12 litter mate controls who received no culture. When the animals were sacrificed (Table I) the incidence and severity of cecitis was essentially the same in the two groups. The slight differences as shown by many observations in this laboratory are not significant.

Hence it can be concluded that the continuous ingestion of huge doses of salmonella over and above the minimal numbers which were prevalent in the laboratory did not serve to increase significantly the incidence of cecitis or to make it appear earlier in the experimental group. If the dose was pushed beyond a certain point there developed not chronic ulcerative cecitis but acute enteritis—an entirely different lesion. Furthermore even in rats with the most advanced cecitis associated with heavy infestation of salmonella severe acute diffuse enteritis never developed spontaneously.

Summary. It appears, then, that no proof has been brought that salmonella is the cause of ulcerative cecitis of rats. In our laboratory a specific strain of salmonella was, to be sure, intimately associated with the lesions and this organism further was shown to be pathogenic for rats, since an acute diffuse enteritis was readily produced and the organism was again recovered from the lesions. Chronic cecitis, however, failed to develop to a significantly greater extent than in untreated controls. It is possible that some other agent is the primary cause of cecitis and that salmonella is merely an associated organism or one which tends to act as a secondary invader. Further search for such a primary agent is in progress.

We are indebted to Miss Gail Reeves for assistance with the cultures.