sponsible for the original illness, or without the renewal of the activity of the infectious agent does the anaphylactic shock merely activate old lesions? Is the exacerbation a true herpetic encephalitis, or is it merely a flare-up of an old inflammatory locus due to some non-specific stimulus? The evidence available at the moment indicates that we are dealing with a renewal of the essential disease process. From the point of view of the symptomatology, it may be observed that the exacerbations frequently show more severe and more widespread evidence of disease than do the initial infections. This would indicate enlargement of the affected area in the nervous system. Even more convincing is the evidence already reported[44] of recovery of *Herpes simplex* virus from the nervous system of these rabbits as long as 9 months after the initial infection. The virus is to be found in the nervous system not only in the active stages of the disease, but also during quiescent remissions. To interpret these results in terms of the relationship of antigen-antibody reactions to the dynamics of infection is speculative, but hypotheses based on this line of thinking are intriguing. It seems that these rabbits have become carriers by overcoming the initial infection yet continuing to harbor virus in their tissues. That anaphylactic shock results in a breakdown of this symbiosis in which the virus is present in the central nervous system without signs of disease may indicate that immunity to the virus suffers a temporary lapse during or following the anaphylactic shock which allows the virus once again to express its virulence. To claim that anaphylactic shock is in any way a specific means of precipitating latent neurotropic virus infection is not intended, but whatever might be the alteration in the immune or physiologic state of the animals which is responsible for disruption of the established host-parasite balance, it is effectively produced by anaphylactic shock. Although the recently recognized encephalitis following pertussis immunization shows a striking parallelism to this phenomenon, we are unaware of the demonstration of identical disturbances in recognized human disease. Careful elucidations of the factors involved in the largely unexplored realm of post-infectious and undiagnosed encephalitides commonly occurring in childhood, and in exacerbations of symptomatology in the post-encephalitic patients might reveal mechanisms in common with the experimental disease.

Summary. 1. Evidence that virus disease may develop a latent state is reviewed with an account of the reports of successful activations of latent infections.

2. Nineteen instances of precipitation of latent herpetic infection in rabbits by anaphylactic shock are presented.

3. Recovery of *Herpes simplex* virus from rabbit central nervous system during periods of (a) quiescence, (b) chronic encephalitis, (c) spontaneous exacerbations, and (d) anaphylactically induced precipitations of encephalitis is reported.

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Invasion by *Shigella sonnei* of Tissues of Mice Following Gavage with Viable Shigella.*

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In a previous publication[1] we reported that white mice did not show any signs of infection but did develop a considerable degree of active immunity against intraabdominal chal-

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1 Cooper, Merlin L., and Keller, Helen M., PROC. SOC. EXP. BIOL. AND MED., 1947, **64**, 442.

TABLE I.
Number of Mice in Whom Viable Shigella Were Found Outside the Gastrointestinal Tract Following Gavage with Viable *Shigella sonnei*.

Source of cultures	Incidence of positive cultures Time of culture after gavage			Total
	15-30 min.	45-120 min.	24 hrs	
Spleen	14/29*	6/22	1/20	21/71
Liver	15/29	6/22	1/20	22/71
Kidney	13/29	7/22	1/20	21/71
Mes. Gl.	27/29	15/22	1/20	43/71
Lung	22/29	10/22	2/20	34/71
Heart	18/29	6/22	1/20	25/71
Tail	2/29	0/22	1/20	3/71

* Numerator = No. of mice with positive cultures. Denominator = No. of mice cultured.

lenge following administration by gavage of viable *Shigella sonnei*.

This evidence of antigenic stimulus raised the question whether soluble antigen was absorbed from the gastrointestinal tract or whether the Shigella, still viable, might invade or be transported from the gastrointestinal tract into various tissues of the mice.

Data are presented in this report showing the results when cultures were made of various tissues of mice sacrificed at intervals following gavage with viable *Shigella sonnei*. Tail blood was also cultured.

Methods. The strain of *Shigella sonnei* (Ch) used in these experiments had been isolated by us several years ago from the stool of a patient (Ch) acutely ill with bacillary dysentery in the Children's Hospital. It has remained highly mouse virulent. Brain heart infusion (Difco) cultures of this strain of Shigella 18 to 20 hours of age were used for gavaging. The viable bacterial counts were usually 1.2 billion organisms per ml.

For gavaging a 2 ml luer-lock syringe was used with a blunt 18 gauge needle 2 inches in length. The needle was passed over the tongue and down the esophagus into the stomach where 1 ml of culture was deposited.

At intervals after gavage, tail blood was obtained for culture. The distal half of the tail was painted with tincture of mercresin for 3 minutes. The mercresin was removed with an alcohol sponge and the tail was dried with a sterile dry sponge. The end of the tail was clipped with sterile scissors and 2 or 3 drops of blood obtained and cultured in brain heart infusion (Difco). The mouse was then sacrificed by inhalation of ether. The abdomen and thorax were opened under sterile conditions and the spleen, kidney, central mesenteric gland, part of the liver, part of the lungs and finally the heart were each removed in the order mentioned with separate sterile instruments. Sterile gauze was packed around organs to absorb local bleeding. Each specimen of tissue was cultured in separate tubes of brain heart infusion (Difco). All positive cultures were studied and the organism present identified.

Data in Table I show the number of mice in which *Shigella sonnei* were found in different tissues outside the gastrointestinal tract at intervals after giving them by gavage 1.2 billion viable *Shigella sonnei*. Of 29 mice sacrificed and cultured 15 to 30 minutes after gavage, *Shigella sonnei* were cultured from: the central mesenteric glands of 27 mice; the lungs of 22; the hearts of 18; the livers of 15; the spleens of 14; the kidneys of 13, and the tail blood of only 2 mice. Of 22 mice sacrificed and cultured 45 minutes to 2 hours after gavage, *Shigella sonnei* were cultured from: the mesenteric glands of 15 mice; the lungs of 10; the kidneys of 7; and the hearts, livers and spleens of 6 mice. All tail blood cultures from this group of 22 mice were sterile. Cultures from tissues of mice sacrificed 24 hours after gavage were usually negative. Of a group of 20 mice sacrificed at this time positive cultures were obtained from only 2 animals.

The highest incidence of positive cultures came from the central mesenteric glands, a finding to be expected if the organisms were

TABLE II.
Cultures of Mouse Tissues Removed Within 5 to 10 Minutes After Giving Various Numbers of Viable *Shigella sonnei* by Gavage.

Mouse wt, g	Dose of culture, millions	Spleen	Liver	Kidney	Mesenteric gland	Lung	Heart	Tail blood
8	1200	+	+	+	+	+	+	—
8	1200	+	+	+	+	+	+	+
8	1200	—	+	+	+	+	+	—
8	1200	+	+	+	+	+	+	—
8	1200	—	—	—	+	+	+	—
8	1200	—	—	+	+	+	+	
8	750	+	+	+	+	+	+	
10	300	+	+	+	+	+	+	
10	150	+	+	+	+	+	+	
10	150	—	—	—	—	+	—	
10	15	—	+	+	+	+	+	
9	13	—	—	—	+	—	—	
9	1.5	—	—	—	—	—	—	
10	1.3	—	—	—	+	—	—	
11	0.15	—	—	—	—	—	—	
10	0.01	—	—	—	+	—	+	

transported from the intestinal tract by way of the lymphatic system.

The occurrence of the second highest incidence of positive cultures from lung tissue raises the question of the possibility of aspiration of culture at the time of gavage. This possibility is difficult of exclude, but if a tightly fitting syringe is used, there is no evidence of leakage from the syringe during the process of gavaging. The volume of culture deposited in the stomach was not large enough to overflow up the esophagus and into the lungs.

The occurrence of the third highest incidence of positive cultures from the heart indicates that the blood is another means of their transportation. With positive heart cultures the majority of other tissues cultured might be expected to show, as indeed they did show, the presence of the organisms. Of a group of 23 mice sacrificed 15 to 60 minutes after gavage, all with positive heart cultures, there were 22 mice with positive mesenteric gland cultures; 21 with positive lung cultures; 19 with positive liver cultures; 17 with positive spleen cultures; 15 with positive kidney cultures and 2 with positive tail blood cultures. On the other hand, if heart cultures were negative, fewer cultures from other tissues might be expected to be positive. This was found to be the case, except for cultures of the mesenteric glands, all of which showed the presence of *Shigella sonnei*. For example, of a group of 19 mice sacrificed, 15 to 60 minutes after gavage, all with negative heart cultures, the Shigella were found in the mesenteric glands of all 19 mice; in the lungs of 8; in the kidneys of 5 and in the spleens and livers of 3 mice.

The role of the reticuloendothelial cells in removing the Shigella from the circulation and tissues is most likely great. However, examination of tissue sections from some of these mice failed to show any recognizable activity of the cells of this system. We are indebted to Dr. Ralph J. Johansmann for these studies.

Influence of the number of Shigella given by gavage on their invasion outside the gastrointestinal tract. Data in Table II show the results of culturing tissues removed from mice weighing 8 to 11 g within 5 to 10 minutes after they had been given various numbers of viable *Shigella sonnei* (Ch) by gavage. It is observed that doses above 13 million organisms usually resulted in positive cultures while doses of 13 million and less gave very few positive cultures. When the same type of experiment was done with mice weighing 17 to 18 g, doses of 150 million viable Shigella were the minimal number above which most cultures of tissues were positive and below which few cultures were positive. These data indicate not only that the number of viable

Shigella given by gavage was a factor influencing invasion from the gastrointestinal tract, but that within 5 minutes after their administration by gavage they could be cultured from tissues of the mice.

Summary. *Shigella sonnei,* when given by gavage to white mice, invaded beyond the walls of the gastrointestinal tract; were found within 5 to 30 minutes in cultures of spleens, livers, kidneys, central mesenteric glands, lungs and hearts of the majority of mice; and were seldom cultured from these tissues after 2 hours from the time of gavage. The Shigella were found most often in cultures of the central mesenteric glands and least often in cultures of tail blood.

The number of viable Shigella and the weight of the mice were factors influencing the invasion by the Shigella from the gastrointestinal tract. The minimal number of viable Shigella which, when given by gavage, invaded beyond the gastrointestinal tract, was 150 million for mice weighing 17 to 18 g and 13 million for mice weighing 8 to 11 g.

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Effect of Non-Specific Protein (Aolan) upon Twelve-Hour Nocturnal Gastric Secretion in Man.*

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A recent study[1] demonstrated that nocturnal and 24-hour gastric secretion may diminish in man during the intramuscular injection of large quantities of an enterogastrone concentrate. This decrease is variable in degree, temporary in duration, and often followed by an increased output of acid. Since the concentrate contains a mixture of proteins, the possibility of a non-specific effect was considered. The present study was undertaken to further clarify this question.

Previous investigations of the effect of non-specific proteins upon gastric acidity have dealt with secretion stimulated by various test meals or by histamine. Vanzant and Snell[2] observed, in nine healthy dogs injected intravenously with a killed culture of *B. prodigiosus,* a decrease in the volume and acidity during the febrile period, followed by a more prolonged rise, and 48 hours later by normal values. Meyer, Cohen and Carlson[3] also noted a temporary decrease in gastric acidity during the fever induced by *B. prodigiosus.* The acidity of the fasting contents removed during the febrile period in 6 of 17 patients with peptic ulcer, treated with triple typhoid vaccine or Lilly's type "H" antigen, was unchanged in 2 and decreased in 4; in one case the acidity increased 3-fold several hours after the termination of fever. Following the treatment, there was no constant change in acidity.[2] Most writers have reported a decrease in gastric secretion during fever, although the results vary considerably.[4] Martin[5] found no constant rise or fall in the acidity of patients with peptic ulcer given repeated intramuscular injections of 10 cc of a purified milk preparation (Aolan).

Method of Study. Ten patients, 9 males and 1 female, between the ages of 36 and 61 years, were studied. A duodenal ulcer was present in 9 and a jejunal ulcer in 1 male patient. The 12-hour nocturnal gastric secre-

* This study was supported in part by a grant from the Upjohn Co., Kalamazoo, Mich.

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