

the considerable fluctuations in NA concentration during the recovery period, and the longer recovery period than for the myocardium. It can be tentatively suggested that the differences in the response of the vein to the stressor are due to the fact that the apparatus for NA resynthesis is weaker in the smooth muscle of the vessels than in the myocardium of the ventricles and, in particular, of the auricles. It is also possible that the smooth muscle of the vessel has lower resistance than the myocardium to stress.

With all these explanations it seems probable that stress injury to the cardiovascular system may be more severe in the vascular muscles, where the most profound changes in NA content after stress were discovered.

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#### STATE OF THE SMALL INTESTINE IN RABBITS INFECTED WITH *Salmonella*

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The degree of involvement of different parts of the small intestine in salmonellosis has not yet been adequately studied. Yet the results of such investigations could tell us more about the mechanism of development of the fundamental functional and morphological disturbances in this infection.

The object of this investigation was to study the role of different parts of the small intestine in rabbits in the genesis of disturbances of digestive function in experimental salmonellosis. Activity of hydrolytic enzymes (lactase, maltase, alkaline phosphatase) was accordingly determined in the mucosa of the duodenum, jejunum, and ileum of rabbits infected with *Salmonella typhimurium*, with differences in the severity of the morphological changes in these respective zones. The effect of morphological and biochemical changes in the small intestine on the development of diarrhea also was studied.

#### EXPERIMENTAL METHODS

Salmonellosis was produced in 110 male chinchilla rabbits weighing 1000-1200 g. All the animals had previously been quarantined and tested bacteriologically for salmonellas. After starvation for 48 h the rabbits were given 2 ml of 5% soda solution. Next, 84 rabbits were infected perorally with 5 billion *S. typhimurium* cells in suspension with milk, and 26 control rabbits were given milk only. Experimental salmonellosis was confirmed by clinical, bacteriological, and serological tests. The disease in the rabbits was mild, moderately severe, or severe. Some of the animals with the severe form of the illness died at various times after infection. Experimental rabbits were killed by air embolism 1, 3, 5, 7, 9, 14,

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TABLE 1. Activity of Hydrolytic Enzymes of Mucosa of Small Intestine (in units/g protein) Compared with Its Morphological State in Course of Experimental Salmonellosis ( $M \pm m$ )

Morphological state of small intestine	Period of development, days	Number of observations	Duodenum			Number of observations	Jejunum			Ileum		
			lactase	maltase	alkaline phosphatase		lactase	maltase	alkaline phosphatase	lactase	maltase	alkaline phosphatase
Control (n=26)	1-3	26	1.5±0.2	37.5±5.3	60.2±9.7	26	2.1±0.4	67.9±10.9	92.8±12.3	1.1±0.1	46.9±10.7	58.1±10.3
Acute catarrhal inflammation (n=19)	5-9	19	1.3±0.4	26.9±6.3	23.7±6.0	2	0.4±0.09	42.3±14.6	54.1±19.9	0.9±0.2	20.8±9.9	40.3±7.5
	11-21	4	0.9±0.5	13.1±1.0	21.9±1.9	3	1.7±0.1	42.0±1.3	40.1±6.3	0.6	7.1	8.8
Erosive enteritis, ulceration of necrotic lymphoid follicles (n=16)	5-9	4	1.3±0.4	29.4±14.6	40.5±20.7	4	1.7±0.6	19.9±10.7	38.2±12.0	0.5±0.2	2.2±0.2	10.6±6.4
	11-21	4	0.85±0.2	10.1±0.4	11.2±3.3	4	0.4±0.4	12.8±4.4	35.0±15.0	<0.01	7.6±3.3	30.7±4.9
	11-21	1	<0.05	<0.001	17.4	—	<0.001	<0.001	<0.05	>0.05	6.0±1.8	<0.02
	11-21	1	0.56	21.7	17.4	—	—	—	—	1.7±0.6	<0.01	34.5±28.1
Reparative and immunomorphologic reactions (n=21)	11-21	4	1.3±0.4	27.7±4.9	43.5±11.8	5	2.3±1.0	43.8±11.8	57.8±25.1	4.3±3.0	26.6±13.1	58.6±39.0
	27	10	3.7±1.4	72.9±26.3	83.9±32.4	10	3.9±0.3	53.4±12.7	117.5±26.6	4.9±0.6	62.2±13.1	118.9±21.0
							<0.001			<0.001		<0.01

Legend. Here and in Table 2, values of P given compared with control. n) Number of animals used in experiment.

TABLE 2. Correlation between Enzyme Activity in Small Intestine (in units/g protein) and Disturbance of Digestion in Rabbits Infected with *S. typhimurium* ( $M \pm m$ )

State of animals' stools	No. of observations	Duodenum			Jejunum			Ileum		
		lactase	maltase	alkaline phosphatase	lactase	maltase	alkaline phosphatase	lactase	maltase	alkaline phosphatase
Normal	18	1.5±0.1	26.4±4.0	35.3±6.8	1.6±0.2	52.2±6.2	79.2±10.3	1.4±0.2	17.8±3.7	32.5±5.5
Diarrhea with mucus	9	0.9±0.3	30.7±9.5	51.5±23.8	1.0±0.2	22.0±4.3	46.4±11.0	1.2±0.2	9.4±1.5	19.6±3.0
					P<0.02	P<0.001	P<0.01		P<0.001	P<0.001

17, 21, 27, 33, 40, and 56 days after infection. Several samples were taken from each rabbit from the duodenum, jejunum, and ileum. Activity of lactase and maltase [6] and alkaline phosphatase [8] was determined in homogenates of the mucosa of these parts of the small intestine in the 56 killed animals only. Activity of the enzymes was expressed in units/g protein of the homogenate. Protein was determined by Lowry's method [7]. All the data were analyzed statistically [2].

Parallel morphological and bacterioscopic investigations were carried out on all animals (killed and dying). Salmonellas in the tissues were revealed by the indirect Coons' method [1, 9].

#### EXPERIMENTAL RESULTS

On analysis of the morphological changes in the small intestine of the experimental rabbits infected with *S. typhimurium* three principal states could be distinguished: acute catarrhal inflammation (25 rabbits), erosive enteritis with ulceration of necrotic lymphoid follicles of Peyer's patches (37 rabbits), and reparative and immunomorphologic reactions (22). Each of the above forms corresponded to a particular period of illness of the animal.

Acute catarrhal inflammation of the small intestine was found in the experimental rabbits at three periods: the beginning of development (1st-3rd day), the height of the disease (5th-9th day), and the beginning of decline of the infectious process (11th-21st day). At the beginning of development of the infection alkaline phosphatase activity in the duodenum and lactase activity in the jejunum fell (Table 1). At the height of the infectious process, small hemorrhages appeared in the mucosa of different parts of the small intestine and a deficiency of maltase and alkaline phosphatase was found. At the beginning of decline of the infectious process activity of the enzymes in the duodenum returned to normal. In the jejunum maltase and alkaline phosphatase activity remained sharply reduced, whereas in the ileum a deficiency of all three enzymes was observed.

Erosive enteritis and ulceration of necrotic lymphoid follicles of Peyer's patches were found in the small intestine at the height of the disease (5th-9th day) and at the beginning of its decline (11th-21st day). Activity of the various enzymes was sharply reduced at the height of the disease in the duodenum and jejunum. In the ileum there was a marked deficiency of maltase and alkaline phosphatase activity (Table 1). At the beginning of decline of the infectious process necrotic lymphoid follicles were found, but only in the ileum. The epithelial cells were loosely arranged, but basically unchanged, and only maltase activity was reduced in this region.

Reparative and immunomorphologic reactions in the small intestine of the experimental rabbits occurred at the beginning of the decline (11th-21st day) and completion of the infectious process (27th-56th day). At the beginning of decline of the infectious process there was still a tendency for the maltase and alkaline phosphatase levels in all parts of the small intestine to fall, except in the ileum, in which alkaline phosphatase activity reached normal. Lactase activity also returned to normal in the small intestine. During the period of completion of the infectious process lactase activity was sharply increased in the jejunum and lactase and alkaline phosphatase activity in the ileum. Activity of the remaining hydrolytic enzymes in the small intestine was restored to normal (Table 1).

In the period from the 4th to the 11th day after infection diarrhea with mucus was observed in some of the experimental rabbits. An attempt was made to compare the morphological state and enzyme activity of different parts of the small intestine in experimental rabbits with and without diarrhea. Small hemorrhages were observed in the mucosa of the small intestine of the rabbits with diarrhea, and in addition, erosive enteritis with involvement of the lymphoid follicles of Peyer's patches was found in the jejunum and ileum. A deficiency of all three enzymes was found in these animals in the jejunum and a deficiency of maltase and alkaline phosphatase in the ileum (Table 2).

Acute catarrhal inflammation was found in the mucosa of the small intestine of experimental rabbits with formed stools, and necrotic single follicles could be seen in the Peyer's patches of the jejunum and ileum of three animals. Alkaline phosphatase activity in the duodenum and maltase and alkaline phosphatase activity in the ileum were sharply reduced. Enzyme activity in the jejunum was normal. The diarrhea in these rabbits was evidently associated mainly with the enzymopathy of the jejunum.

In salmonellosis of rabbits all parts of the small intestine were thus involved in the pathological process. The enzymopathy developed in the presence of acute catarrhal inflammation and it was more severe still in animals with erosive enteritis with ulceration of the necrotic lymphoid follicles of Peyer's patches in the small intestine, most frequently at the height of the disease, and it lasted until the 21st day of investigation. These findings indicate significant disturbances of membrane digestion in the small intestine for a long period of time, both in acute catarrhal inflammation and in erosive enteritis. Pathological changes appeared in the proximal zones, as was found in our experiments and observations on patients with acute intestinal infections [5], but also to a far greater degree in the distal zones of the small intestine, i.e., the morphological and biochemical changes had a proximal-distal orientation. A similar orientation of changes in different parameters also was demonstrated by other workers in disturbances of the functional state of the small intestine [3].

It has recently been established [4] that defects of membrane digestion accompany the development of intestinal dysfunction and are one cause of diarrhea. In fact, in the present investigation morphological changes in different parts of the small intestine and the enzyme deficiency in the experimental animals were more marked when clinical manifestations of digestive disorder were present. According to our observations, definite morphological changes combined with disturbances of the enzyme-forming function in the jejunum played the decisive role in the development of diarrhea in the experimental rabbits.

In the present experiments the maximal activity of all enzymes studied in healthy rabbits was found to be in the jejunum. At the beginning of development of the disease and at the height of the infectious process, this state of affairs also remained true in the experimental rabbits. At the end of the disease, at the period of culmination of the infectious process, maximal lactase and alkaline phosphatase activity (above normal) had shifted to the ileum. In all probability these facts reflect disturbances of the systemic mechanisms of regulation of the intestine in animals exposed to infection with salmonella.

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