pears as a late sequel it may be due to gradually developing atrophy of the duodenal mucosa brought about by changes in the normal physiological functions in this region which such an operation might well incur. It is likely that in pernicious anemia there is an atrophy or inactivity of the pyloric gland (Brunner’s glands) organ (10). The absence of pernicious anemia in many cases of gastric achylia with atrophy of the mucosa would also be explained. Whether an inability to produce this ferment in the duodenum could be compensated for by its production in the stomach cannot be decided at present, but is of the utmost interest in relation to sprue as in this disease the blood picture of typical pernicious anemia may develop with the presence of Castle’s intrinsic factor in the stomach (19).

The results of the experiments recorded in this report naturally give rise to many other interesting questions concerning the etiology of all the macrocytic hyperchromic anemias which it would be premature to consider at present except on a theoretical basis. However, the possibility of this unknown ferment being related to enterokinase and its production in the jejunum or ileum as well as in the duodenum must be considered.

REFERENCES


Histidine in Experimental Gastric Ulcer

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HISTIDINE hydrochloride was introduced by Weiss and Aaron (1) in 1933 for the treatment of peptic ulcer in man. In their investigation on dogs they used the Mann and Williamson (2) operation for the production of peptic ulcer, the principle of which is the diversion of alkaline duodenal, pancreatic and biliary secretions into the terminal ileum. As a result, protein digestion to the amino acid end stage, is interfered with. They concluded that deficiency of the essential amino acid, histidine, was responsible for the ulcer formation, since substitution therapy of histidine by injection prevented the occurrence of these lesions.

In this country, Volini and McLoughlin (3) produced gastric ulcers in rats by giving histamine parenterally and by enema. In their report they state that these ulcers did not occur, when the animals were protected by previous injections of histidine.

Fontes and Bauer (4) repeated the experiment of Weiss and Aaron substituting oral administration of histidine for the parenteral method, and reported ulcer prevention in only 30% of the animals. They questioned whether the lack of histidine is the sole factor in the production of experimental ulcer.

Ivy (5) questions the basis of histidine-deficiency-theory. He believes “Weiss and Aaron did not ‘run’ their Exalto-Mann Williamson dogs long enough.” Recently Sandweiss, Saltzstein and Glazer (6) performed the Mann-Williamson operation on twelve dogs in an attempt to repeat the experiment of Weiss and Aaron. They found that the animals developed ulcers even though they received daily histidine injections. Flood and Mullins (7) found that 6 out of 11 dogs re-
TABLE I

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Rats</th>
<th>Feeding</th>
<th>Fluids</th>
<th>Injections</th>
<th>Results</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15</td>
<td>Fasting for two days, Steenbock Bills Diet and fresh vegetables on third day.</td>
<td>2% pepsin and 0.3% HCl</td>
<td>Daily ½ c.c. Histidine</td>
<td>14 animals had ulcers</td>
<td>93%</td>
</tr>
<tr>
<td>B</td>
<td>15</td>
<td></td>
<td>2% pepsin and 0.3% HCl</td>
<td>None</td>
<td>14 animals had ulcers</td>
<td>93%</td>
</tr>
<tr>
<td>C</td>
<td>10</td>
<td></td>
<td>Water</td>
<td>Daily ½ c.c. Histidine</td>
<td>5 animals had ulcers</td>
<td>50%</td>
</tr>
<tr>
<td>D</td>
<td>20</td>
<td></td>
<td>Water</td>
<td>None</td>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>

ceiving daily injections of histidine monohydrochloride after surgical duodenal drainage developed ulcers.

Our present investigation was undertaken to evaluate the efficacy of histidine monohydrochloride in the prevention of experimental gastric ulcer in the rat. Our previously described method of ulcer production (8, 9), based on the feeding of pepsin-hydrochloric acid, was employed in a somewhat modified form. A 2% solution of commercial pepsin (1:10,000 Parke, Davis & Co.) in 0.3% hydrochloric acid, instead of the originally described 20% solution was found equally effective.

EXPERIMENTAL

Sixty rats of the original Wistar strain, averaging four months in age were used in this experiment. The animals were divided into four groups as shown in Table I. The rats in all the groups were fasted for two days and fed the Steenbock Bills (10) stock diet with fresh lettuce and sliced carrots on the third day, in recurrent cycles for a period of sixteen days. Stoppered flasks containing a 2% solution of pepsin (1:10,000 Parke, Davis & Co.) and 0.3% hydrochloric acid were attached to the cages of groups A and B so that the animals could partake of these solutions ad lib. In groups C and D a continuous supply of water was available. In groups A and C the rats received daily injections of 0.5 c.c. of histidine monohydrochloride (Larostidin-Hoffman La Roche, Inc.) for nineteen days. Three of these injections were given prior to the onset of the experiment. To prevent leakage, the point of injection was sealed with collodion.

RESULTS

At autopsy, the pepsin hydrochloric acid group (A) that had received 19 daily injections of histidine revealed an incidence of about 93% of multiple gastric lesions of the pro-stomach. The incidence was equivalent to that of the pepsin hydrochloric acid group (B) that had received no histidine injections.

Autopsy findings in group (C) which received no pepsin hydrochloric acid mixture with daily injection of histidine disclosed that 5 of 10 rats (50%) had multiple gastric lesions. A control group (D) under a similar regime without histidine injections developed no gastric lesions.

The lesions had raised margins and umbilicated centers. The gross and microscopic picture (Fig. 1) of submucosal edema, cellular infiltration with varying degrees of desquamation and mucous membrane erosion in the rats which received histidine injections, was similar to that previously described (8, 9).

DISCUSSION

Histidine monohydrochloride is being subjected to universal trial in the treatment of peptic ulcer in man. Its use is based upon the histidine-deficiency-theory of Weiss and Aaron and on their reports in animal investigation.

The recent clinical investigations of Sandweiss, Martin, Flood and Mullins in the use of histidine in the therapy of peptic ulcer are not in full accord with the earlier favorable reports of foreign and American investigators. The original work of Weiss and Aaron on dogs has not been confirmed by other investigators. Recently, the value of histidine in prevention of experimental gastric ulcer in the dog has been questioned by Ivy (5) and Sandweiss, et al (6). The favorable reports of Volini and McLaughlin in preventing ex-

Fig. 1. Microscopic appearance of section of experimentally produced ulcer of the rat's stomach.