

time though usually there is depression of strength of the sinus contraction before there is measurable slowing of rate.

By one method or another, it is usually possible to produce atrial inotropic effects in the turtle heart without accompanying chronotropic effects. The usual interpretation placed on the Engelmann hypothesis is that the "chronotropic fibers" produce only chronotropic effects, while "inotropic fibers" produce only inotropic effects. Our experiments on the turtle heart do not exclude the possibility that the sinus venosus and the pacemaker within the sinus are innervated by inotropic and chronotropic fibers of different function and differing from each other either by number or by threshold. Using the heart as our only indicator, however, we have not been able to find any consistent method of differentiating fibers causing sinus inotropic effects from fibers causing slowing of the pacemaker.

6604

Change in Viscosity of Mucin with pH.

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For many years physiologists have known that mucin plays a lubricating, protective, and soothing rôle in gastro-intestinal function. It is synthesized in the mucous cells and is the characteristic constituent of mucus. The slimy, viscid mucus spreads over the surface of the mucosa and facilitates the passage of food particles over the mucosa with minimum of injury.

Fogelson¹ and Atkinson² have shown that when patients with peptic ulcer are given mucin, there is prompt relief of the subjective symptoms without recurrence in most patients for as long as one year.

Since mucin is a physiological secretory product of the gastro-intestinal tract and since mucin administered orally to ulcer patients gives every indication of healing, it suggests that the metabolic difficulty leading to ulcer formation may be a disturbance of mucin metabolism.

¹ Fogelson, S. J., *J. Am. Med. Assn.*, 1931, **96**, 673.

² Atkinson, A. J., *J. Am. Med. Assn.*, 1932, **98**, 1153.

This is the first of a series of papers on the study of mucin metabolism, its importance in the functioning of mucous membrane, and its probable bearing upon ulcer formation.

Fogelson¹ and Atkinson² have pointed out that mucin has a high acid combining power and thus helps to control gastric acidity. Jones and Ivy³ have shown that the buffer action of mucin is less than the buffer action of peptones. Since peptones are not peculiarly beneficial in ulcer therapy, they conclude that control of gastric acidity is not the important beneficial factor in mucin therapy.

It is obvious that the more viscous and tenacious the mucin is, the more effective it will be in protecting the mucosa. We have studied the change in viscosity of mucin with pH at the temperatures 25° and 37°C.

We used Wilson's Prepared Gastric Mucin, prepared by the method of Fogelson. The samples* were made up by incorporating phosphate buffer mixtures, sodium hydroxide, or 0.1 N hydrochloric acid to portions of isoelectric gastric mucin in such proportions that they gave emulsions varying in pH from 2 to 8. The pHs were determined by the quinhydrone electrode. Five percent emulsions were made up by adding water to 10 gm. samples of mucin and making them up to 200 cc. Care was always exercised to insure that all of the mucin was dispersed in the water. The emulsions were allowed to flow from a 100 cc. capillary pipette, kept at a constant temperature. The time of flow was recorded. The time of flow for water was obtained for comparison. When the time of flow is plotted against pH, it is found that the viscosity is at a maximum at the isoelectric point, 4.98. In this respect, mucin differs from proteins in general in that they show their minimum viscosity at their isoelectric point. The time of flow of a 5% emulsion of mucin at a pH of 4.98 at 37°C. is approximately 2½ times greater than the time of flow at a pH of 7.4, and the time of flow at a pH of 2 is 1½ times greater than at a pH of 7.4. We were interested in relative rates of flow and not absolute viscosity; hence we have not calculated viscosities in absolute units. It is significant that mucin shows its maximum viscosity at its isoelectric point, for it indicates that mucin has a greater protective action upon gastric mucosa in the presence of hydrochloric acid than it has in its absence.

In view of this data, we may visualize the protective action of mucin on the surface of the cells of the mucosa in microscopic

¹Jones, K. K., and Ivy, A. C., *PROC. SOC. EXP. BIOL. AND MED.*, 1931, **29**, 218.

* We are indebted to Dr. David Klein of the Wilson Laboratories for these samples.

dimensions as follows: Mucin is synthesized by the mucous cells at approximately pH 7.4 and presumably is secreted in the mucus at a pH of 7.4. Ivy and Oyama⁴ found that mucus from pouches of the pyloric antrum of dogs had a pH of 7.0 to 7.5. The mucus spreads over the surface of the cell and the adjacent cells in a microscopic layer. When the gastric juice comes in contact with the alkali mucinate, isoelectric and acid mucin is formed. The viscosity of this mixture will depend upon the relative amounts of alkali mucinate, isoelectric mucin, and acid mucin present. Whatever the proportions may be, the viscosity will be greater than it was at the time of secretion. The increase in viscosity further retards the diffusion of hydrochloric acid and pepsin through the layer so that there is a progressive increase in pH towards the surface of the cell. The continual secretion of mucus maintains a pH very near 7.4 at the surface of the cell. This offers a probable explanation why the stomach does not digest itself. When a petechial injury to the mucosa occurs, the large excess of tenacious mucin slips over the injured area and protects it from the action of gastric juice. This may explain the marked healing ability of the mucosa. The outer layer of mucus is continually being rubbed off by the food particles sliding over the surface. A part of it may coat these particles with the result that they slide over the mucosa with less trauma. It becomes mixed with the gastric contents and passes into the intestine.

If we have described correctly the events that take place in the thin mucus layer on the surface of the cells lining the digestive tract, it is evident that in a condition in which there is a disturbance of mucin metabolism, there is less protection for the cells against the corrosive action of gastric juice. When an injury occurs, there is less mucus available to cover the injury and to protect it from the corrosive action of the gastric juice.

We have shown that the viscosity of gastric mucin changes with pH, passing through a maximum at its isoelectric point, 4.98. We have suggested the importance of mucin metabolism in the functioning of the mucosa of the digestive tract and that a disturbance in the level of mucin metabolism may be a predisposing cause of ulcer formation.

Further investigations on other conditions which affect the viscosity of mucin are in progress.

⁴ Ivy, A. C., and Oyama, Yutaka, *Am. J. Physiol.*, 1921, **57**, 51.