dominate for several trials and then be superseded by the other. Yet there can be no doubt that both responses were genuine and also that they were unstable (appearing and disappearing) even though the stimulating conditions remained the same.

Frequency graphs of the flexing twitch as well as of the extension response were so irregular that they were quite unrecognizable as learning curves. The only similarity to the typical curve of learning was that each response was absent at the start of training and increased somewhat in frequency during the later trials. When both the crossed extension and the flexion reactions were considered together, the combined frequency of responsiveness for all animals rose gradually for the first 300 trials (*ca.* one week) and continued at approximately 20 per cent responsiveness for the remaining 700 trials (*ca.* the two additional weeks).

In spite of this irregular level of about 20 per cent which persisted when both responses for all subjects were pooled, we could find no evidence of retention, over the intervals between experimental sessions, in the behavior of any one individual considered by itself. It should be clear, moreover, that the spinal behavior of the present subjects cannot be satisfactorily fitted into the conditioning formula, since that behavior was a combination of two antagonistic responses, now one occurring, now the other.

The conclusion to be drawn from these results is certainly not that spinal conditioning must be some sort of an artifact, but simply that we have not been able to establish it in chronic spinal animals under the conditions of the present experiments. The fluctuating responses of our preparations seem to us to be more adequately described as temporary changes in reflex behavior.

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A Gastric Mucigogue Action of the Alkyl Sulfates

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The continued introduction of new remedies for the management of gastric and duodenal ulcer is sufficient evidence that the last word on such remedies has not been written. In the past the problem has been concerned chiefly with the effect of the extrinsic agent upon gastric acidity and to a less extent with its effect on peptic activity. Certain of the detergents have recently attracted attention on account of their antipeptic action. The present studies supply the first evidence that these detergents can stimulate an intrinsic gastric mechanism—secretion of mucus—which serves to protect the mucosa, mechanically, by its antacid effect, as well as to enhance any antipeptic activity which the agent itself might possess.

In a recent series of articles Shoch and Fogelson (*8*) reported that sodium alkyl sulfate inactivates pepsin *in vitro* without altering the pH of the solution; that it does the same *in vivo* (*9*) and, when administered to dogs with gastric ulcers produced experimentally by histamine, prolongs their lives considerably (*9*); and that it gave strikingly good clinical results in patients whose ulcers appeared to be intractable under other forms of therapy (*2*). The *in vitro* effects of these agents have been confirmed by others (*4*) and by ourselves. Regarding the *in vivo* effect, no such uniformity of results has been reported. Kirsner and Wolff (*5*), as well as Steigmann and Marks (*10*), failed to obtain the beneficial clinical results described by Fogelson and Shoch.

On administering to rats either of two highly purified products,[1] sodium dodecyl sulfate (C_{12}) and sodium "Lorol" sulfate (a mixture of C_{12} chiefly, plus some C_{14} and C_{16}), we observed in many of the animals a copious gastric secretion which appeared to be very rich in mucus. These results will be reported elsewhere. In view of the importance of mucus and its specific component, mucin, in protecting the gastric mucous membrane from destruction (ulceration) by the gastric juice, we were especially interested in the mucigogue action of the aforementioned agents. To determine whether these agents acted similarly in other animal species and also to obtain adequate quantities of mucus for study, we conducted experiments on dogs, the results of which form the substance of this report.

In fasting dogs under nembutal anesthesia, the stomach was isolated by ligation of the esophagus in the neck in conjunction with ligation of the pylorus either alone or with the addition of a ligature around the antrofundal juncture, according to a technique previously described (*6*). The latter procedure established a pyloric and a main stomach compartment. The whole stomach or the compartments were fistulized, as the case might be. The whole stomach or the pouches were lavaged thoroughly with saline at 38° C. until the last lavage returned clear (2 to 4 lavages). The gastric contents were then allowed to drain and, when the secreted material was represented only by

[1] Supplied through the courtesy of Dr. J. H. Shipp, Fine Chemicals Division, E. I. du Pont de Nemours Company.

alkaline mucus, a control specimen of an hour's secretion was then collected, in 15-minute fractions for the dodecyl sulfate or sodium "Lorol" sulfate in saline or distilled water, warmed to body temperature, was then introduced slowly through the fistula. The quantity introduced was sufficient to fill the whole stomach or pouch at a pressure of 5 to 6 cm. of water. The test agent was allowed to remain in the stomach at this pressure for 1 to 1.5 hour. The gastric contents were drained completely, and the gastric secretion was collected. A 2-per cent solution of sodium first hour and subsequently in 30- or 60-minute fractions for an additional 2 or 3 hours. The specimens were analyzed for mucin by two methods[2] (gravimetric and colorimetric) developed in our laboratory. Since the gastric secretion following the introduction of the alkyl sulfates was always alkaline, the alkalinity was determined—by acidification, followed by removal of CO_2 and back titration with alkali. Pepsin was determined by Nierenstein's and Schiff's modification (*7*) of Mett's method; and pH was determined colorimetrically and, when possible, with the glass electrode, using the Beckman pH meter.

In the evaluation of the effects of the sodium alkyl sulfates upon gastric secretory function, two phases can be distinguished: (1) immediate effect, as reflected in the composition and physical properties of the instilled solution while in the stomach; (2) aftereffect, as manifested by the secretory response of the mucous membrane after the stomach is emptied.

The volume of fluid recovered from the stomach after 1 to 1.5 hour was never greater than the volume of fluid instilled. On the contrary, when the instillate was an aqueous (hypotonic) solution of the detergent, a small decrease (about 7 per cent) in the volume of the gastric contents was actually observed. Although the aqueous alkyl sulfate solution, when introduced into the stomach, contained no chloride, the gastric contents recovered contained a considerable amount (e.g. 38.9 m.eq. for the experiment illustrated in Fig. 1). They were quite viscous and contained much mucin (0.21 per cent).

The volume of mucus secreted during this period could not be determined directly but could be calculated. If we assume that the mucus secreted during the period in which the alkyl sulfate solution was in the stomach had the same concentration of glucuronic acid derivatives as that secreted for the second hourly period following the withdrawal of the test solution, the volume of mucus added to the instillate by the stomach mucosa was fairly large (e.g. for Dog 4 in the experiment illustrated in Fig. 1, 25.5 cc.).

[2] To be reported.

Similar calculations on the assumption that the chloride concentrations of the two specimens were equal would lead to erroneous values for the volume of mucus added by the stomach (e.g. for Dog 4 in the experiment illustrated in Fig. 1, 86 cc.).

The results of such calculations are, however, of value in other respects. Teorell (*11*) views the gastric mucosa as a dialyzing membrane which is permeable to sodium chloride among other substances. These data offer impressive evidence that the chloride added by the stomach to the alkyl sulfate solutions is only partly the result of an actual secretion of chloride with the mucus, being derived to a greater extent from tissue fluid (blood) by diffusion. Furthermore, since the chloride addition is accompanied by an actual decrease in the volume of solution introduced into the stomach, a corresponding and quite considerable amount of water must have been absorbed. These results are of especial interest, since the problems of the absorption by, and diffusion through, the gastric mucosa are still moot questions in gastric physiology.

The effect of the alkyl sulfates on gastric secretion is not limited to the period of contact with the mucosa. After the withdrawal of the agent the secretion of mucus continues at a very high, although gradually diminishing, rate for several hours.

Fig. 1 shows data of the rate of secretion of mucus and the output of mucin for a representative experiment. Our other experiments gave strikingly similar results. According to Babkin and his associates (*1*), rhythmic stimulation of the vagi with a weak current is a rather specific stimulus for the secretion of mucus. Babkin selected one of Vine-

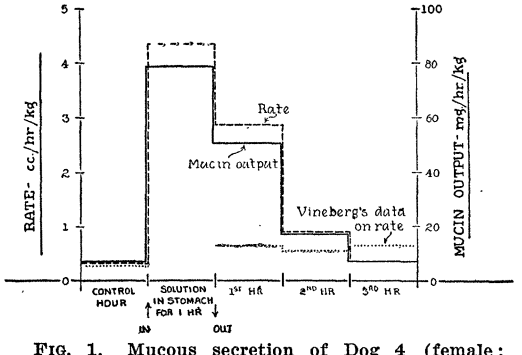

FIG. 1. Mucous secretion of Dog 4 (female; weight, 7 kg.; nembutal anesthesia; esophagus and pylorus tied; gastric fistula; stomach filled with 2-per cent aqueous sodium dodecyl sulfate for 1 hour).

berg's experiments (*12*) as representative of such an effect in the dog. When we calculated from Vineberg's table the volume of secretion per hour per kilogram body weight (results incorporated in Fig. 1), on which basis we calculated our own data, the

mucigogue effect of the agents we employed was found to be much greater than that of such a powerful stimulant as rhythmic stimulation of the vagi.

The mechanism for the stimulation of mucus secretion by the alkyl sulfates appears to be mainly, if not exclusively, a local one. The introduction of a 2-per cent solution of the alkyl sulfates into an isolated pyloric pouch in a dog under anesthesia was without effect upon the secretion of mucus from the body of the stomach. Furthermore, mucus secretion stimulated by these agents was not appreciably influenced by atropinization of the animal.

hyperemia after the use of sodium dodecyl sulfate. However, after the use of sodium "Lorol" sulfate the gastric mucosa displayed areas the condition of which no longer could be considered as a response within the limits of physiological stimulation. Comparing our results with those recently reported by Hollander (*3*) for a variety of mucus stimulants, sodium dodecyl sulfate appears at this stage of the investigation to be the most innocuous stimulant of gastric mucus secretion.

Evidence is accumulating to show that a constantly renewed layer of mucus is the chief agent which protects the mucous membrane of the stomach from digestion by such a highly destructive agent as active gastric juice. Any breakdown of this mechanism will contribute to the development of ulceration. An agent specifically stimulating mucus secretion should, therefore, enhance such a protective mechanism. If we consider that in addition to their mucigogue property the alkyl sulfates also have the ability to inactivate pepsin under certain conditions, these agents appear to have promise for the treatment of "peptic" ulcers, provided conditions of administration can be devised to permit effective action of the drug.

TABLE 1

COMPOSITION OF GASTRIC SECRETION IN RESPONSE TO 2-PER CENT AQUEOUS SODIUM ALKYL SULFATE

Alkyl sulfate	No. of samples	Chloride m.eq./liter		No. of samples	pH		No. of samples	Alkalinity m.eq./liter	
		Range	Mean		Range	Method		Range	Mean
Sodium dodecyl sulfate	16	95–134	118	20	7.5 –8.7	Color.	9	23–37	29
				5	8.27–8.42	Electro.			
Sodium "Lorol" sulfate	6	95–127	115	7	7.1 –8.6	Color.	5	27–31	30

The mucus secreted under the influence of the alkyl sulfates has physical and chemical properties very similar to those described in the literature as most representative of pure gastric mucus. This mucus appears as one of two types: one, opaque and so viscous that, in handling, it could only be divided by cutting with scissors; the other, clear, gelatinous and quite viscous, but still fluid enough to flow, though with great difficulty, through a small glass cannula.

The analytical data (Table 1) for chloride, alkalinity, and pH values of the mucus secreted are in good agreement with those reported by Vineberg (*12*) and by Hollander (*3*). We consider the action of the alkyl sulfates, in the concentration studied, upon the gastric mucosa to be quite selective and limited to the mucous cells, since the pH and chloride values of all specimens were typical for pure mucous and only the merest traces of peptic activity were seen in a few.

The samples of mucus obtained by the use of sodium dodecyl sulfate were found on microscopic examination to contain only a few cellular elements—single leucocytes and columnar cells in various stages of disintegration. These are considered normal constituents of mucus. Careful gross examination of the gastric mucosa immediately after the completion of the experiment showed only an active physiological

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