ceiving the injection of Jan. 18th and their data are not included among those of Fig. 2. The other 2 rabbits (male grey) appeared to be somewhat less susceptible to the treatment than were the 2 albinos. Their data are represented by Fig. 2. The data of curve *a* were obtained on Dec. 20th following the injection of a dose of insulin slightly less than the convulsive dose and those of curve *b* on Dec. 22nd following the injection of one-half of the convulsive dose of insulin. Those of curve *c* were obtained on Jan. 18th following the injection of glycine and one-half of the convulsive dose of insulin. A definite effect of glycine on insulin action is also indicated here.

The data of Fig. 3 were obtained with a third group of 2 rabbits (black, male). After determining the response to a subconvulsive dose of insulin (curve *a*) and to one-half of a convulsive dose (curve *b*) these animals were injected with glycine only on Jan. 6th, 7th, 8th, 10th, and 12th. On Jan. 18th they received one-half of the convulsive dose of insulin but no glycine. A comparison of curve *c* with curves *a* and *b* indicates the effectiveness of the initial treatment with glycine upon the subsequent action of the injected insulin.

Many variables suggest themselves for further investigation. In view of the concern over the prediction of a possible shortage of insulin in the near future these experimental facts would seem of interest to a further search for a more favorable insulin economy. It should also be of interest to note how a similar treatment might affect humans who are predisposed to the conditions of diabetes.

Summary. Repeated injections of small amounts of glycine (3 mg per kg body weight) appear to increase the action of subsequent injections of insulin for a prolonged period of time.

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Production of Irritative and Destructive Changes in the Gastric Mucosa Followed by Regeneration.*

ENRIQUE SANCHEZ-PALOMERA AND OWEN H. WANGENSTEEN.
From the Department of Surgery, University of Minnesota Medical School, Minneapolis.

Some progress has been made in the last 3 decades concerning our knowledge of the normal and pathological physiology of the stomach. Special emphasis has been lent study of the functions of the peptic and parietal cells; by contrast, our knowledge of the gastric mucous epithelium and its function is meagre. Hollander and his associates have been probing with care for some time this aspect of the problem of functions and morphology of the gastric mucosa; with few exceptions the functions of the gastric mucous epithelium and the other mucous secreting cells have not been given due consideration.

In this study, investigations of some functions of the mucous secreting cells were carried out; also the mechanism of regeneration of the gastric mucosa was studied.

Methods and experiments. The gastric mucous secreting cells were stimulated by placing various substances into the stomach with both ends ligated. Cats and dogs were employed in the experiment. Mustard oil and clove oil in concentrations of from 0.5 to 2 % (in corn oil), and eugenol in watery solutions up to 10% were used.

The animals were anesthetized with nembu-

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tal in doses of 15 mg per pound. When the operation was completed the animals were allowed to recover. After periods varying from 3 to 10 hours following operation, the animals were sacrificed.

In another small group, after the period of exposure to the irritant, the abdomens of the animals were re-opened, the ligatures on the stomach were removed, the stomach was emptied and the wound was closed. The same procedure was repeated 2 or 3 weeks later. In all cases biopsies were taken before and after the completion of the experiment. In the group of surviving animals, biopsies were also taken 24 to 48 hours after the stimulation was stopped.

The specimens were immediately fixed with formalin and stained with hematoxylin-eosin and Mayer's muci-carmin.

Comparative studies of the action of the irritants on closed loops of small bowel and colon were also made. In these cases the procedure was essentially the same as that described by Florey and Webb.[1]

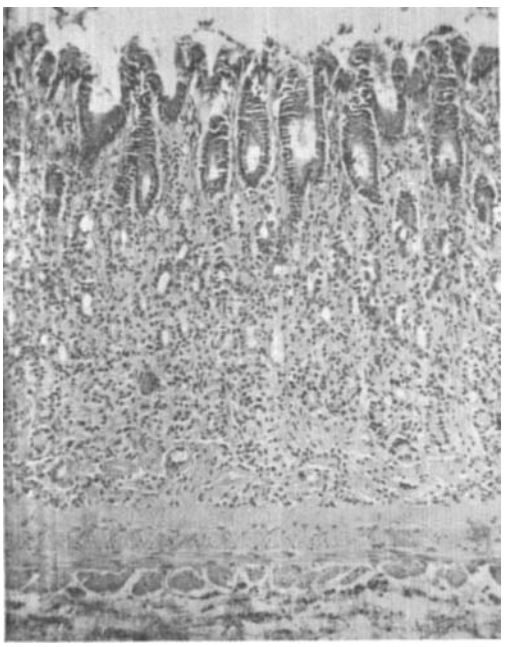

FIG. 1.
Stomach of a cat after 7 hours exposure to 1½% solution of mustard oil in corn oil. Early stage of mucosal changes; deepening of the foveolae, early epithelial desquamation. (Mayer's muci-carmin stain in all the microphotographs.)

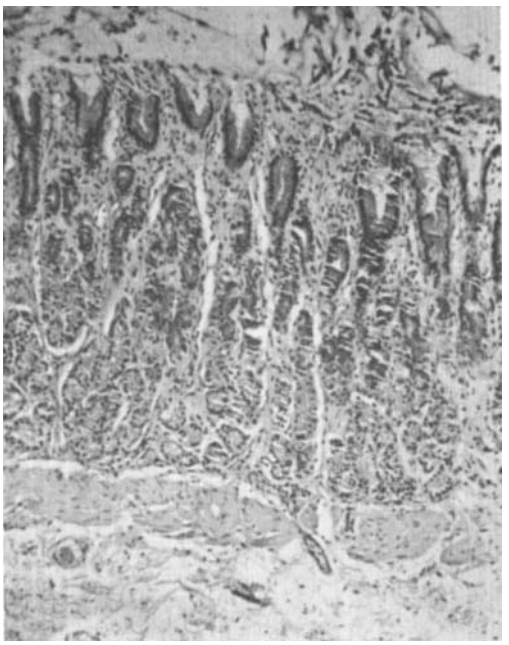

FIG. 2.
Stomach of a dog after 6 hours exposure to 10% aqueous solution of eugenol. This shows a more advanced stage than is shown in Fig. 1. There is definite loss of epithelium in the inter-foveolar areas.

Result. The results obtained in the colon and small bowel by Florey and Webb[1] were confirmed. In short, depletion of the goblet cells of the colon was readily produced. Similarly, diminution of the number of goblet cells was obtained in the small bowel.

In the stomach profuse macroscopic secretion of mucus was obtained with no obvious histological change. When the stimulation was stronger or the period of application increased, necrosis of the mucosa occurred. The process of necrosis was found to develop in the same general manner in colon, small bowel and stomach, except for the fact that the small bowel was the most susceptible and the stomach quite resistant to the irritative action. Edema, hyperemia, extravasation of red blood cells and leucocytic infiltration were noticed first. Later on, the most superficial portions

[1] Florey, H., and Webb, R. A., *Brit. J. Exp. Path.*, 1931, **12**, 286.

FIG. 3.
Stomach of a cat after exposure to 10% eugenol solution for 12 hours. Careful fixation of the whole stomach and attached mucus. The section shows a layer of epithelium already shed sticking to the new one.

of the epithelium were destroyed; the exposed cells of the stroma disintegrated and became spread over the denuded surface. A section, at that stage, showed an "umbrella" formed by cellular debris and mucous covering the mucosa. This layer acted as a protective covering and prevented necrosis of the walls of the pits. Further action of the irritant caused a progressive destruction of the remaining mucosa until ulceration occurred.

In the stomach, necrosis and regeneration were more thoroughly studied when irritants were applied to the mucosa. Deepening of the foveolae was first observed. (Fig. 1) Some time later the most superficial segments of epithelium became detached from the body of the mucosa, leaving only the deepest portions of the foveolae. (Fig. 2) If irritation ceased at this stage immediate regeneration took place. Under a protective layer of cellular debris and mucus, (Fig. 3) similar to the crust forming after injury to the epidermis), proliferation started at the bottom of the gastric pits. Growth of the cells from these areas restored the continuity of the surface epithelium and the mucosa looked thinner thereafter. The healed erosions in human stomachs show similar mucosal thinning. The process may be compared with the regeneration of the epithelium around skin appendages and the tips of the dermal papillae. If the entire thickness is destroyed, regeneration takes place from the margins of the wound. Similarly, if the entire thickness of the gastric mucosa is destroyed, regeneration takes place from the margins of the wound. Ferguson[2] demonstrated this experimentally and it can be seen also in pathological human material.

If destruction had not reached the bottom of the pits, it was followed by complete regeneration of the epithelial continuity in less than 48 hours. (Fig. 4)

In the cases in which a period of acute irritation was followed by recuperation of the animal, the procedure was repeated subse-

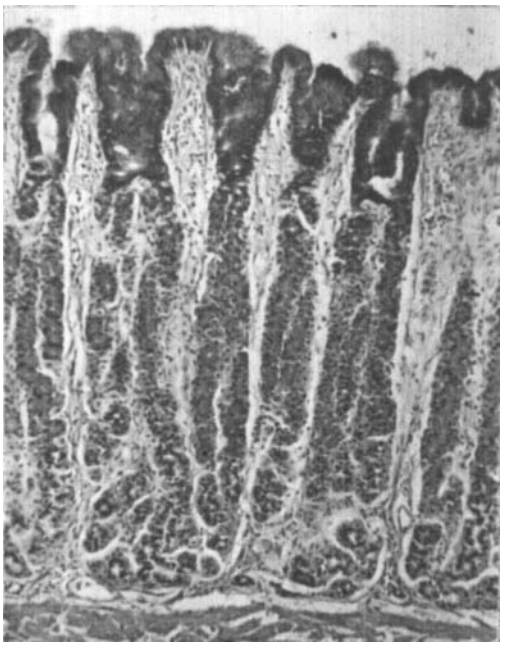

FIG. 4.
Same stomach as in Fig. 2, after regeneration. This biopsy was taken 40 hours after the stimulation was discontinued. The dark stained cells reaching almost to the muscularis mucosa are mucus-neck cells.

[2] Ferguson, A. N., *Am. J. Anat.*, 1928, **42**, 403.

quently. Biopsies of the mucosa before this second period of irritation was started showed changes consisting of cystic areas scattered in the body of the mucosa, areas of degeneration and a ragged contour of the epithelial surface as observed in the section; moreover, some foveolae were deeper than others, instead of exhibiting as is usual a fairly even depth. The mucosa, at this stage, proved to be more susceptible to the action of the irritant than in the initial period.

Discussion. The regeneration of the gastric mucosa as described may explain, in a very simple way, the much discussed resistance of this viscus to auto-digestion. We know that mucous secretion affords a protective mechanism to the gastric mucosa. The surface mucus restrains the acid-peptic juice from coming into direct and intimate contact with the mucosa. Evidence of this is offered by the experiments described, and has been obtained among others by Whitlow.[3] It is also known that mucus is increased whenever any kind of trauma, either mechanical or chemical, is applied to the mucosa. If, in addition to the layer of surface mucus, one considers the mucus contained within the epithelial cells, the concept of a more effective barrier suggests itself. Cells and mucus, the latter tenaciously adherent to the former, offer a protection which can be favorably compared to that present in the other segments of the gastro-intestinal tract. Moreover, before the cells of the epithelium loose their ability to secrete mucus they are shed and are immediately replaced by a layer of new ones, with a full secretory capacity. (Fig. 4)

If the rate of dissolution of the mucosa exceeds the rate of regeneration which may be variable, mucosal defects form, from which ulcers of the wall may develop. In the main, the regenerative capacity of the gastric mucosa is great and this condition accounts reasonably for the circumstance that the gastric mucosa does not digest itself.

Dragstedt and Vaughn[4] observed that spleen and kidney transplanted to the stomach were covered by a layer of columnar epithelium. Similarly, Varco and Wangensteen[5] noticed that omentum employed to cover stomach defects (in which approximation of the gastric walls was precluded by the insertion of metallic rings), became covered by gastric epithelium. Protection against digestion in these tissues was very likely afforded by the newly-formed epithelial layer. This protective mechanism, the "mucous barrier," as it has been called by Farrell,[6] Ivy,[7] and Hollander,[8] may be of greater importance in the pathogenesis of gastric ulcer than previously considered.

Conclusions. 1. Changes in the gastric mucosa produced by continuous irritation are described.

2. The sequence of events following irritation is compared in colon, small bowel, and stomach.

3. The process of regeneration after superficial destruction of the mucosa is described and is offered as a possible simple explanation for the resistance of the stomach to auto-digestion.

4. The possible implication of this mechanism in the pathogenesis of gastric ulceration is suggested.

[3] Whitlow, J. E., Thesis, M.S., 1920, Loyola Univ. Med. School.

[4] Dragstedt, L. R., and Vaughn, A. M., *Arch. Surg.*, 1924, **8**, 791.

[5] Varco, R. L., and Wangensteen, O. H., unpublished observations, 1940.

[6] Farrell, J. T., *Am. J. Phys.*, 1928, **85**, 672.

[7] Ivy, A. C., *J. Nat. Cancer Inst.*, 1945, **5**, 313.

[8] Hollander, F., Stein, J., and Lauber, F. U., *Gastroent.*, 1946, **6**, 576.