example, that if stimulated just at the beginning of diastole the heart muscle gives a small contraction and that the contraction, which may be obtained later by artificial stimulation, increases in extent the farther the diastole has progressed.

4. If the above statements are correct it follows that the store of energy-yielding material in the heart exists in some non-irritable form and that during the phase of diastole a portion is converted into an irritable form capable of being acted on by a stimulus.

5. The presence of certain inorganic salts is necessary for this transformation from the non-irritable to the irritable condition.

In order to picture the relations of the inorganic salts to this process the hypothesis which I have adopted as a heuristic principle to guide my own investigations, may be stated as follows: The well-nourished heart contains a large supply of energy-yielding material, which is in stable form, so that it neither dissociates spontaneously, nor can be made to do so by the action of external stimuli. It is possible that this stable, non-dissociable form consists of a compound between it and the potassium or the potassium salts, and that herein lies the functional importance of the large amount of potassium contained in the tissue. This compound reacts with the calcium or with the calcium and sodium salts, and a portion of the potassium is replaced and a compound is formed which is unstable. At the end of the diastolic period this compound reaches a condition of instability such that it dissociates spontaneously, giving rise to the chain of events that culminates in the normal systole. Before spontaneous dissociation occurs it may be hastened prematurely by an external stimulus, as we know to be the case when a mechanical or electrical shock is applied to the heart at any time after diastole has begun.

From this point of view the rôle of the calcium, or of the calcium and sodium salts consists in replacing the potassium and converting a part of the store of stable material into an unstable, easily dissociable compound. We are not obliged, therefore, to assume the existence of any specific inner stimulus. An hypothesis of this character accounts readily for some of the most characteristic features of the heart beat.

Each contraction must be maximal since it involves the dissociation of all the material existing in unstable form. The contractions must be rhythmic since, after each contraction a certain interval, which will be constant when the conditions are uniform, is needed for the production of more of the unstable material. At each systole the heart will exhibit a refractory phase, since the ready-formed, unstable material has been used up and the rest of the energy-yielding substance exists in a stable, non-irritable form. In terms of the hypothesis the refractory phase should pass off gradually as new, unstable material accumulates, and this we know to be the case, since a weaker stimulus is required to force the heart to contract the later it is applied in the diastolic phase.

Whether or not this or any other of the hypotheses described turns out to be correct, we may congratulate ourselves at least that the labors of the experimental physiologists during the last quarter of a century have added to our store of knowledge this new and important fact, namely, that the inorganic salts of the blood and lymph play an essential rôle in the production of the heart beat.

ULCER OF THE STOMACH: PATHOGENESIS AND PATHOLOGY.

EXPERIMENTS IN PRODUCING ARTIFICIAL GASTRIC ULCER AND GENUINE INDUCED PEPTIC ULCER.*

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CHICAGO.

DEFINITION.

By artificial gastric ulcer is meant ulcer produced by experimental means, as by some local, mechanical or chemical injury; by induced ulcer is meant ulcer produced by more indirect and natural means, such as feeding methods, as presented in this paper. The term peptic is retained on account of long usage.

INTRODUCTION.

Ulcer of the stomach is one of the most important

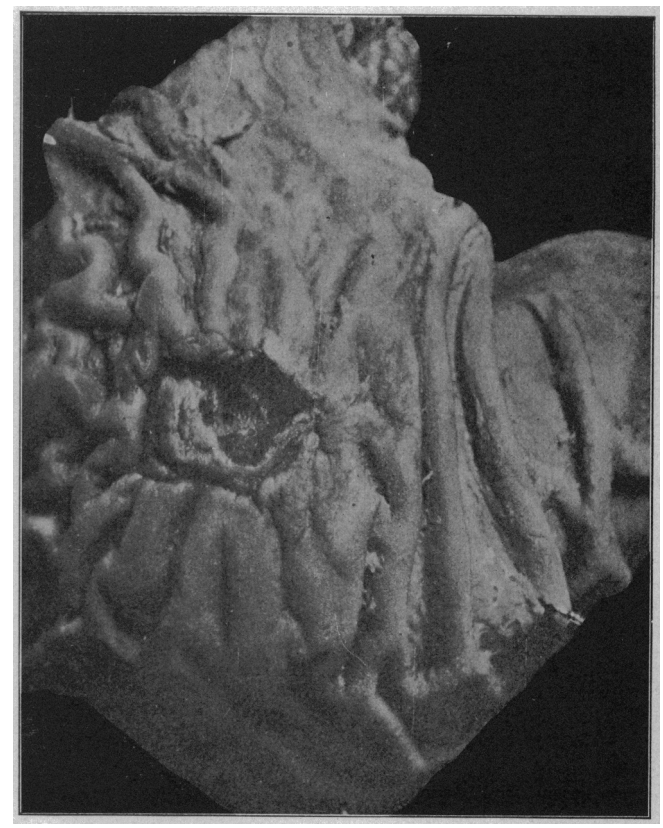

Fig. 1.—Deep ulcer in which perforation occurred, resulting in general peritonitis and death.

pathologic questions that engage the attention of scientific workers.

Clinically, it has led to the investigation of numerous conditions with which it is directly or indirectly associated, such as the local manifestations of pain, hemorrhage, perforaton; the secondary results, as adhesions, cicatrices, and contractions; carcinoma formed at the site of the ulcer, and, finally, the systemic conditions of toxemia, lowered vitality, anemia, etc.

The pathogenesis of gastric ulcer, however, is what has called forth the best scientific effort. The rôle that

* Presented before the International Medical Congress, Lisbon, 1906. The preliminary report on these experiments was first presented in the symposium on Gastric Ulcer before the American Gastro-Enterological Association, 1904, and withheld from publication for more careful revision and research. Presented before the joint meeting of the Chicago Pathological Society and Chicago Medical Society, March 21, 1906.

* From the Research Laboratory of the Turck Institute, Chicago.

cytolysis and autocytolysis play in the formation and persistence of ulcer must be recognized as an important one. It points back to the fundamental problem: What prevents self-destruction of the stomach; and, moreover, what prevents autocytolysis of all tissues of the body? That some sort of protection existed to prevent self-destruction was even recognized by the ancients, who attributed it to some supernatural power.

Stahl[1] regarded our protection to be the "sensitive soul." He states: "This very preservation of a thing essentially destructible by which its destruction through its own activity is prevented is exactly what we ought to understand by the common word 'vital.' In any case the fermentation which takes place in the alimentary canal is not an ordinary fermentation, such as occurs in a merely compound, not-living body, but a most special character is impressed on the change by energy of the soul."

John Hunter,[2] in his vital principle, expressed a similar idea, and in place of the "sensitive soul" he believed that the "vital power" protected the body by some inherent energy.

As cellular pathology developed, the word tissues was added to the same vital power of Hunter, and, as Riegel[3] expresses it, "The main reason why the stomach does not digest itself is unquestionably the vital resisting power of the tissues."

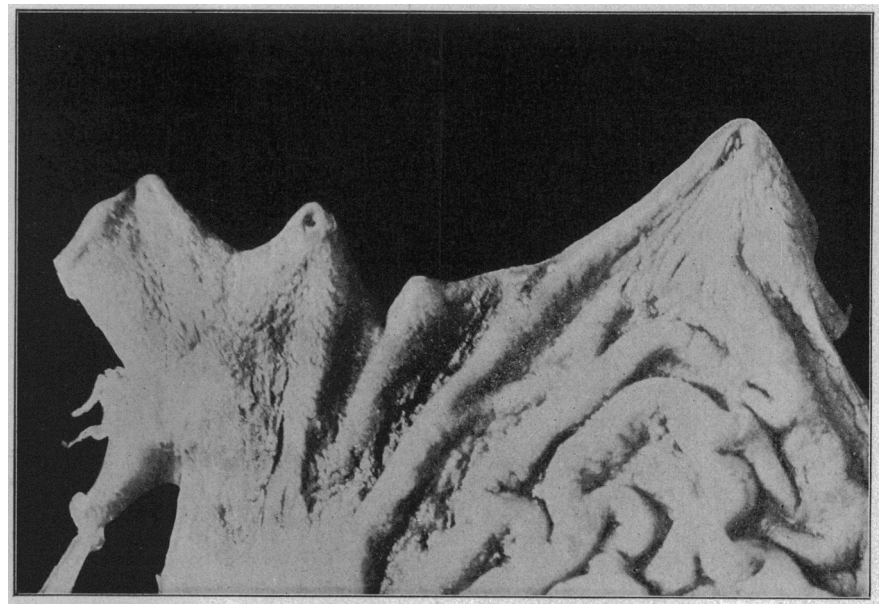

Fig. 2.—Deep ulcer, near pylorus, from which hemorrhage occurred, resulting in death. (The ulcer is at the bottom of the central diagonal sulcus.)

The conception of resistance of the tissue against the formation of ulcer has developed various ideas of local protection, either as a vital power residing in the cell or some secretion acting as a mechanical or chemical protection. Thus Vaughan Harley[4] thought the mucus acted as a protective coat of mail to the mucosa of the stomach, and Claud Bernard[5] believed that the regeneration of cells rapidly replaced those destroyed by the gastric fluid.

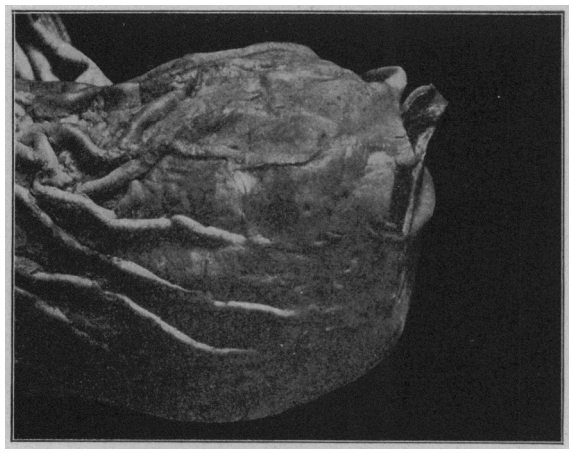

Fig. 3.—Multiple peptic ulcer, mucous surface, large ulcer in center. Smaller ones shown by depressions above.

The modern idea of this local protection is shown in Weinland's[6] work, who holds that an anti-pepsin ferment residing in and as a part of the gland cells protects them from destruction.

A.—GENERAL PROTECTION.

The Sensitive Soul	Stahl
Vital Force	Hunter
"Vital Resisting Power of the Tissues"	Riegel
Alkalinity of the Blood	Pavy[7]

B.—LOCAL PROTECTION.

The Mucus Acting as a Protective Coat to the Mucosa	Vaughan Harley
Constant Reproduction of Exfoliated Epithelium	Claud Bernard
Antipepsin Ferment Residing in and as a Part of the Gland Cell	Weinland

From the large amount of experimental work on blood serum, by numerous investigators, we are able now to clothe our ideas of "protective bodies" in more technical and definite language. We may speak now of natural histogenic immunity, of hemolysins, of agglutinins, of precipitins, of cytotoxins, etc. We may go a step further in our understanding of this same histogenic immunity towards infectious diseases in the light of amboceptors, and of the alexins or complements, with their

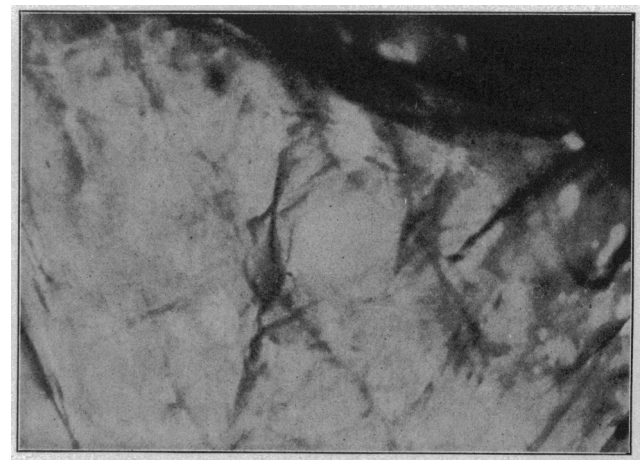

Fig. 4.—Same by transmitted light. Multiple ulcers shown by the light spots with light transmitted through the gastric walls. Note thinness of wall in center ulcer.

1. Stahl (1660-1734): "De mixti et vivi corporis vera diversitate."
2. Hunter (1728-1793): "The Digestion of the Stomach After Death," Phil. trans., 1772.
3. Riegel: "Diseases of Stomach," (Nothnagel's Practice), 1903, p. 561.
4. Vaughan Harley: British Review, vol. xlix, 1860.
5. Claud Bernard: Lecons de phys. Exp., Paris, 1856.
6. Weinland: Zeitft. f. Biolog., vol. xliv, 1903.
7. Pavy: Guy's Hosp. Reports, 1868.

respective toxophore, haptophore, or receptor groups. It is easy to understand what a clear field of investigation was opened in the study of natural and acquired immunity towards infectious diseases in the light of amboceptors and complements of toxins and antitoxins. It is no less evident to one investigating the problem of the

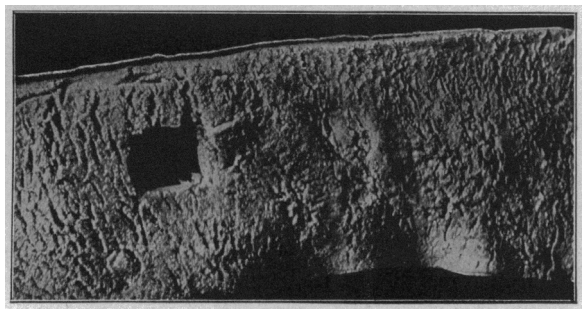

Fig. 5.—Duodenal ulcer, second portion.

production and persistence of gastric ulcer that we have here, not a question of local pathology, but of general blood pathology, of complement and amboceptor, of cytolysis and autocytolysis.

HISTORY OF EXPERIMENTS BY PREVIOUS INVESTIGATORS.

In the following classified list of methods adopted by various observers, it will be observed that most of the efforts to produce ulcer by artificial methods have been directed towards obtaining purely local cellular changes. This is apparently the direct influence of Virchow and his school in experiments and clinical observation of the pathology and pathogenesis of ulcer up to the present time. Virchow offered the hypothesis of vascular obstruction or aneurismal dilatation of vessels, but these are far too inconstantly found in ulcer.

Fig. 6.—Duodenal ulcer at jejunal junction.

Ulcers produced by some form of mechanical injury to the stomach wall heal even more readily than in other parts of the body, and attempts to produce ulcer, by chemical injury, either fail to produce the lesion, or the lesion heals more or less promptly. As anemia is frequently associated with ulcer, various attempts have been made to produce ulcer by combining resection and some mechanical injury, as resection of the mucosa, with bleeding, or the injection of laked blood or chemical substances, as practiced by Cohnheim, Silbermann and others. If the anemia was sufficiently profound and the injury well-marked, ulcers were produced in the stomach, just as one would expect in injury to any part of the body.

The production of ulcer of the stomach by destroying areas in the brain, or section of the cord or vagi, can not be satisfactorily explained, but seems rather too violent and foreign to the conditions present in ulcer of the stomach. One explanation of the cause of ulcers produced by the above methods might be suggested by the work of Pawlow, who noted loss of motor power of the stomach after section of vagi, and of the recent work of Ophüls, who noted great dilatation of the stomach after section of both vagi below the diaphragm. Both these conditions would be very important factors in causing change in the bacterial growth in the stomach and intestines. How far this bacterial factor may be an ex-

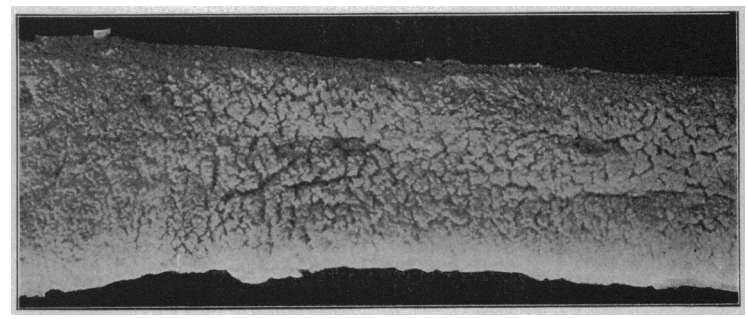

Fig. 7.—Duodenal ulcers, near pylorus.

planation of the ulcers produced after injury to the peripheral and central nervous system will require further investigation.

The following tables of the different authors' experiments in the production of artificial gastric ulcers are classified and arranged for convenience and ready reference. A few clinical and postmortem observations are included in these tables:

TABLES OF EXPERIMENTS BY PREVIOUS INVESTIGATORS.

A. MECHANICAL AND PHYSICAL INJURY.

		RESULT.
Ritter[8]	Violent bruises	
Decker[9]	Heat	Ulcer
Matthes[10]	Trauma (with 5 per cent. HCl)	Ulcer
Schmidt[11]	Trauma (with HCl)	
Körte[12]	Pinching stomach with clamps	Ulcer

B. CHEMICAL.

Roth	Crystals of nitrate of silver introduced into stomach	Ulcer

1. HCL AS A NECESSARY FACTOR.

Riegel[13]	HCl necessary	
Matthes[10]	Trauma (without HCl)	Negative
	Trauma (with 5 per cent. HCl)	Ulcer
Schmidt[11]	HCl and trauma	
Ewald[14]	HCl essential factor	

2. CONTRA HCL.

Pawlow[15]	Hyperacidity a consequence.
Du Misinl[16]	Superacidity without significance.
Ageron[17]	HCl may be persistently absent.

8. Ritter: Beits. f. klin. Med., 1887, p. 12.
9. Decker: Berl. klin. Wochft., 1887, p. 21.
10. Matthes: Ziegler's Beitr., vol. xiii, 1897.
11. Schmidt: Inaug. Dissert., Leipzig, 1895, p. 6.
12. Körte: Inaug. Dissert, Strassburg, 1875.
13. Riegel: Zeits. f. klin. Med., vol. xii, p. 434.
14. Ewald: "Diseases of the Stomach," 1899.
15. Pawlow: "The Work of the Digestive Glands," 1902.
16. Du Misinl: See Riegel, "Diseases of the Stomach," 1903, p. 570.
17. Ageron: Münch. med. Wochft., July 29, 1902.

Kavetsky[18]	Synchronous ulcer of the stomach and bladder.	

C. GENERAL DYSEMIA.

Virchow[19]	Anemia and chlorosis.	
Quincke and Daetwyler[20]	Anemia by producing gradual hemorrhage and local trauma.	Ulcer, which healed with difficulty.
Silbermann[21]	Hemoglobinemia	Ulcer
Fütterer[22]	Hemoglobinemia	Ulcer
Cohnheim[23]	Hemoglobinemia by mechanical injury and injection of laked blood	Ulcers

D. DISTURBANCE OF LOCAL CIRCULATION.

Virchow[24]	Embolism, thrombi, aneurism or varicose veins.	
Klebs and Welti[25]	Thrombi.	
Panum[26]	Injection of emulsion of wax into femoral vein.	Gastric infarcts, ulcer.
Talma[27]	Ligation of esophagus and pylorus	Ulcer
Rindfleisch[28]	Venous stasis; prolonged ischemia.	
Axel Key[29]	Prolonged ischemia due to contraction of gastric muscle.	No experiments.
Müller[30]	Tied portal vein	Ulcer

E. INJURIES TO NERVES AND NERVE CENTERS.

Schiff[31]	Intersection of thalami and peduncles	Ulcer
Ebstein[32]		
Brown-Sequard[33]	Anterior corp. quadrigemina	Uicer
Vidova[34]	Injection of Alcohol into vagus	Negative
Vidova[34]	Section of the sympathetic	Ulcer
Yzeren[35]	Section of the sympathetic with section of vagi below the diaphragm	Ulcer
Saitta[36]	Section of the sympathetic with section of vagi below the diaphragm	Ulcer
Ophüls[37]	Section of the sympathetic with section of vagi below the diaphragm	Ulcer
K ch and Ewald[38]	Section of cord, and 5 per cent HCl in stomach	Ulcer

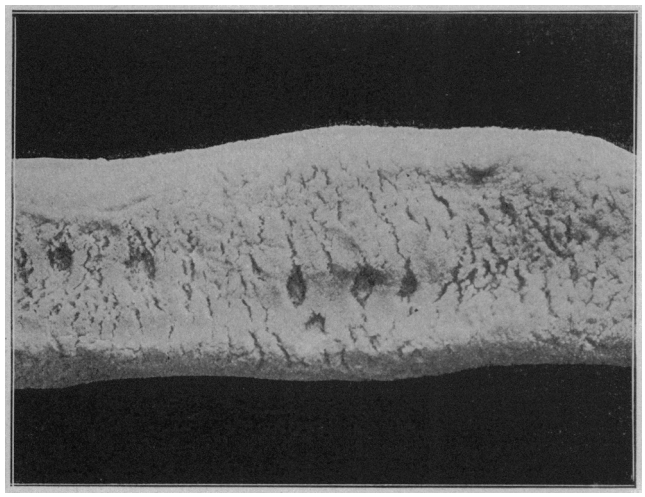

Fig. 8.—Deep peptic ulcers of duodenum (first portion).

F. LOCAL INFECTION.

Cohnheim[23]	Injection. Infected suspensions of lead chromate	Erosions and ulcers.
Böttcher[39]	Infection as cause of ulcer	Opposed by Körte.
Nauwerck[40]	Infection observed at edge of ulcer.	

The following tabulated record of my experiments is introduced here, although many of the methods apparently come under the above classification, yet they are sufficiently distinct to permit a separate presentation:

AUTHOR'S EXPERIMENTS.

A. MECHANICAL.	RESULTS.
Excision of the mucous membrane. Also application of local irritants and removal of mucous membrane by nippers, observed through a permanent gastric fistula.[41]	No visible lesion.
Trauma and hemorrhage by wire brush. (Repeated for one month.)[41]	Hemorrhagic erosions.
Cardiac and pyloric ligations.[41]	
Partial ligations of portal vein.[41]	No erosion.
Ligations of veins of stomach.[41]	Erosions near ligation.
B. CHEMICAL.	
Application of tannic acid, gastric juice to mucosa with the gyromele.[41 42 43]	Negative.
Application of chromic acid, silver nitrate crystals with gyromele.[41 42 43]	Negative.
Same; pyloric end partially tied.[41]	Hemorrhagic erosions.
Tannic acid daily for several weeks.[41]	Negative.
Mustard oil, large doses.[44]	Acute gastritis only.
Mustard oil for 14 months.[45]	Chronic gastritis. No ulcer.
C. LOCAL INFECTION.	
Sarcinæ and yeast introduced into stomach; pylorus partially tied.[46]	Negative.
Stomach contents from infected stomach injected into dog's stomach through fistulous opening.[48]	Increased HCl. No ulcer.

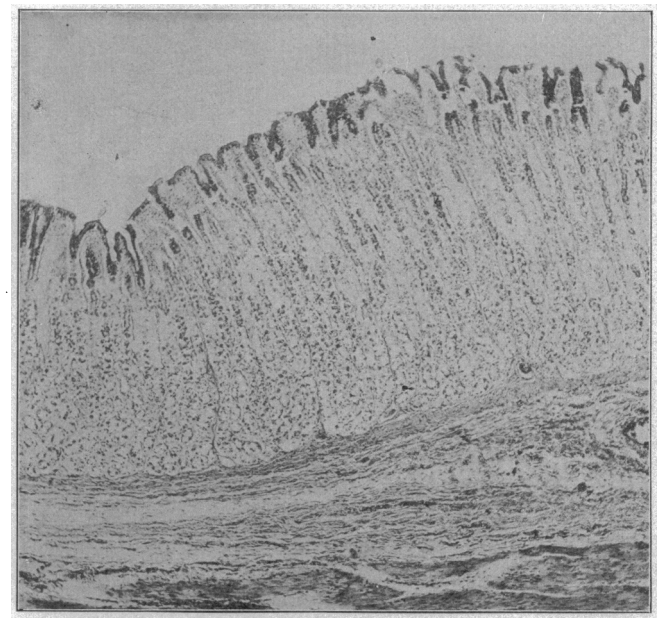

Fig. 9.—Stomach of dog. The mucosa is practically normal. The glandular structure is well shown and the surface epithelium is intact. (Low power.)

D. INJECTION OF TOXINS.

Diphtheritic toxin injected into stomach wall.[47]	No ulcer; pinhead hemorrhagic foci in duodenum.
Same.[47]	Same. Local necrosis near pylorus.
Diphtheritic toxin injected into mesenteric vessels.[47]	No ulcer; foci of necrosis after two weeks in duodenum and near pylorus.
Intravenous injection of extracts and emulsions of gastric mucous membrane.[48]	Necrosis of mucous membrane near pylorus.
Intravenous and subcutaneous injection of stomach contents from patients into animals.[49]	No ulcer.

E. SYSTEMIC DISTURBANCES.

Shock and infection. Laparotomy. Exposure of stomach to air three hours; repeated. Inoculation peritoneal cavity.[50 45]	No ulcer.

18. Kavetsky: Prag. Vratch., 1902, No. 24.
19. Virchow: "Anemia and Chlorosis."
20. Quincke and Daetwyler: Deuts. med. Wochft., 1882, p. 6.
21. Silbermann: Deuts. med. Wochft., 1886, No. 29, p. 497.
22. Fütterer: THE JOURNAL A. M. A., March 15, 1892; also Oct. 15, 1904.
23. Cohnheim: "Lehrbuch der Pathol. Anat."
24. Virchow: Virchow's Archiv., vol. v, p. 360.
25. Klebs and Welti: "Thrombi."
26. Panum: "Virchow's Archiv.," vol. xxv, 1862.
27. Talma: Zeits. f. klin. Med., vol. xvii, p. 10.
28. Rindfleisch: "Lehrbuch der Pathol. Anat."
29. Axel Key: Gurlt. Virchow's Jahr., 1871.
30. Müller: Enlangen, 1860.
31. Schiff: "Leçons sur la physiologie de la digestion," 1862.
32. Ebstein: Deuts. Archiv. f. klin. Med., vol. liv.
33. Brown-Sequard.
34. Vidova: Archiv. f. Verdauungsk., vol. viii, No. 3.
35. Yzeran: Zeits. f. klin. Med., 1901, xliii, 81.
36. Saitta: Gaz. degli. Osp. Milan. vol. xxi, 599.
37. Ophüls: Jour. Exp. Med., vol. viii, No. 1.
38. Koch and Ewald: Klin. der Verdauungsk, vol. i, No. 3, p. 122.
39. Böttcher: Dorpater Berichte, 1873.
40. Nauwerck: Münch. med. Wochft., No. 35, 1897.
41. Turck: "Experimental Observations on Erosions of the Stomach," Ft. Wayne Med. Jour. Mag., January, 1897.
42. Turck: Wiener med. Wochft., Nos. 1 and 2, 1895.
43. Turck: Medical News, April 4, 1896.
44. Turck: N. Y. Med. Jour., Oct. 25, 1902.
45. Turck: THE JOURNAL A. M. A., June, 1897; also N. Y. Med. Record, Aug. 11, 1900; Wien. med. Wochft., No. 48, 1901.
46. Turck: THE JOURNAL A. M. A., March, 1896.
47. Turck: Trans. Chicago Path. Soc., April, 1903.
48. Turck: Medical Standard, Chicago, December, 1903.
49. Turck: N. Y. Med. Jour., Feb. 22, 1896.
50. Turck: Amer. Therapist, November, 1900.

Prolonged use of chloroform and ether; two to six hours.[51]	No ulcer.
Guinea pigs and rabbits closely confined in small cages.[52]	Six ulcers; two spontaneous, four by local lesions.

F. INJECTION OF PEPTONES.

Intravenous and subcutaneous injection of peptones for two to four weeks after removing portions of the mucous membrane of the stomach.	Six dogs: Two scars, two delayed healing, two negative.

In the above series of my experiments, most of which have been previously reported, those of injecting mustard oil into the stomach and those of animals kept in confinement, are of special interest.

In the experiments with mustard oil, increasing doses were injected into the dog's stomach at intervals of two to three days for nine to fourteen months. One hundred c.c. of a 1/500 emulsion of the oil was injected at the outset, but the dose was gradually increased, so that at the end of three months 125 c.c. of a 1/50 emulsion could be given, and later the oil was simply added to the dog's food.

Vomiting and acute gastric symptoms followed the earlier injections, but later no reactionary symptoms occurred. At the end of nine months dog No. 1 died. At the end of eleven months dog No. 2 died. No ulcer was found in the stomach or intestines in either dog No. 1 or dog No. 2. At the end of fourteen months dog No. 3 was chloroformed. The dog was emaciated. The stomach was dilated and occupied a large

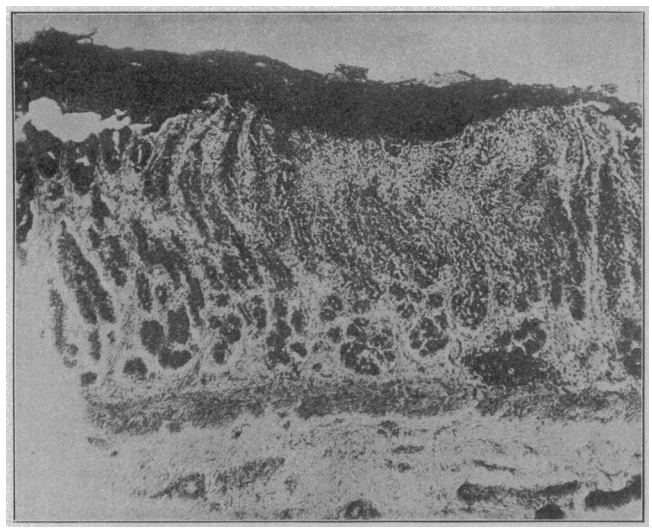

Fig. 10.—Stomach of dog, early stage. The black mass on the surface and the finger-like projection downward into the crypts is an accumulation of mucus, cellulur débris, blood serum, etc. (Low power.)

portion of the abdominal cavity, the greater curvature extending to the line of the anterior superior spinous process. The mucous membrane in the fundus of the stomach showed etat mamillæ. Microscopic examination showed chronic gastritis. No ulcer was found in the stomach or intestines.

Failure after such radical means as the feeding of mustard oil for fourteen months demonstrated the futility of attempting to produce ulcer by simply local irritation.

The possibility of systemic disturbances, altered metabolism, impaired nutrition being etiologic factors in the production of ulcer led to the experiment of confining animals in very close quarters for a long period of time.

Ninety-six guinea pigs and 36 rabbits were used in the experiment, which was continued nine months. The animals were confined in small sterilized cages (made of wood, except the bottom, which was of wire netting), 4x6x6 inches. The top was closed by a hinge cover, light being excluded, but air admitted through two small holes on either side. The cages were placed in sterilized pans, in a solution of permanganate of potassium, and were sterilized every other day. The animals were thus restricted to a small allowance of air, light and exercise, but were given the usual amount of food, and kept in as sterile cages as possible.

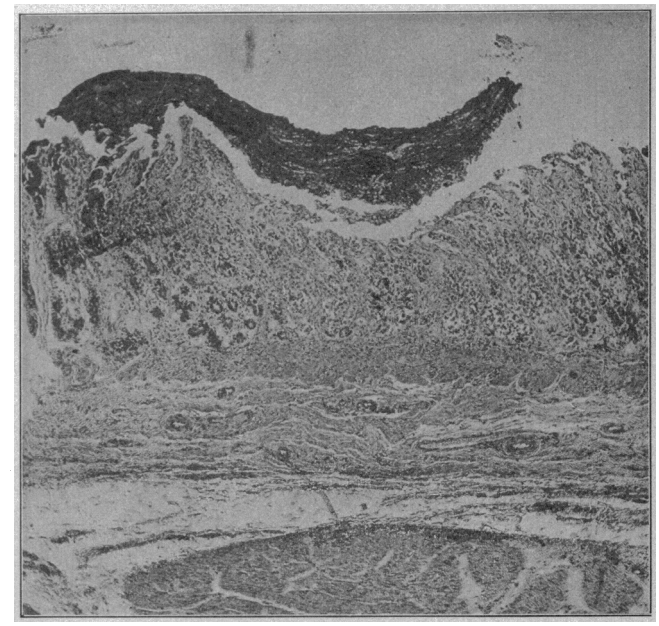

Fig. 11.—Stomach of dog, later stage, with necrosis of the mucosa. The plug is still adherent to the ulcer cavity. The surface epithelium has disappeared—disarrangement of glandular structure. (Low power.)

At the outset a blood count and hemoglobin estimation were made, and again after two to three months' confinement, and finally after seven to eight months. As soon as an animal

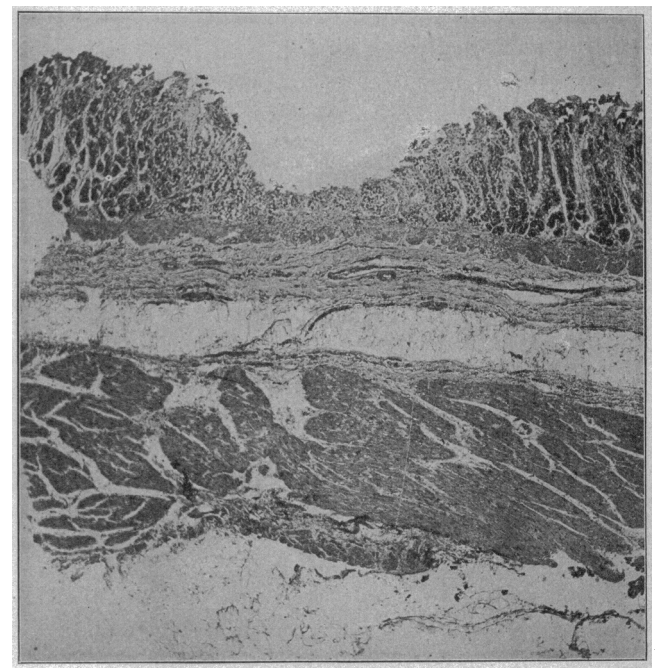

Fig. 12.—Stomach of dog. More advanced stage, with necrosis reaching almost the muscularis, exposing a small blood vessel. (Low power.)

showed any signs of infection it was removed. During the first two or three months the animals gained in weight as a result of deficient exercise and oxidation, but later became emaciated.

51. Turck: THE JOURNAL A. M. A., May 2, 1903.
52. Turck: Proc. C. Med. Soc., January, 1901; also Chicago Med. Rec., vol. xxi, No. 1, 1901.

Red Cells.		Percentage of Hemoglobin		Months.	Result.
Before	After	Before	After		
6,408,000	3,296,000	85	75	4	Ulcer
5,840,000	4,900,000	80	70	4½	Ulcer
6,410,000	4,850,000	85	60	6	Ulcer
4,992,000	4,200,000	75	60	5-½	Ulcer
5,120,000	4,250,000	70-75	60	5	Ulcer
5,360,000	4,120,000	80	65	6	Ulcer
6,200,000	3,130,000	85	65	6	No ulcer
5,450,000	3,800,000	80	50-55	5	No ulcer

Result, after nine months: All the rabbits died. Of the 96 guinea pigs, only 6 survived. In 4 of these animals ulcers produced by removing portions of the mucous membrane failed to heal. Two induced peptic ulcers were found in the other 2 guinea pigs.

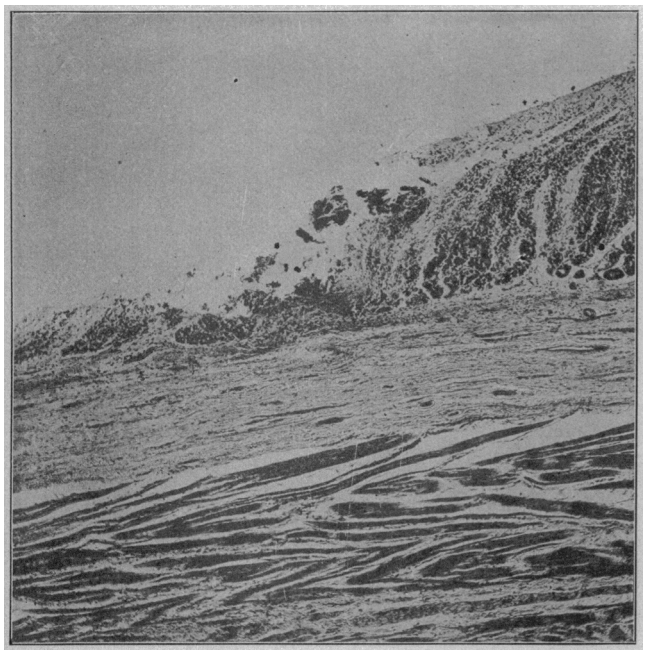

Fig. 13.—Stomach of dog. Edge of ulcer reaching to the muscularis, showing marked degenerative changes with breaking down of the entire glandular structure. (Low power.)

For the first time, then, in the author's long series of experiments, induced peptic ulcers were formed, but in such a small per cent. of the animals that even positive results were of little value in solving the problem of the

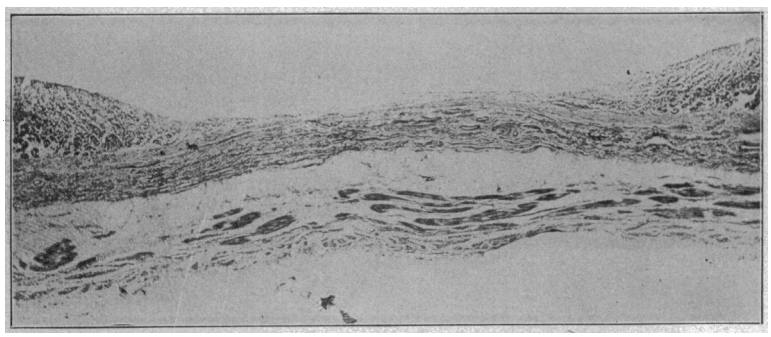

Fig. 14.—Smooth walled ulcer. No inflammatory changes. (Low power.)

etiology of peptic ulcer. They suggested, however, the possibility that systemic conditions were important factors, that alterations in the toxic state of the alimentary canal, with consequent changes in the blood, might play some rôle in the formation of ulcers. The next step was to select some more definite means of modifying the normal conditions of the alimentary tract and general system.

Experiments were begun with *Bacillus coli communis* because it is the organism found normally present in such large numbers in the intestines, and is the organism which multiplies so luxuriantly in catarrhal and atonic conditions of the stomach. Morphologically and culturally no difference could be found between the strain of *B. coli* isolated from the stools of normal individuals, and that from cases of ulcer of the stomach. But the possibility of a difference in their pathology led the author to use in his experiments strains isolated from the feces of cases of ulcer of the stomach. The toxin of *B. coli* being intracellular suggested the experiments of using killed as well as living cultures. In my earlier experiments the bacteria were introduced directly into the circulation, but later they were fed the animals. By this latter method the bacterial status of the alimentary canal could be more directly modified, and a better approach be made to more natural conditions.

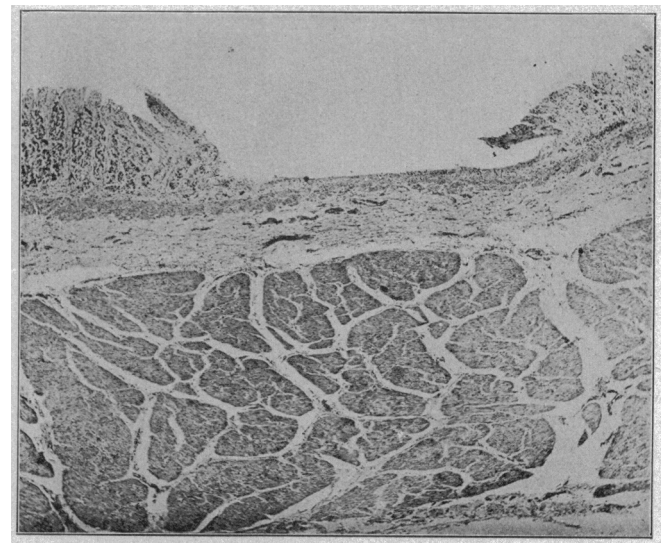

Fig. 15.—Ulcer with undermining of the mucosa. (Low power.)

Meat extractives were fed certain of the animals in connection with the bacteria, as will be seen by reference to the table of experiments with *B. coli*. It was found that *B. coli* grew most luxuriantly in media containing meat extractives, hence the possibility was suggested that a more active growth might be produced in an alimentary canal which contained meat extractives.

Positive results have been obtained thus far in every experiment in which cultures of *B. coli* were fed to dogs. The number and extent of the ulcers have varied, however, from a few ulcers in the duodenum to numerous typical peptic ulcers in the stomach. In one case death resulted from hemorrhage from a large ulcer at the pylorus.

To give these positive results true scientific value, it was essential to find out the percentage of gastric ulcer in a large number of dogs not experimented with.

The dogs were obtained from two different sources—one, healthy dogs that had been asphyxiated at the city pound; the other, dogs that had died from disease, injury, poisoning, etc. From the first source, 189 dogs were examined; from the second, 82, making a total of 271. Antemortem observations as to the general condition of the dogs could be made at the city pound, because the dogs were kept there ten days before being killed. The stomachs and intestines, after being removed from the bodies, were treated in a uniform manner, e. g., opened, washed in weak creolin solution, hardened for six hours in

dilute formalin, and finally examined very carefully macroscopically. Of the 189 healthy dogs examined, few showed any changes in the alimentary tract; of the 82 dying from disease, poisoning or injury, many showed diseased conditions of the various organs. But no peptic ulcers were found in either the stomach or intestine of any of the 271 dogs examined. Absolutely negative findings of peptic ulcers in both the healthy street dogs and the diseased animals shows that the percentage of ulcers present in dogs is at most exceedingly small.

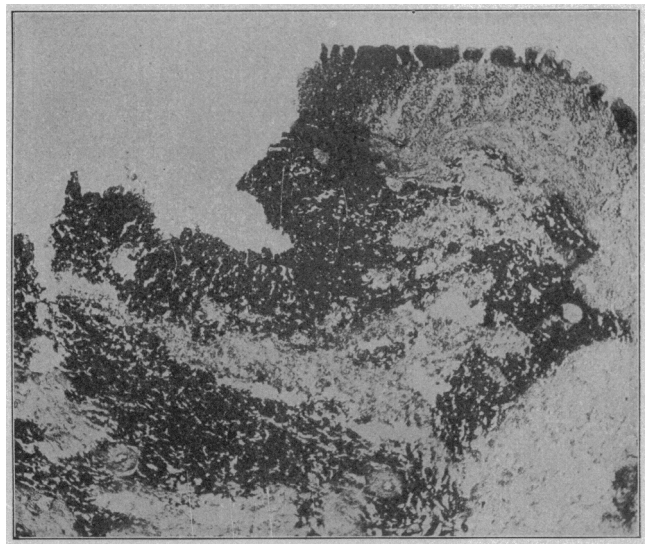

Fig. 16.—Destructive changes in the submucosa, showing necrotic areas which refuse to stain.

EXPERIMENT: WITH BACILLUS COLI COMMUNIS.

I. INOCULATION EXPERIMENTS WITH DOGS.
   1. Intravenous injections of living cultures of *B. coli communis.*
   2. Intravenous injections of cultures of *B. coli communis* killed by heat.

II. FEEDING EXPERIMENTS WITH MICE AND RATS.
   1. (a) Feeding raw beef.
      (b) Feeding raw beef and *B. coli communis.*
   2. (a) Feeding beef extractives.
      (b) Feeding beef extractives and *B. coli communis.*
   3. (a) Feeding extract free beef.
      (b) Feeding extract free beef and *B. coli communis.*

III. FEEDING EXPERIMENTS WITH DOGS.
   1. Feeding bouillon culture of *B. coli communis.*
   2. Feeding cultures of *B. coli communis* and beef extract.
   3. Feeding beef extract.

EXPERIMENTS IN INJECTING LIVING CULTURES OF B. COLI COMMUNIS INTO DOGS AND RABBITS (I, 1).

FIRST SERIES OF INJECTING EXPERIMENTS.

Methods.—The strain of *B. coli* used was isolated from water and from the feces of cases of ulcer of the stomach.

The injections were made subcutaneously, intraperitoneally, and into the internal jugular vein, at intervals of two to five days. Six dogs and twelve rabbits were used in this experiment. After a period of one month, the abdomen was opened under aseptic precautions, and an artificial ulcer made by removing a portion of the mucous membrane of the stomach. The injections were continued, and at the end of two weeks the abdomen was again opened.

Results.—In most of the animals the lesion was entirely healed, so that not even its site could be detected. Scars were visible in some of the stomachs and defective healing in others. In four animals ulcers were found, which did not show a tendency to heal.

SECOND SERIES OF INJECTING EXPERIMENTS.

Methods.—The strain of *B. coli* used was isolated from the feces of cases of ulcer of the stomach.

The injections were made into the external jugular vein of dogs and were continued for six months, at intervals of two to ten days. Four c.c of a twenty-four hour bouillon culture of *B. coli* was used for two months; then the amount was increased to emulsions of the surface growth of two petri dishes, and later of four petri dishes.

Results.—The reaction to the injection at first was anorexia and vomiting, with general lassitude for a day or two. After an interval of ten days the reaction to inoculation would be considerable, but would be much less pronounced, if the inoculation was then repeated in a day or two. Later, that is, after three months of such inoculation, no reaction could be obtained, even though large numbers of bacteria were introduced.

B. coli was agglutinated by the dog's serum in dilution 1/5,000 ten days after the first inoculation.

Operation.—An artificial ulcer was produced in the stomach four and one-half months after the first injection. The injections were continued two months longer.

Postmortem.—The dog was chloroformed three months after the production of the artificial ulcer, and the stomach and intestines examined for ulcers. The lesion produced at the time of the operation had entirely healed. No ulcers were found in the stomach. In the duodenum and ileum numerous oval-shaped raised areas were found, with depressed centers resembling Peyer's patches. The entire bowel was very pale, with the exception of a few hyperemic areas. Two irregular patches of erosion were found in the ileum. No ulcers were found in the intestines.

EXPERIMENT IN INJECTING INTRAVENOUSLY DEAD CULTURES OF B. COLI COMMUNIS (I, 2).

Methods.—The strain of *B. coli* was isolated from the feces of cases of ulcer of the stomach. The injections were made into the external jugular vein, and were continued for four months, at intervals of two to four days. Emulsions of the surface growth on two to eight petri dishes were used after being boiled to kill the bacteria. The constitutional reaction to inoculation was much less than in the case of living cultures.

Operation.—An artificial ulcer was made in the stomach three months after the first injection. The external wound healed readily. The injections were continued one month longer, and then the dog was chloroformed.

Postmortem.—No ulcers were found in the stomach. The duodenum showed six typical peptic ulcers, about 5 cm. from the pylorus. The ulcers were grouped together, somewhat oval in outline (6x4 mm.), transverse to the long axis of the bowel, with abrupt margins, and floor smooth and covered with a mucous-like accumulation (Fig. 8).

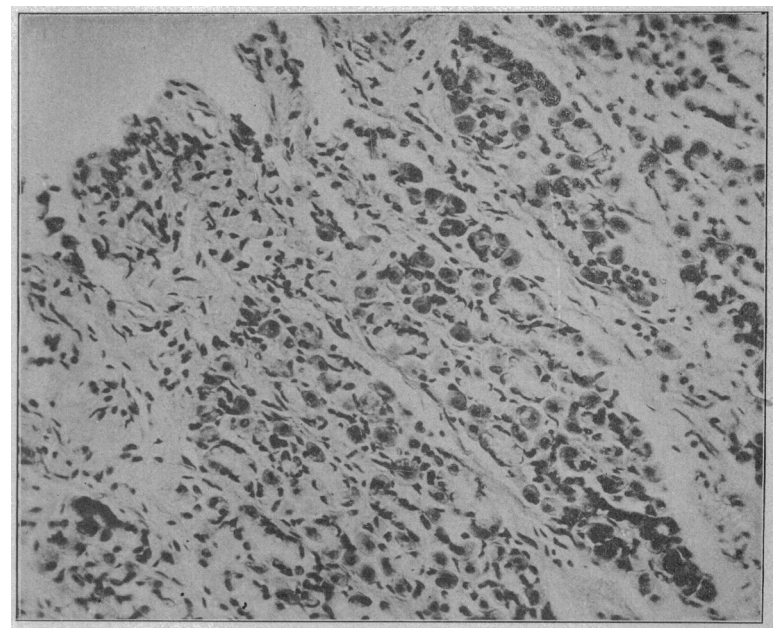

Fig. 17—Showing the increased proliferation parietal cells and the degenerated, broken down and disarranged chief cells. Surface epithelium disappeared. (High power.)

FEEDING EXPERIMENTS WITH MICE AND RATS (II).

The object of these experiments was to determine the relative effect of the feeding of *B. coli communis* with and without meat extractives.

Methods.—The meat juice obtained by pressing raw beef was used in the experiments with beef extractives. The extract free beef was prepared from the pressed meat, and after being steamed under 15 pounds' pressure for one hour was again pressed and fed the rats dry.

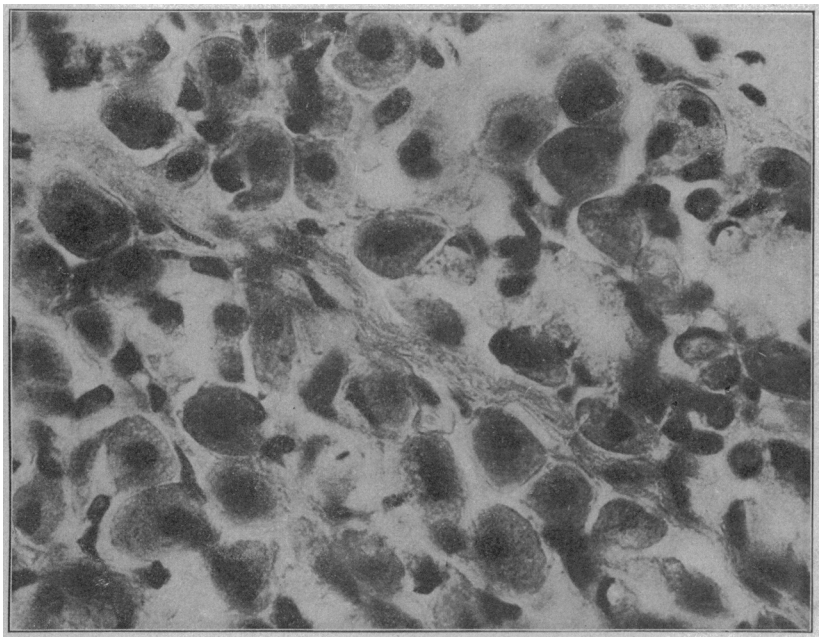

Fig. 18.—Showing the parietal cells. They are larger and increased in numbers; between them are seen a few degenerated chief cells. (Oil immersion, 1/12.)

Bouillon cultures of *B. coli* were added to the raw beef in one experiment, to the beef extract in a second experiment, and to the extract free beef in a third experiment. The rats were given as much of the cultures as they would take. As controls a second series of rats were given raw beef, beef extract and extract free beef respectively. The experiment was continued one month.

Results.—At the end of a month the rats fed on extractives and extractives containing *B. coli* died. The other rats of the series were killed at the same time for comparison.

During the course of the experiment little if any difference was noted in the behavior of the rats fed meat and extract free beef with and without bacteria. The extractive fed rats showed some bloating of the abdomen early in the experiment. They drank readily all the extractives and cultures fed them, but appeared restless and hungry.

Postmortem.—Negative so far as macroscopic appearances were concerned in all except the extractive fed rats. These showed a marked decrease in fat. Their organs, especially the liver, were pale in color.

FEEDING EXPERIMENTS WITH DOGS (III).

FEEDING BOUILLON CULTURES OF B. COLI COMMUNIS (III, 1.)

Methods.—Increasing quantities of a 24 to a 48 hour growth of *B. coli communis* in bouillon were fed daily to the dogs, together with an ordinary meat diet, beginning with small amounts and increasing to 1,000 c.c. Watery emulsions of the surface growth on agar plates were occasionally substituted.

The strain of *B. coli communis* used was obtained from the feces of cases of ulcer of the stomach. The length of time of feeding the dogs varied, in one case being 81 days before death occurred, and in another case 102 days.

RESULTS OF THE FEEDING.

Bacteria in Blood: The blood remained sterile during the course of the experiment. The heart's blood at death was also sterile.

Bacteria of the Stomach: Nearly pure cultures of *B. coli communis* were obtained from the stomach 9 hours after each feeding of the bacteria.

Effect on the Blood.—Agglutination: *B. coli* was agglutinated by the dog's serum in dilution 1 to 500 and slightly in dilution 1 to 1,000 after 20 days' feeding. Marked hemolysis of the blood was present 20 days after feeding.

Coagulability: Coagulation of the blood was slow, the clot formed being soft.

General Constitutional Reaction: The dog appeared perfectly normal until one week before death, when symptoms of hemorrhage gradually developed, e. g., coffee ground vomit, tarry stools, loss of strength and appetite, lowered temperature, with death in shock.

Postmortem.—Dog No. 1 (Series III, 1). Liver and kidney showed marked venous congestion. Stomach and intestines contained coffee-colored liquid. Stomach had large blood clot at pylorus and some coagulated blood over mucous membrane. Multiple peptic ulcers were found in the stomach and one large one at the plyorus, from which the hemorrhage occurred, resulting in death (Figs. 2, 3, 4).

Dog No. 2 (Series III, 1). A dog which had been under feeding experiment with *B. coli* was placed under anesthesia, abdomen opened, stomach found flabby and a small well-formed ulcer was found on anterior wall near the pylorus, which perforated on inflation of the stomach with air; the contents escaped through the opening, which showed sharpened edges ("punched out" appearance) the size of a dime; about a pint of fluid was found in the stomach; free HCl absent; peptones present.

Dog No. 3 (Series III, 1). Dog fed 500 c.c. bouillon cultures of *B. coli* daily for two months, then chloroformed.

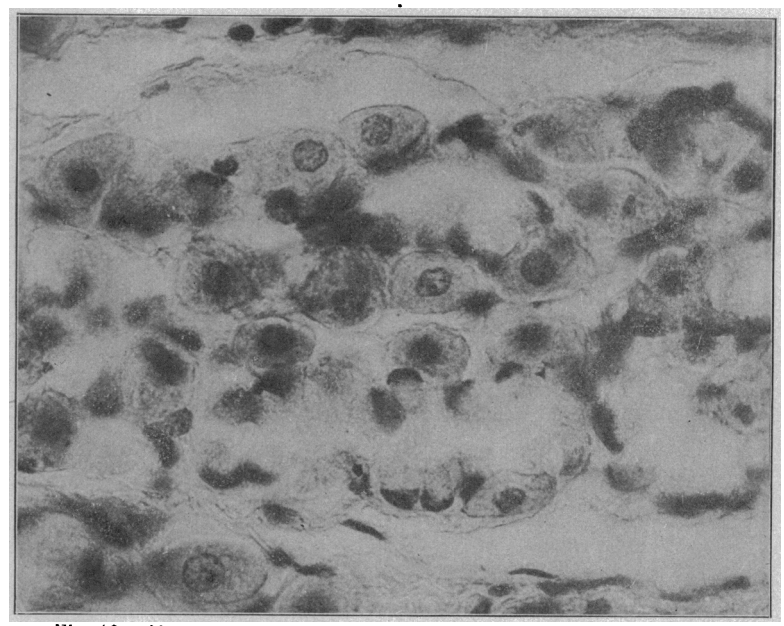

Fig. 19.—Showing the parietal and chief cells. Note the large size of the parietal cells, showing beginning degeneration; also, the crescent shaped nuclei of the degenerated chief cells. (1/12 oil immersion.)

At postmortem the stomach was found to be large, full of food. Mucous membrane hyperemic. In the pylorus were 6 round, pale colored raised areas about 3 mm. in diameter, with central depressions, margins raised and somewhat irregular in outline. No ulcers were found in the stomach.

Intestines.—Mucous membrane pale. In the duodenum were

three typical peptic ulcers in the wall opposite to the mesenteric attachment longitudinal to the axis of the bowel, circular in outline when stretched. Floor of the ulcers was smooth, clean cut, margins raised and abrupt (Fig. 5). No ulcers were found in the ileum or colon.

FEEDING BOUILLON CULTURES OF B. COLI COMMUNIS AND BEEF EXTRACTIVES (III, 2).

Methods.—Beef extract was fed the dogs in saturated watery solution or in capsules, approximately 25 gm. being fed daily, together with an ordinary meat diet. Cultures of *B. coli communis* were fed as in experiments III, 1. The length of time of feeding the dogs was 104 days.

RESULTS OF THE FEEDING.

Effect on the Blood: Experiments III, 2, same as in experiments III, 1.

General Constitutional Reaction.—Diarrhea was produced in three days, which lasted four to six days and was more pronounced in the case of the *B. coli* fed dog. Whenever during the course of the experiment the above feeding was stopped for a few days, there was a recurrence of the diarrhea on beginning the feeding again. With the exception of the above diarrhea both dogs remained perfectly healthy for three months, then the *B. coli* fed dog began to show some slight indisposition.

Operation.—After 100 days' feeding of beef extract and *B. coli communis* an exploratory operation was made, but no ulcers of the stomach were found. An artificial ulcer was made by removing a small portion of the mucosa in the posterior wall near the pylorus. Three days after the operation the dog died of peritonitis resulting from perforation of the artificial ulcer (Fig. 1).

Postmortem.—General peritonitis. Perforation of the stomach at site of artificial ulcer. Perfect closure of incision in anterior wall of the stomach made at the time of operation, with no signs of inflammation there. Venous congestion of liver and kidney. Duodenum showed 13 peptic ulcers (Figs. 6 and 7).

HISTOLOGIC EXAMINATION OF LIVER, KIDNEY, STOMACH AND INTESTINES OF DOG OF EXPERIMENT III, 1.

Dog died of hemorrhage from pyloric ulcer after being fed cultures of *B. coli* for 81 days.

Liver.—Marked degenerative changes are present in the liver cells of the central portions of the lobules. The liver columns here are broken up into one or more cells. The cells have a shrunken appearance, are irregular or roundish in outline, stain diffusely with eosin, or are broken down as granular or vacuolated masses. In these cells the nuclei have disappeared, while in others the nuclei appear as faintly bluish irregular rings. In the peripheral portion of the lobules, the liver cells contain numerous small vacuoles, are somewhat granular, and stain fairly well. The liver columns throughout are compressed by the congestion of the intertubular capillaries. Many leucocytes are seen in these vessels.

The blood vessels in the portal system are all engorged with blood. There is no increase in the stroma of the portal system, but it has an edematous appearance. The bile ducts are closed by their swollen epithelial cells.

Kidney.—Histologic examination of the kidney sections also shows marked degenerative changes. These are present largely in the secretory (convoluted) tubules. The epithelial cells lining these tubules are swollen and cloudy and fill the lumen of the tubules; others are granular and vacuolated; their outlines have disappeared, are fused together and broken down. In these cells the nuclei stain very poorly or have disappeared. The glomeruli have a swollen or cloudy appearance. The capillaries of the tufts are engorged with blood. The glomeruli are separated from Bowman's capsule, the spaces of which are filled with granular detritus.

The tissue throughout has an edematous appearance. The intertubular capillaries are all distended with blood.

Intestine.—Histologic examination of the sections from swollen Peyer's patches shows acute catarrhal changes with marked swelling of the follicles. The surface of the mucosa is covered with a bluish-stained, viscid mucous material in which are intermingled many detached epithelial cells, some leucocytes, red blood cells and bacteria. Some of the surface epithelial cells have an elongated appearance, the ends of which are lost in the exudate. The glands are all swollen and filled with bluish homogeneous material. The goblet cells are swollen and filled with mucus. The capillaries in the mucosa are all engorged with blood. The Peyer's patches are well defined and swollen. There is a great increase in lymphoid cells in the follicles as well as surrounding the follicles infiltrating the surrounding tissue. The central portions of the follicles are paler and stain pinkish with eosin, due largely to an increase of the epithelial cells, many of which are undergoing degeneration. There are no changes in the other coats except the engorged blood vessels.

Stomach.—For histologic examination, sections were taken from various areas of the stomach wall, e. g., those which showed typical ulcers; those with slight defects in the mucosa, and others in which no changes could be detected with the naked eye. The tissues were hardened in bichrom-acetic-alcohol imbedded in paraffin and stained with the usual stains, hematoxylin and eosin, polychrome methylen blue and toluidin blue, etc.

For the sake of clearness those sections will be described first which appear almost normal and show the least changes, followed by those which show changes of a more marked character. As seen in Figure 9 the mucous membrane has a normal appearance; the glandular structures are all fairly well preserved. Here and there the surface columnar epithelial cells are disarranged or entirely broken away (possibly due to the technic), exposing the connective tissue stroma of the columns. The stroma in the mucosa appears normal in amount and shows no changes. The capillaries are tortuous, distended with blood and plainly seen beneath the surface and the deeper portions of the mucosa. The chief cells of the glands do not show very well and their arrangement is somewhat broken up; otherwise they appear normal. The parietal (acid) cells are prominent, large, stain well and show an occasional mitotic figure or a deeply stained nucleus. In certain areas they appear to be increased in number.

Catarrhal Stage (Fig. 10.)—In tracing the different stages of the formation of ulcer, the catarrhal stage appears to be the earliest. First we find the surface of the mucosa covered by a more or less homogeneous pink (eosin) stained material, which has a resemblance to serum and in which are seen many red blood corpuscles, a few leucocytes, fragments and débris of detached columnar epithelial cells and many long bacilli. In other sections the material on the surface is made up of bands or layers, staining blue or bluish red with polychrome methylen blue and toluidin blue. From the staining reactions and appearance this material consists largely of mucus. These mucous bands also dip down into the neck of the glands, almost to one-half of their depth, and on close examination with the high power are shown to be intimately connected with the columnar epithelial cells. The surface epithelium and the cells lining the glands are well preserved, especially in the deeper portions of the mucosa.

In some areas, the surface cells are detached in groups and have a swollen appearance. The protoplasm of the cells is vesicular and vacuolated. Their shape is oval, elongated, spindle-shaped and tortuous. They usually have a greatly elongated and drawn out appearance like strings. The nuclei of these cells have an elongated and flattened appearance, and stain diffusely. These elongated cells become lost or appear to be intimately connected with the mucous bands which cover the surface of the mucosa and which fill up the glands themselves. As a result of the accumulation of this material, the glands are greatly distorted, the necks or openings of the glands widened or pressed apart. The deeper glands in the mucosa, also show a swollen appearance, their lumen being closed by the swollen cells. The protoplasm of these cells stains reddish blue (polychrome methylen blue) and is highly granular. The stroma of the mucosa has a swollen edematous appearance. In some areas there is a great infiltration with red blood corpuscles and a few leucocytes. All the blood vessels (smaller veins and capillaries) in the mucosa and submucosa are engorged with blood. The muscularis is normal.

From the above description it will be seen that we have in these sections, first a great outpouring of mucus, some serum and red blood corpuscles, followed by desquamation of the surface and lining cells of the glands, and later a mucoid degeneration of the cells themselves, which become entangled and intimately connected with the mucous secretion of the surface, and through various influences are easily detached or broken away from their lining, leaving defects underneath.

The further process with loss of the glandular tissue is the next step in the formation of ulcer which can be seen in another series of sections taken from a different area of the stomach walls, and which is shown well in Figures 11 and 12.

As shown in the photographs, there is a necrotic mass fitting into the concavity of the mucosa or supposed ulcerated area. In some sections the base of the concavity in the mucosa reached to the muscularis. The necrotic mass may still be connected to the mucosa by bands or may lie loosely attached, giving the edges a ragged appearance. With the high power the necrotic mass is seen to be composed largely of detached, proliferated and broken-down cells derived from the mucosa, and is made up of thick bluish stained bands, in which are entangled epithelial cells, acid or parietal cells, red blood corpuscles, and connective tissue cells. The glandular structure beneath the necrotic mass on either side is greatly disarranged and has lost the glandular outline.

The epithelial cells (chief cells) are scattered irregularly throughout the stroma (Fig. 17). They show marked degenerative changes; are small and irregular in shape; their protoplasm is vacuolated and the cell body deformed or compressed, while their nuclei are small, elongated, distorted and pale or refuse to stain. These chief cells seem to be crushed out of existence largely by the acid or parietal cells. The latter are so numerous that they almost replace the entire field of the mucosa and are proliferating in large numbers. The proliferation of the parietal cells is a marked feature in all these sections (Figs. 17, 18, 19). Mitotic figures are very numerous; many of the cells contain two nuclei. They vary in size, being sometimes two and four times their natural size. Hand in hand with proliferation of these cells there are also degenerative changes going on. The protoplasm stains deeply or poorly, or may be granular or broken up. Some cells are vacuolated and swollen; their nuclei appear vesicular, granular and have a pale and distorted appearance. These cells in some areas are so numerous that 50 can be counted in a single field with the high power. The connective tissue stroma in these areas is disarranged or broken down by the proliferated cells. Underneath the necrotic mass the stroma has lost its usual character; it is looser in texture, fibrillar or homogeneous and granular and refuses to stain well; throughout the stroma in these areas there are hemorrhagic extravasations. As the various cellular elements break down, the loosely fibrillar stroma collapses and later also breaks down, leaving larger and smaller defects in the mucosa.

Some distance away from this area the stroma appears somewhat increased. The surface epithelium has more or less disappeared or become detached, exposing the stroma underneath. Here also is active proliferation of the parietal cells; they are seen in solid columns, one on the other, while the chief cells are disarranged and imbedded between the parietal cells. The chief cells are small, irregular, vacuolated and distorted with peculiar vesicular nuclei, or they may be so overwhelmed by the parietal cells that their outlines are lost.

The mechanical factor in the destruction of the chief cells by the proliferated acid cells is only a secondary feature.

Primarily marked cytolytic changes are to be noted in the chief cells themselves. In areas where the glandular structure is fairly well preserved, the chief cells may still be attached to the basement membrane, or if detached, lie loosely in the lumen of the glands. Here the chief cells are small, distorted and shrunken, with almost complete loss of protoplasmic contents. Their nuclei are peculiarly distorted into half-moon shapes and stain faintly, the cells appearing in areas as shadow ghost cells. These changes are purely cytolytic.

Other sections of this series show more advanced stages of the same process. As seen in Figure 12, the necrotic mass has dropped out or broken away, exposing a more or less well-defined, irregular smooth ulcer, reaching almost to the muscularis and exposing at the base a larger sized blood vessel, which is broken down, showing how hemorrhages occur. Otherwise the changes are as described above. There are no changes in the submucosa or muscularis except engorgement of the veins and capillaries with blood.

DESCRIPTION OF THE TYPICAL ULCER.

The typical ulcer, as shown in Figures 13, 14, 15, is a well-defined smooth-walled concavity. It gradually slopes inward and downward from either side to the base at the muscularis mucosa. In some sections the concavity is more or less square, or somewhat irregular in outline; in others the edges may be overlapping with undermining beneath. The edges or walls of the ulcer as a rule are smooth and consist of remnants of the stroma. It is a poorly stained or colorless loose fibrillar, almost fibrin-like, homogeneous or granular material, in which are imbedded round, oval or elongated nuclei, fragments of epithelial cells especially parietal cells, which in certain parts are fairly well preserved and stain well. There are no inflammatory changes of any kind present. The same appearance of the stroma is noted some distance from the ulcer. The surface of the mucosa has the same appearance as the edges of the ulcer. The surface epithelium has all disappeared. The deeper glands show changes as described in previous specimens. The chief cells are disarranged and crowded out by the large increased number of the parietal cells. The deeper glands are fairly well preserved, but have a swollen, cloudy and granular appearance.

The outline of the cells has disappeared and the individual cells have fused together, so that the gland is composed of a coarsely granular mass, through which are scattered deeply stained nuclei. Some of these glands in cross section show the early changes in the parietal and chief cells. The chief cells are swollen, opaque or coarsely granular, while the parietal cells show beginning proliferation. They stain intensely pink (eosin), are increased in size, and crowd or press the chief cells inward into the lumen of the glands. In the upper portion of the mucosa the glandular outline becomes gradually deranged. The parietal cells are increased in number, while the chief cells crowded in between are small, appear as shadows or have disappeared. Usually nearer the ulcer, both kinds of cells are scattered irregularly through the tissues. Degenerative changes are seen in both kind of cells, but they are more pronounced in the chief than in the acid cells.

SUMMARY.

According to my experiments the factors concerned in the production and persistence of ulcer of the stomach

and duodenum appear to indicate a dual condition. Some toxic condition seems to be produced which overcomes natural resistance, resulting in cytolysis, and possibly some chemical substances formed within the alimentary tract, which when absorbed may neutralize the protective bodies in the blood and tissues resulting in autocytolysis.

This hypothesis must present itself after a careful study of the local and systemic changes that take place in the production of induced peptic ulcer. In my experiments in feeding cultures of the colon bacillus, pronounced changes were revealed in the blood and tissues. Agglutination of *B. coli* by the dog's serum in high dilution was noted; hemolysis of the blood was evident; cytolysis and autocytolysis of the cells of the mucous membrane of the stomach, of the kidney and of the liver were marked on microscopic examination. But there was no bacteriemia, no inflammatory reaction in the form of round cell infiltration such as one would expect in a reactionary inflammation induced by pyogenic micro-organisms or toxins. It was not the picture of reaction to an infection, not the picture of a local, acting agent, but rather of a systemic condition, and of an induced cellular change.

What have we accomplished by our experiments? Gastric ulcers have been produced by other investigators, as will be seen by reference to the literature, but for the first time we have, by our feeding experiments, brought about spontaneous or induced peptic ulcer in the stomach and duodenum. We are as yet at the experimental threshhold, for our experiments have been comparatively few in number, but a percentage of 100 in our results signifies a true grasp of an etiologic factor. We are at least justified in saying that we have now a firm working basis for the further investigation of the pathogenesis of gastric ulcer. There are now a number of problems before us under investigation. Perhaps the widest field is opened in the study of the blood changes in these animals. Further determinations must be made of the hemolytic, agglutinating, bacteriolytic and phagocytic strength of the blood, and its coagulability, reaction, the action of the serum on digestion, the hemoglobin curve, the number of red and white blood corpuscles and the differential count of the leucocytes. It is of prime importance that the pathology of ulcer be further studied by histologic examinations of the ulcers at various stages of their development, that an examination be made also of the liver, kidney, spleen, lymph glands and bone marrow. The problem of altered metabolism must be studied by an analysis of the urine, feces, stomach contents, etc. It must be determined also whether the feeding of bacteria other than *B. coli* will produce ulcer, and whether all animals are equally susceptible.

CONCLUSIONS.

1. Ulcer of the stomach and duodenum can be produced in dogs by feeding *B. coli communis* for a variable length of time.

2. We have now for the first time a firm basis by which to solve the finer or underlying etiology of ulcer.

TRYPSIN IN MALIGNANT GROWTHS.

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CHICAGO.

Following the experiments of Beard of Edinburgh with the use of trypsin in Jensen tumors in mice and his suggestion for the use of trypsin in carcinoma, many attempts undoubtedly are being made at present with trypsin in inoperable malignant growths.

I have used trypsin in seven cases of inoperable carcinoma in different parts of the body and in one inoperable round-cell sarcoma of the thigh. I began the work ten weeks ago, and in some of the cases continued the injections for six weeks. All except one were hopeless cases from the standpoint of operation or *x*-rays, but in none of them was cachexia marked. I have used Fairchild's sterilized trypsin solution with the commercial name of *injectio trypsi,* which, I believe, was the preparation used by Beard. Beard's successful dose of one drop in mice is equivalent to 600 drops in an adult of 150 pounds weight. I began with injections of from 5 to 10 drops daily, and in some cases rapidly increased it to a maximum dose of 60 drops daily.

The results can be readily epitomized. Sometimes the doses—whether small or large—caused little pain and no subsequent irritation at the site of injection; in one or two patients there was bitter complaint occasionally after an injection; frequent inflammatory swellings resulted, and in six or eight instances abscesses developed at the site of injection. These developed several days after the injections, and I believe the question of accidental infection can be eliminated because the injections were given with scrupulous attention to aseptic technic and other patients who were having hypodermic injections at the same time of other drugs developed no abscesses. The abscesses which formed began as ordinary phlegmonous swellings. When they opened there was a discharge, not of ordinary pus, but of a thick, sticky, almost transparent serous fluid containing broken-down cheesy masses. After evacuation of an abscess there was left an unhealthy sinus with dirty-grayish, flabby walls, and in three or four instances these enlarged until they formed unhealthy, deep, indolent sinuses of the diameter of a finger or larger. These are slow to heal, but are painless.

I think that in one case in which there was a circumscribed mass of carcinoma in the pectoral muscle on the front of the shoulder there has been very distinct benefit from the injections. In this case there was a phlegmonous swelling which was opened with the discharge of more than two ounces of fluid and broken-down tissue, but the opening did not become larger and the cavity is now healed. As a result of the procedure the carcinomatous mass has disappeared as though it had been digested. I believe that in this case positive benefit has been done.

In the other cases I believe appreciable harm has been done to the patients. In several instances after large injections the patients have had chills. Except for these chills, there has been no immediate constitutional effect; but in all the patients who had numerous injections cachexia has developed and they have failed more rapidly than they were failing before. The experience has been so uniform that I have no doubt the trypsin has done the patients harm. The one case in which there has seemed to be benefit showed only a circumscribed mass, and in a similar case I should try trypsin again, but unless I could hope with a few injections to destroy a localized mass I should not at present feel justified in using the remedy. In none of the other cases has there been any appreciable influence on the neoplasms.

I know that so short and so small an experience is in no way convincing, but, as it has forced on me some conclusions and as there are no published reports on the effect of trypsin in human carcinoma, I venture to believe the experience is worth recording at this time.