It is evident from the data obtained that there is about as much variation in the commercial coatings, as in those prepared in the laboratory. On considering the keratin coating No. 1, we find total disintegration in the stomach, the average time being about one hour. These tablets are of no value for enteric medication. From experience we have had with keratin as an enteric coating we concluded that the adverse results were caused by a faulty method of application. The results of the experiments for keratin No. 2, showed that 13 tablets disintegrated in the colon, 4 in the small intestine, and 1 in the stomach. The point of disintegration of 7 was unknown, and 3 were excreted. This coating proved to be 80.95% efficient. In making this calculation for the various coatings, results were disregarded in all cases where the exact point of disintegration was unknown. The results from the keratin No. 2 coating indicate an exceptionally good enteric coating. The experiments for the shellac coating show that these tablets are of no value for enteric medication. The average time for disintegration was between 70 and 100 minutes. Faulty application cannot be claimed for this coating as other tablets purchased on the market disintegrated in about the same average time. In the case of the salol resin mixture, 13 tablets disintegrated in the stomach and 22 tablets in the intestine. Five tablets had not disintegrated when the last picture was taken, and their fate was not determined. This enteric coating was 63.00% efficient. The results of the experiments using salol shellac showed that 8 tablets disintegrated in the small intestine and 4 in the stomach. Four capsules disintegrated in the small intestine and 5 in the stomach. The fate of 3 capsules was not determined. The average time of disintegration for the tablets was 6 hours and of the capsules was 4 hours. The percentage efficiency of the tablets was 66.66% and of the capsules was 44.44%. In this case, it appears that the tablets are a better means of medication than the capsules.

It may be concluded that none of the enteric coatings studied was perfect. The best results would seem to be obtained with keratin when properly applied. However, if one considered the absorption rate of the colon less than that of the small intestine, the salol mixtures would be better. Capsules with the same type of enteric coating as a tablet are not as efficient, due no doubt to mechanical difficulties as the capsules roll thin on the ends during the coating process. Shellac by itself is of no value as an enteric coating.

The authors wish to thank the Abbott Laboratories Inc., North Chicago, Ill., G. D. Searle Co., Chicago, Ill., Sharp and Dohme Co., Baltimore, Md., and the Smith Dorsey Co., Lincoln, Nebr., for their coöperation in coating tablets for this study. The authors also wish to thank the students of the College of Pharmacy, University of Nebraska, for their assistance as subjects in this study.

ENTERIC COATINGS. I. A LABORATORY METHOD FOR THE STUDY AND CONTROL OF ENTERIC COATINGS.*

BY MILTON WRUBLE.

Several years ago a preliminary report on enteric coatings was made by the writer (1). Since that time the opportunity has presented itself to study the prob-

* The Research Laboratories, The Upjohn Company, Kalamazoo, Michigan. (June 26, 1935.)

lem more intensively and in a more comprehensive manner because of the availability of apparatus and working facilities.

p_H of Gastric and Intestinal Juices.—The normal acidity of the gastric juice due to the free hydrochloric acid present ranges from about p_H 1.6 to p_H 1.8. However, it usually varies over a much wider range.

Vanzant, Alvarez, Eusterman, Dunn and Berkson (2) have studied the gastric acidity of 3746 persons in whom careful examination did not reveal any disease which could perceivably affect the mucous membrane or the secretory activity of the stomach.

They found a steady increase in the incidence of achlorhydria from youth to old age and that free gastric acidity appears to increase rapidly from childhood to the age of 20 years when adult values are reached. They also found that about the age of puberty, the average value for boys begins to rise considerably above that for girls.

Boldyreff (3), who has made extensive investigations in this field, has proved that in the normal organism during digestion, as well as in the empty stomach, the acidity of the gastric contents is mainly regulated by the alkali of the pancreatic juice regurgitated from the duodenum into the stomach.

He has further shown (4) that the entrance of duodenal secretions into the stomach occurs, as a purely physiological phenomenon, (*a*) when the stomach and duodenum are empty, (*b*) with abundance of acid in these organs, (*c*) with abundance of fat in these organs and with any strong irritation of the duodenal mucosa caused by hot or cold liquids, alcohol, etc.

Much evidence has been presented within recent years to show that in the human small intestine the reactions may vary from distinctly acid to slightly alkaline. Long and Fenger (5) have made an important contribution in this direction.

Howell makes the following statement (6): "The secretions emptying into the small intestine, the succus entericus, the bile and the pancreatic juice, all have a slightly alkaline reaction and we should expect, therefore, to find the reaction of the intestinal contents on the alkaline side. Most observers have reported, however, that during digestion the reaction of the contents is acid."

Recent work with dogs by Bollman and Mann at the Mayo Clinic (7) has shown that during digestion the reaction in the duodenum may vary between p_H 3.8 and p_H 6.6. In the jejunum they found the reaction to be on the acid side. In the ileum they observed that even during digestion the reaction did not drop below the neutral point p_H 7.0.

Temperature.—Hepburn, Eberhard, Ricketts and Rieger (8) measured temperatures in the gastrointestinal tract with a recording thermometer. In a group of 257 healthy, active individuals the gastric temperature was between 97.5 and 102.2° F. In a group of 53 subjects the temperature of the upper part of the intestine lay between 98° and 100.1° F.

The ingestion of either ice water or ice cream produced marked decrease in gastric temperature, followed by a rise, at first quite rapid, then progressively slower. The average recovery time exceeded one-half hour. The use of ice water in a test-meal was found to delay the gastric emptying time by from 15 to 30 minutes.

The authors obtained evidence that leakage of a cold beverage through the pylorus lowers the temperature of the upper part of the intestine by several degrees. This observation may throw light on the etiology of the gastroenteric disturbances in patients who have a rapid emptying time and partake copiously of cold beverages.

The ingestion of hot coffee produced a marked increase in gastric temperatures followed by a decrease, at first rapid then progressively slower.

Motility or Emptying Rate of Stomach.—The peristaltic activity of the healthy stomach begins shortly after the ingestion of the meal, but its advent may be retarded or even inhibited by nervous states and emotions.

The motility of the stomach depends on several factors. The average emptying rate in patients without obstructive lesions lies between three and five hours. Briggs (9) made such a study with 100 normal individuals employing the barium meal. He obtained the following figures: The stomach emptied in two and a half hours in 1 per cent; in three hours in 6 per cent; in three and a half hours in 9 per cent; in four hours in 44 per cent; in four and a half hours in 32 per cent and in five hours in 8 per cent.

Campbell and Conybeare (10) independently examined a group of healthy male students by means of the fractional test-meals and also radiographically. They demonstrated that hypertonus, hyperacidity and rapid emptying of a barium meal occurred most frequently in men of the broad-chested, vigorous, athletic type; hypotonus, low acidity and slow emptying for the most part in narrow-chested men below the average of physical development and not taking regular exercise.

Bukey and Brew (11) in their study of the emptying time of the stomach with reference to pills and tablets, arrived at the following conclusions:

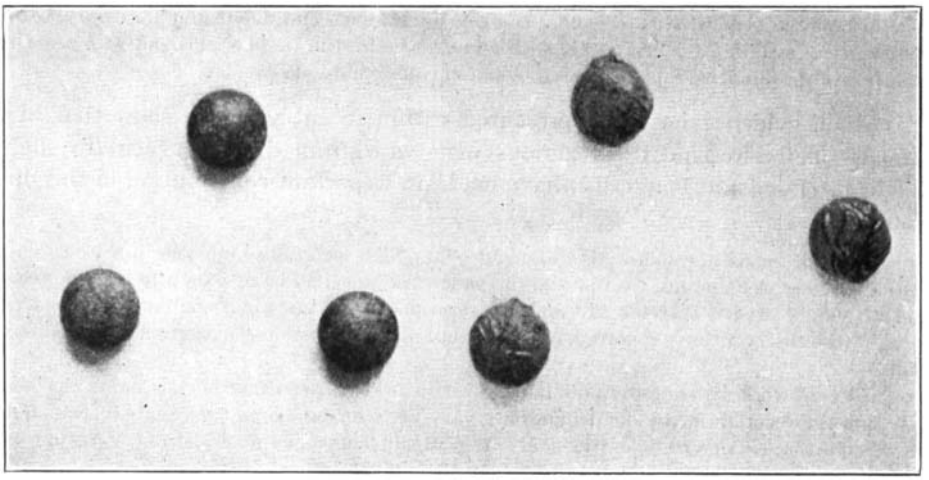

Fig. 1. Fig. 2.

(1) The size and shape of a pill, tablet or capsule have no effect on the length of time it will remain in the stomach.

(2) The same individual does not react uniformly toward this type of medication with reference to emptying time.

(3) Emptying time may be influenced by diet.

(4) The type of coating does not have any effect on the length of time that pills, tablets and capsules will remain in the stomach.

Motility may be impaired or exaggerated by disease. Abnormal rapid emptying or hypermotility occurs in a certain proportion of cases of duodenal ulcer with hypertonus.

EXPERIMENTAL.

The actual *in vitro* study of enteric coatings may be conveniently carried out in an apparatus in which the tablets are allowed to rotate in buffers covering the gastric and intestinal ranges at temperatures between 37.5° to 40° C. The apparatus employed (12) was a modification of a type used in earlier investigations in this field. The disintegration point was observed in each case.

While it is true that such a mechanical test can be but a mere approach to the actual picture of conditions in the stomachs and intestines of individuals of widely varying characteristics, still it has been possible to establish a relationship in this manner and thus such a procedure has been of real value in the laboratory study and control of enteric coatings.

Hundreds of tablets and capsules have been studied as described, in this laboratory. From the numerous observations made it is significant to note that in every case the coating surface of the tablets immersed in buffers from p_H 1.2 to p_H 6.4 showed little change even after rotating for eight hours or more while those immersed in buffers beginning with p_H 6.4 and upward showed evidence of attack and a definite shriveling effect within 5 to 15 minutes. See Figs. 1 and 2.

Examination of the latter tablets indicates that the enteric coating has permitted the passage of fluids through it by becoming permeable while in the other case the coating has remained entirely impervious even after many hours of rotation and contact.

DISCUSSION.

Recent investigations have definitely indicated that our earlier notions regarding the acidity and alkalinity of the stomach and small intestines, respectively, are erroneous. More often the small intestine is slightly acid in reaction and the p_H of the stomach will doubtless vary over a considerable range because of regurgitation and the other factors already enumerated.

In addition, therefore, to the requisite physical and chemical properties that a coating must possess and the fact that it must be physiologically inert, it must also resist the wide and variable acid range in the stomach and commence to disintegrate at the slightly acid reaction found in the small intestine. If a coating requires a decidedly alkaline reaction before disintegration commences, the tablet or capsule will in all probability pass through the small intestine without disintegration taking place.

CONCLUSIONS.

1. A laboratory method for the study and control of enteric coating has been described.

2. The extreme sensitivity of this coating in buffers is noted.

REFERENCES.

(1) Wruble, M., "Enteric Coatings," *Am. J. Pharm.*, 102, 318 (1930).

(2) Vanzant, F. R., Alvarez, W. C., Eusterman, G. B., Dunn, H. L., Berkson, J., "The Normal Range of Gastric Acidity from Youth to Old Age," *Arch. Int. Med.*, 49, 345 (1932).

(3) Boldyreff, W. N., "The Self-Regulation of the Acidity of the Gastric Contents," *Bull. Battle Creek Sanit. and Hosp. Clinic*, 22, 65 (1927); *Ibid.*, 24, 379 (1929).

(4) *Ibid.*, 24, 392 (1929).

(5) Long, J. H., and Fenger, F., "On the Normal Reaction of the Intestinal Tract," *J. Am. Chem. Soc.*, 39, 1278 (1917).

> "In the human small intestine the reaction may vary from distinctly acid to slightly alkaline on the part which may be reached by the Rehfus tube where the tube is far enough down to secure a uniform mixture of contents. The acid reaction is apparently as common as the alkaline, but the degree of acidity is not sufficient to check the tryptic digestion, which in some instances seems to be favored by a reaction on the acid side of neutrality. The reaction found must vary with the state of diges-

tive acidity and is simply an equilibrium condition between the chyme and the alkaline juices poured into the duodenum. Any reaction near neutrality may obtain."

(6) "Textbook of Physiology," 11th Edition, page 829.

(7) *Mayo Clinic Proceedings*, May 12, 1930, from Howell, 11th Edition, page 829.

(8) Hepburn, J. S., Eberhard, H. M., Ricketts, R., Rieger, C. L. W., "Temperature of the Gastrointestinal Tract," *Arch. Int. Med.*, 52, 603 (1933).

(9) Ryle, J. A., "Gastric Function in Health and Disease," 23 (1926).

(10) *Ibid.*, page 19.

(11) Bukey, F. S., Brew, M., "A Study of the Emptying Time of the Stomach with Reference to Pills and Tablets," JOUR. A. PH. A., 23, 1217 (1934).

(12) Wruble, M., "Enteric Coatings," *Am. J. Pharm.*, 102, 318 (1930).

(*To be continued.*)

AN UNUSUAL MORTAR AND PESTLE.*

BY JOHN E. KRAMER.[1]

In one of the museum cases of the Philadelphia College of Pharmacy and Science there is an unusual mortar and pestle attracting the attention of even the most casual passer-by. The mortar is made of bronze, $6\frac{1}{2}$ inches high, 5 inches in diameter at the bottom and 6 inches across the top. Two handles, one projecting from either side, about half way up from the bottom, are the first things to catch the eye. Further inspection reveals a band across the mortar bearing the inscription "NAPOLEON-EMPEREUR." Immediately the investigating spirit is aroused, and close scrutiny reveals a smaller band running around the top with the words "A Besancon Bieillemand-Pharmacien-Drogiste" cast in the band. Between these bands can be seen wreaths and eagles, alternating, and in the space between the lower band and the bottom of the piece, emblems of two figures facing each other and more wreaths alternate.

A Monarch's Mortar.

The pestle is also of bronze and is $9\frac{1}{2}$ inches long. Through the center it is $1\frac{1}{2}$ inches in diameter but at the ends the diameter reaches $3\frac{3}{4}$ inches. There appear two imperial shields and eagles and the inscription "Anno 1802." These pieces were presented to the College by Dr. David Costelo of New York.

It was just one year after the date on this pestle that the Pharmaceutical Society was founded in Paris. And it was in 1804 that Napoleon, at the beginning of his greatest bid for fame, secured a popular vote changing France to an empire, and secured for himself the title of Emperor of France. Evidently, with the acquisition of this new title, Napoleon had all his belongings stamped accordingly, hence the band around the middle of the mortar.

The royal courts of those days had, by appointment, doctors, druggists and others to satisfy the various needs of the emperors and their retinues. Bieillemand was the favored pharmacist at this time and used this mortar in which to mix the potions and pill masses for the great Corsican and his court. The position was no

* Section on Historical Pharmacy, A. PH. A., Toronto meeting, 1932.

[1] Philadelphia College of Pharmacy and Science.