2. Frog Nerve-Muscle Preparation:
   Depression: Alcohol, ether, chloroform.
   Contraction: Relieved by strychnine: Nicotine.
   Prevented by strychnine: Coniine.
   Paralysis: Sparteine.
3. Frog Lymph Sac:
   Characteristic position: Nicotine.
   Negative: Coniine.
4. Mice, Intraperitoneal Injection:
   Depression: Alcohol, ether, chloroform, chloral.
   Stimulation: Phenol, aniline, carbon bisulfide.
   Blood changes, red color: Hydrocyanic acid.

CONCLUSION.

Methods of testing common poisons in the acid and the alkaline distillate from minced viscera have been developed to orient and to confirm chemical toxicological identification.

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A NEW ENTERIC COATING AND A LABORATORY METHOD FOR ITS CONTROL.*

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INTRODUCTION.

For many years enteric coatings of one kind or another have been applied to pills, capsules and tablets. In 1884, Unna (1) used keratin which was considered to be the first real enteric coating. Thirteen years later Hausmann and Weyland (2) created a new wave of interest when they developed formalin-gelatin. In 1915, Toplis (3) suggested stearic acid, and a few years later Freeman (4) supported its use as an efficient coating. Ammoniated white shellac was used by both Hilton (5) and Wruble (7), the former applying it in combination with salol. In 1932, Husa and Magid (6) reported the use of a mixture of salol, stearic acid and shellac. The most recent work was reported in June 1937 by Mills (9) who used a combination of cetyl alcohol and mastic, for which she claimed an efficiency of 98 per cent.

Generally, commercial enteric coatings have not been applied in a manner giving consistently efficient results. Also, there have been many different interpretations of a satisfactory coating. However, during the last several years radiography has been of great value in determining the behavior of tablets in the gastrointestinal tract. Bukey and Rhodes (10) in 1935 reported a wide variation in the efficiency of commercial enteric coatings, after having tested, radiographically,

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five samples of enteric coated barium sulfate tablets submitted by various pharmaceutical manufacturers.

Figure 1 shows a radiograph made by the authors one hour after the administration of six barium sulfate tablets coated with sandarac, a widely used commercial enteric coating. All but one of the tablets disintegrated in the stomach where traces of barium sulfate could be detected.

Figure 2 shows a radiograph made one and one-half hours after administration of another sample of the same tablets in another subject. That all tablets disintegrated in the stomach was evident, for the radiograph shows white blotches corresponding in position to that of the stomach.

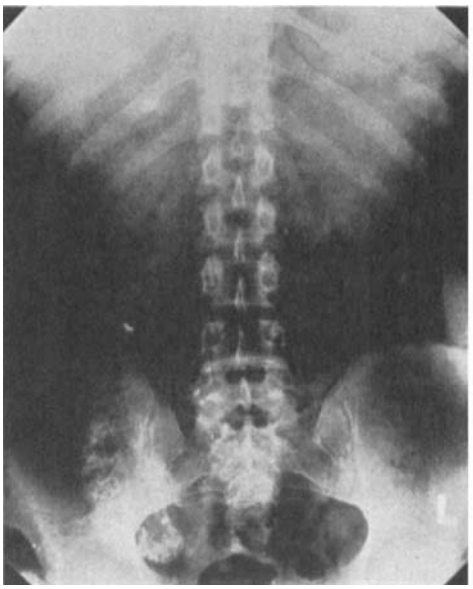


Fig. 1.—Barium sulfate tablets coated with sandarac one hour after administration.

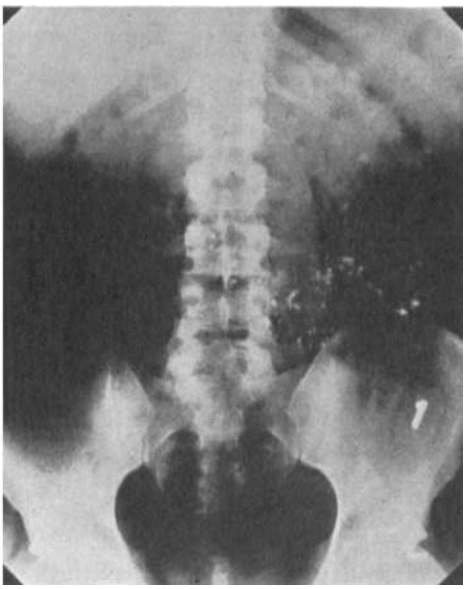


Fig. 2.—Barium sulfate tablets coated with sandarac one and one-half hours after administration.

DISCUSSION.

To understand fully what is required of an enteric coating, it is well to consider briefly the physiological activity and its variations in the alimentary tract from the stomach to the point of excretion. There are several different conditions existing in the gastro-intestinal tracts of several individuals at a given time or in one individual at different times involving p_H and motility.

The majority of workers who have been attacking the enteric problem have based their attack on the assumption that the intestinal contents are always alkaline. Such an assumption is unfounded, however, since the intestinal contents, even when passing through the ileocaecal valve into the colon, are frequently acid in reaction (11). This belief that the contents of the small bowel are always alkaline has been shaken during the past five years, for several workers have presented evidence indicating that the content of the small bowel is frequently acid in reaction. Wruble (8) pointed out the work of Bollman and Mann (12) who found

while working with dogs at the Mayo Clinic, that the reaction in both the duodenum and jejunum is acid during digestion. The p_H in the duodenum varied between 3.8 and 6.6. It follows that a tablet soluble only in an alkaline solution will frequently pass through the entire alimentary tract undissolved.

The variable of greatest importance in the alimentary tract is the emptying rate of the stomach. The length of time a coating must be stable in gastric juice in order to leave the stomach intact has been a controversial subject. One of the chief causes for variation in the emptying rate is the varied bodily activity of different individuals. Campbell and Conybeare (13) proved radiographically that the stomach of an individual who exercises regularly empties more quickly than that of an individual who does not.

Briggs (14) was cited by Wruble as an authority who studied the emptying rate of the stomach by employing a barium meal in 100 normal individuals. He found the stomach emptied in two and one-half hours in 1 per cent; three hours in 6 per cent; three and one-half hours in 9 per cent; four hours in 44 per cent; four and one-half hours in 32 per cent; and five hours in 8 per cent. From this study it may be said that the emptying time of food from the stomach in 99 per cent of patients is between three and five hours, and in 76 per cent between four, and four and one-half hours.

The diet also influences the emptying rate of the stomach. Cannon (15) in 1904 observed that the stomach of an individual emptied quickly on a carbohydrate diet, more slowly on a protein diet, and still more slowly on a fat diet.

Bukey and Brew (16) after completing a radiographic study of the emptying rate of the stomach found that the majority of tablets left the stomach in four hours, and the average emptying time was 5.9 hours. This checks closely with the work of Briggs. They concluded that the emptying rate is not influenced by the size or shape of a tablet nor by the nature of the coating.

Bukey and Brew (17) in a more recent paper reported their findings relative to the influence of diet on the time enteric coated tablets remain in the stomach. They found diets high in carbohydrate or cellulose caused tablets to pass rapidly from the stomach. Passage was less rapid on a protein diet and very slow on a fat diet. Ingestion of large volumes of water was found to retard passage of tablets from the stomach. They also reported that generally, the length of time tablets remain in the stomach increases as the day progresses, due to fatigue and slowing of peristalsis.

When acid chyme is discharged through the pylorus, it passes into the lower duodenum, and jejunum, which are best adapted for absorption. Here it remains for several hours (18). It is at this point that an enteric tablet or capsule should completely disintegrate.

In explaining the formations of feces Bodansky (11) in his "Introduction to Physiological Chemistry" states, "The intestinal contents, upon reaching the ileocaecal valve, are not like feces in appearance and composition. They are semifluid in consistency, and frequently acid in reaction, whereas the feces are usually alkaline. At this stage the intestinal contents consist largely of undigested food remnants, the remains of the digestive and intestinal secretions, and cellular elements, including cell debris from the alimentary tract. The transformation of this material into feces occurs in the large intestine where food residues remain for one or more

days. Here certain substances, especially water, are partly resorbed." Chances are great that a tablet, after having reached the colon, will be excreted intact if it has not disintegrated by the time resorption has taken place.

After having considered the physiological aspects of the problem, it appears that an efficient enteric coating should be stable for nearly six hours, and should then begin to disintegrate quickly, regardless of the p_H of the body fluid that happens to bathe it.

EXPERIMENTAL.

The authors after experimenting with a great variety of coatings used one consisting of a powdered mixture of fatty acid, wax and hygroscopic vegetable components with white shellac as a binding agent.[1] This coating involved timed disintegration and a new method of application.

Stearic acid, of which the formula consisted largely, does not become hard and brittle upon aging as do many enteric materials. Carnauba wax, which has a high melting point, was used to

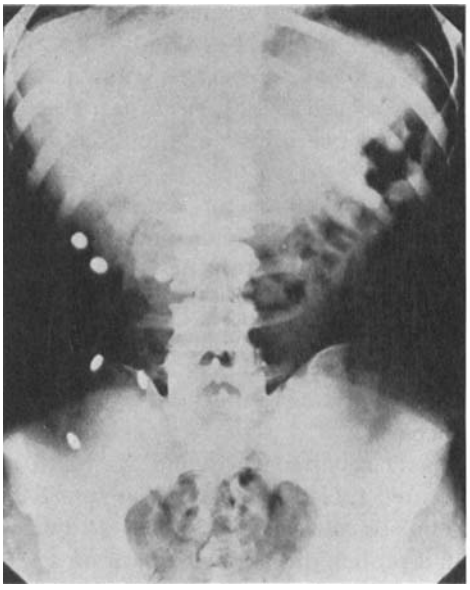


Fig. 3.—Tablets of barium sulfate coated with the enteric powder eight and one-half hours after administration.

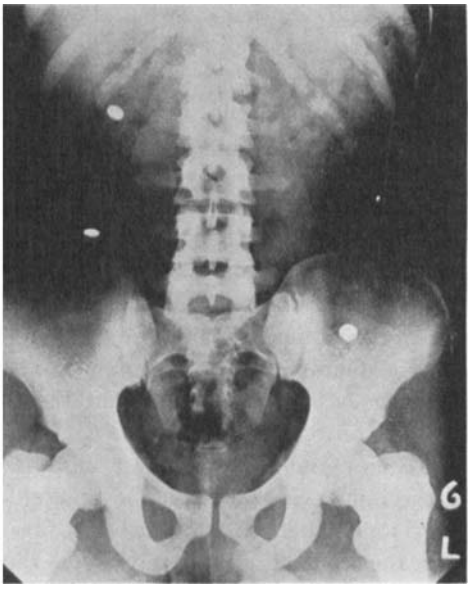


Fig. 4.—Tablets of barium sulfate coated with the enteric powder eleven hours after administration.

overcome the softness of the stearic acid and petrolatum mixture. Powdered agar, and powdered elm bark, because of their ability to absorb moisture and swell, were incorporated as mechanical agents to effect timed disintegration. The mixture was made by melting together 55.5 parts of stearic acid, 24.25 parts of carnauba wax and 1.75 parts of petrolatum, then incorporating 13.9 parts of powdered agar and 4.6 parts of powdered elm bark. Upon cooling, the mixture was ground to a powder.

In order to determine the efficiency of the coating, a large lot of tablets containing barium sulfate was made by compressing with a $^3/_8$-inch die to a thickness of 0.15 inch. The mixture from which the tablets were compressed consisted of barium sulfate 54.5 parts, starch powder 34 parts, powdered sugar 11 parts and stearic acid 0.5 parts. The large lot of tablets was divided into smaller lots of three pounds each for experimental use. Excepting a few variations, and gradually im-

[1] The patents for this coating were granted to Grover C. Miller, Alhambra, California, assignor to Kelp-Ol Laboratories, Inc., Los Angeles, California. The patent numbers are 2,011,586 and 2,011,587.

proving technique, the general procedure for coating was the same for all lots. The coating pan was of the revolving type, $16^1/_2$ inches in diameter. The first step in the application of the coating was carried out by placing the tablets in the pan, then adding a solution of shellac in alcohol. (The quality of the shellac used was such that it would have been suitable for use in food products.) After the shellac had become evenly distributed over the tablets, a quantity of the enteric powder (described above) was sprinkled over them. Each tablet, due to the adhesiveness of the shellac, took up its portion of the powder to produce a smooth coating of uniform thickness. To render the coating more impermeable to fluids, the tablets were arranged in rows on an asbestos board and flamed on both sides with a Bunsen burner. This treatment caused the stearic acid and wax to melt and flow, thus forming a continuous coating. The tablets were then sugar-coated. To determine the efficiency of the coating, six tablets were administered to each of several subjects and radiographs were made at about two-hour intervals until disintegration took place. Of the first few lots that were tested radiographically, some disintegrated too quickly while others did not disintegrate quickly enough, depending upon the thickness of the coating.

Figure 3 shows a radiograph of barium sulfate tablets which were too thickly coated with the enteric powder, taken eight and one-half hours after administration. This coating required too long a time to disintegrate for they should have been completely broken up at the time the radiograph was made. However, a slight haziness around three of the tablets indicates they were in the first stage of disintegration. Figure 4 shows tablets from another lot too thickly coated, eleven hours after administration. One of the tablets administered must have been excreted or hidden behind bony structure for it is not shown. It may be noted that the outlines of these tablets are very sharply defined in the radiograph, indicating that disintegration had not yet begun. It is also interesting to note that the positions of these tablets correspond to the positions of the ascending, transverse and descending colon.

As additional lots of barium sulfate tablets were coated and tested *in vivo* radiographically, it was learned that the ideal tablets began to disintegrate after six hours, and were completely disintegrated after eight hours. This period was found to be optimal because six hours allowed enough time to accommodate the slowly emptying stomachs, and eight hours was short enough so that tablets passing from quickly emptying stomachs still disintegrated before reaching the colon.

To establish a practicable and accurate laboratory method of control, several lots of barium sulfate tablets were coated such that the thickness of each coating equaled that of the tablets found to be optimal when tested *in vivo* radiographically. The new lots, when tested *in vivo*, varied slightly in disintegration time; however, all were found to leave the stomach intact and then disintegrate in the small intestine.

Figure 5 represents a series of radiographs made at intervals recording an eight-hour history of six tablets from one of the lots, in the gastro-intestinal tract. L-1, taken four hours after administration, shows one tablet apparently in the stomach and five in the small intestine. The one which appears to be in the stomach is partially hidden by the bony structure of the spine. At this stage there is no apparent sign of disintegration. L-2, taken five hours after administration, shows six tablets in the small intestine with five of them grouped. L-3, taken six and one-half hours after administration, shows a haziness around the tablet on the upper right, and also around the one on the upper left, which signifies initial disintegration. The sixth tablet is masked by the bony structure of the spine. L-4, taken eight hours after administration, shows that four tablets have completely disintegrated and two are partially disintegrated. Similar radiographic results were obtained when checking the efficiency of many other lots of tablets similarly coated. For the sake of brevity, however, more of such series are not shown here. More than one hundred and twenty different lots of barium sulfate tablets were coated while carrying on this work.

In order to establish a correlation between tests *in vivo*, and *in vitro*, ten tablets from each of the lots found to be satisfactory when tested radiographically, were placed in test-tubes containing artificial gastric juice of the formula proposed by Toplis:

Sodium Chloride	1.400 Gm.
Potassium Chloride	0.500 Gm.
Calcium Chloride	0.060 Gm.
Hydrochloric Acid 36 per cent	6.944 Gm.
Pepsin U. S. P.	3.200 Gm.
Distilled Water *q. s.* to make	1000 cc.

The tubes were then placed in a bath having a constant temperature of 37° C. and observed every thirty minutes for disintegration. All of the samples began to disintegrate in from four hours to four hours and fifty minutes. The beginning of disintegration may be interpreted

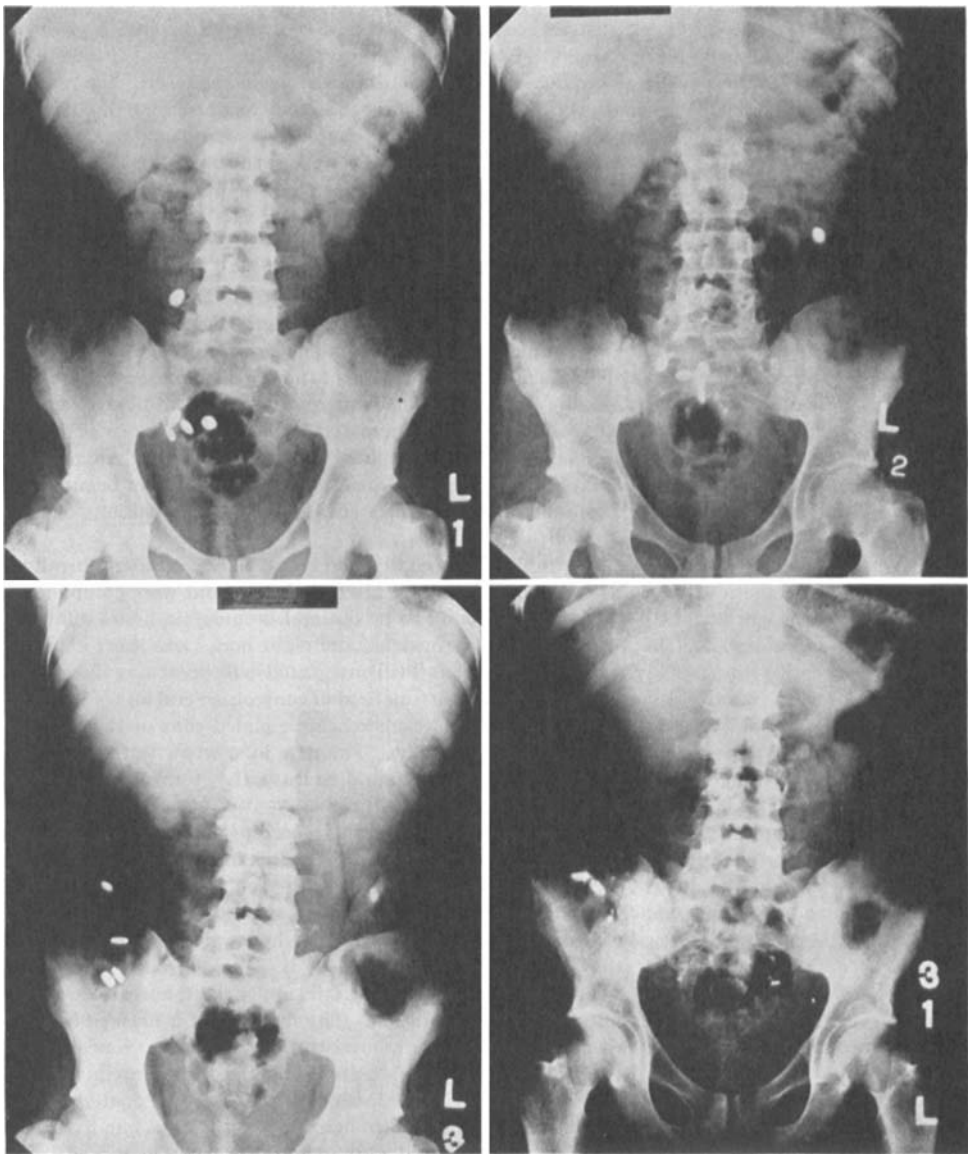


Fig. 5.

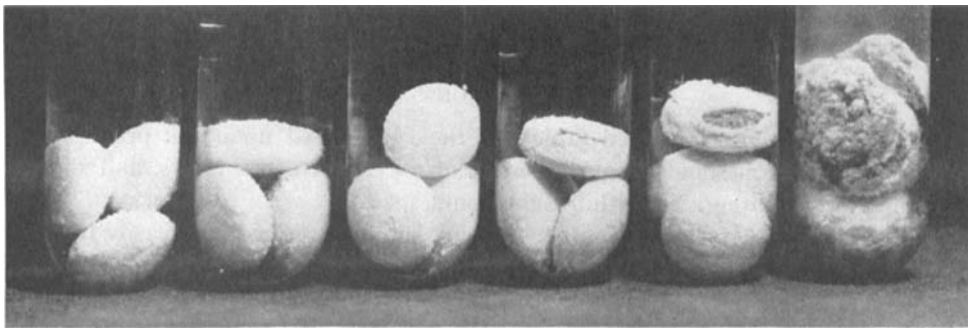
Upper Left.—Four hours after administration. Upper Right.—Five hours after administration.
Lower Left.—Six and one-half hours after administration. Lower Right.—Eight hours after administration.

here as the first appearance of a crack or fracture in the coatings of one or more of the ten tablets. This interpretation is very important for although the first signs of disintegration appeared in from four hours to four hours and fifty minutes, complete disintegration required six or more hours.

Complete disintegration may be interpreted to mean complete liberation of the barium sulfate which forms a suspension and then finally settles to the bottom of the tube. All subsequent lots which began to disintegrate in from four to five hours *in vitro*, were invariably found to be satisfactory when tested *in vivo* radiographically.

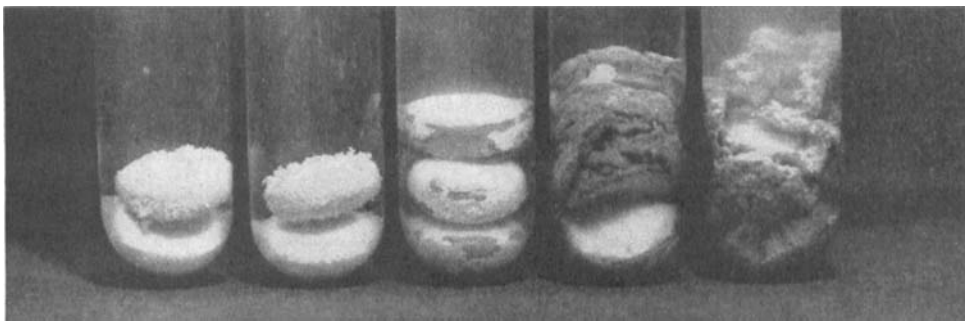
In establishing high and low limits for the disintegration *in vitro*, varying amounts of coating were added to different lots of tablets. Those which began to disintegrate *in vitro* in three hours were satisfactory only for quickly emptying stomachs. The same was true of three and one-half-hour tablets. The three and three-fourths-hour *in vitro* tablets were usually satisfactory *in vivo* but they barely cleared the stomach before disintegrating. The four- to five-hour *in vitro* tablets were invariably satisfactory. One lot which ran as high as six hours *in vitro* was found to reach the colon as shown in Fig. 4.

Figure 6 represents a series of tubes containing enteric coated 5-grain tablets of pituitary, anterior lobe, in artificial gastric juice. Because they are dark in color, pituitary tablets were used for contrast with the lighter color of the coating in the photographs of both Fig. 6 and Fig. 7. To



1 hr. 2 hrs. 3 hrs. 4 hrs. 5 hrs. 6 hrs.

Fig. 6.—Enteric coated tablets of pituitary, anterior lobe, 5 grains, in artificial gastric juice.[1]



$\frac{1}{2}$ hr. 1 hr. $1\frac{1}{2}$ hrs. 2 hrs. $2\frac{1}{2}$ hrs.

Fig. 7.—Enteric coated tablets of pituitary, anterior lobe, 5 grains, in artificial intestinal juice.[1]

show the different stages of disintegration at a given time, the tablets were placed in the tubes at one-hour-intervals through a six-hour period and then photographed.

Figure 7 shows additional samples from the same lot used for Fig. 6 in artificial intestinal fluid. This fluid contained 2.8 Gm. of pancreatin U. S. P., and 15 Gm. of sodium bicarbonate per 1000 cc. It was originally used in a pharmacopœial test for pancreatin and recommended by Toplis for enteric testing. Here, the tablets were placed in the tubes at thirty-minute intervals through a two and one-half hour period and then photographed.

[1] In some of the tubes the coating had sloughed away and hung in suspension. The suspended material hid the real effects of disintegration, therefore, fresh fluids were used to replace the cloudy fluids immediately before the photographs were taken.

From Fig. 6 and Fig. 7 it is evident that the coating is much more soluble in alkaline media than in acid media. This difference in solubility means that the disintegration will be accelerated in some individuals whose small intestines happen to be slightly alkaline. It was the experience of the authors in some radiographic studies, that in a given individual at a given time, tablets having passed from the stomach early began to disintegrate in five and one-half hours, while those having passed from the stomach late began to disintegrate in six hours. In simpler words, disintegration is oftentimes accelerated about one-half hour, due to the slight alkalinity of some intestines. It may not be assumed from this report that any barium sulfate tablet with any coating which begins to disintegrate in from four to five hours in artificial gastric juice will be highly efficient *in vivo*. The coating herein described is dependent upon its moisture-absorbing property and the correlation established between the tests *in vivo* and *in vitro* might not hold for any other type of coating.

The nature of the tablet being coated influences, somewhat, the manner in which it will disintegrate. A hard tablet which dissolves at the surface requires a longer time to disintegrate than does a tablet which may be made quickly disintegrating by the addition of starch. Work will be continued in this direction.

CONCLUSIONS.

1. Efficient enteric coated tablets of the type based upon the principle of timed disintegration should begin to break up *in vivo* after six hours, and should be completely disintegrated within eight hours.

2. The disintegration time of the coating herein described may easily be controlled because of the moisture-absorbing and swelling properties of its vegetable components.

3. A laboratory method of control for enteric coated tablets may be established by correlating the disintegration time *in vitro* with that *in vivo* of enteric coated barium sulfate tablets found to be efficient radiographically.

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