Experimental Production of Pylorospasm and Gastric Retention in Rats

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Plates 40 and 41

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Pylorospasm and gastric retention in man have been regarded as important factors in the genesis of peptic ulcers (1) but the factors controlling pyloric function and gastric evacuation have continued to remain more or less obscure (2). Attempts to produce pylorospasm in dogs do not seem to have met with success (1b). Our own study of the subject began in an attempt to determine whether the gastric acidity of rats was increased by diets low in protein, as had been found to be the case in man (3). The methods used to determine gastric acidity in man could not well be applied to rats, but it seemed possible that the degree of erosion of suitable pieces of metal, introduced into the stomach of rats, might serve as an index of gastric acidity. Such a method was already used by Spallanzani when he gave calcareous materials (pieces of coral and shells) to animals to determine the presence of acid in the stomach (4). Obviously, the degree of erosion of metal could be used as an index of gastric acidity only provided that the length of stay of the metal in the stomach remained fairly uniform. Observations made during an earlier study (5) suggested that variations in the length of stay of metal in the stomach might be indicated by changes in the rate of passage through the entire digestive tract. Hence, it was decided to give rats pieces of iron, steel or aluminum, note the degree of erosion or the percentage of weight lost by the metal and also note its rate of passage through the digestive tract. It soon became evident that, in most instances, a striking increase in erosion occurred when diets low in protein were fed, but it was usually found that the passage of metal through the digestive tract was then also prolonged. Fluoroscopic observations (checked later by direct
inspection when animals were sacrificed) next showed that whenever a marked increase in erosion took place, an increased gastric retention of test material was involved. Possible changes in gastric acidity were therefore more or less obscured by this complication, but data thus secured served very well for a study of the development of gastric retention and pylorospasm.

Methods

Inasmuch as the method chiefly used was primarily devised to obtain data concerning gastric erosion, it was not as simple as one which might have served to yield suitable data regarding gastric retention. After a few preliminary tests, a definite number of weighed pieces of metal were generally given to the rats three times daily—morning, afternoon and evening. Thus, from 50 to 200 pieces of metal of a single type would usually be given to each animal during a 3 day period. Then some other type of test metal would be given during the next 3 days, and so on. No type of test material was again given to a rat until all of the type previously given was recovered or otherwise accounted for.

The following first eight types of test material (steel, iron and aluminum) were used in the main study: (1) 1/16 inch (about 1.6 mm.) stainless steel balls, such as are used in ball bearings (Fig. 1). 200 of these, weighing about 3.2 gm., were generally given during 3 day periods. Before being used, the new steel balls were slightly eroded with HCl to break the smooth surfaces. (2) 1/16 inch ordinary or hardware grade steel balls. The weight of these and the amount given was about the same as in the case of stainless steel balls. This and other types of reused test material that tended to rust were always cleaned with HCl and dried with alcohol and ether before being weighed and given again to the rats. (3) Pieces of No. 15 (Brown and Sharpe gauge) soft iron wire, 2 to 3 mm. long, cut sheer with square-cutting pliers. 100 pieces, weighing about 3 gm., were usually given during 3 day periods. Before this type of material was given to rats, it had been given to rabbits in an attempt to produce gastrointestinal lesions by mechanical irritation (5). The material was consequently somewhat eroded and erosion of this type of material mainly caused pitting at the ends of the pieces. (4) Pieces of No. 15 soft iron wire about twice as long as the preceding, but with the ends rounded in a lathe. 50 pieces, weighing about 3 gm., were generally used in 3 day tests. (5) Pieces of No. 18 soft iron wire, cut sheer after the wire was first cleaned with emery cloth. 100 pieces, weighing about 2.4 gm., were given during 3 day periods. This was the only type of test material that was given only in the form of new material each time—other types were used repeatedly after recovery and cleaning, unless eroded too much. (6) Pieces of No. 18 aluminum wire about 4 mm. long. 100 pieces, weighing about 1.2 gm., were used in 3 day tests. All aluminum material was simply cut sheer with square-cutting pliers and was used after the smooth surface was broken by erosion with HCl in vitro. (7) Pieces of No. 16 aluminum
wire about 4 mm. long. 100 pieces, weighing about 1.8 gm., were used in 3 day
tests. (8) Pieces of No. 16 aluminum wire about 2 mm. long. 108 pieces,
weighing about 1.2 gm., were given during 3 day periods. Occasionally, 2 day
tests were made with correspondingly less material. Single-day tests were also
sometimes made, especially shortly before the animals were sacrificed. In such
tests, 100 steel balls were generally given in 3 or 4 injections made within about 20
minutes. (9) In addition to the foregoing test materials, shanks of 2-56 (No. 2—
56 threads to the inch) iron machine screws (about 2 mm. in diameter), 4 to 6 mm.
long, were used for a single experiment involving a somewhat different method.
The chief observations were made on 10 adult rats—6 males and 4 females.
One male and 1 female were pied (black and white) rats; the rest were albinos.
Metal was given to the 10 rats daily for periods of from 47 to 249 days. The test
material was injected into the esophagus by means of a brass tube fitted with a
plunger, as described elsewhere (5). The animals were kept in individual cages
with screen bottoms. The diets were changed from time to time, particularly in
respect to their protein content. Concentrated food (without added roughage)
was fed and this was given dry, excepting in tests where solutions of alcohol were
added. Fluoroscopic observations were made only when the site of stasis of metal
was in question. A more systematic fluoroscopic study was not made, among
other reasons, because of the possibility that pylorospasm might be relieved by
the irradiation (6). Three of the rats died; the rest were killed with ether. Au-
topsy was performed immediately after death was noted. The digestive tract
was divided into two parts by severing the duodenum. The contents of the two
segments were then removed by flushing with water and, when easily possible,
without slitting the parts. The segments were next fixed by filling them with,
and placing them in, formalin-Zenker solution. After being fixed, the segments
were slit throughout and examined.

RESULTS

In the first place, various tests showed that nearly all of the erosion
undergone by pieces of iron, steel or aluminum, in passing through the
digestive tract of rats, occurred in the stomach and was evidently due
to the HCl. Some erosion occurred in all of the rats used, but only
delays in passage involving a gastric retention of metal were accom-
panied by a marked degree of erosion. This was strikingly illustrated
in the case of Rat 916 (Text-fig. 1) in which a cecal stasis of test ma-
terial involved an average of only about 0.3 per cent erosion while a
subsequent gastric retention led to 52 times as much erosion—an
average of 15.6 per cent among 100 pieces of aluminum; and some of
these pieces were eroded about 90 per cent within 6 days.

When diets low or inadequate in protein were fed, 7 out of the 10
rats used in these tests developed gastric retention. This happened whether the diets were high in fat or high in carbohydrate (Text-figs. 1, 2 and 3), although diets high in carbohydrate were somewhat more effective here. Some of the variations in the results of protein restriction were evidently due to differences in the previous diets of the rats. Thus, Rat 916 (Text-fig. 1), which had previously been kept on an adequate stock diet, developed gastric retention only after a prolonged period of protein restriction, while Rat 866 (Text-fig. 2), which had been kept during the previous 3 months on diets low in fat and including large additions of kaolin and sand, developed gastric retention immediately after it was placed on a diet of white bread only; and this retention persisted when the diet was changed to one high in fat but still low in protein. In all (4) of the 7 rats in which we tried to produce gastric retention a second time with diets low in protein, after clearing up the first retention by protein realimentation, this proved to be possible.

In most cases, the gastric retention of metal did not develop until after the animals lost more or less weight and this might suggest that the retention was a consequence of a general weakening of the rats as a result of undernutrition. However, tests in which Rat 912 (Text-fig. 3) and another rat (Rat 911) were given only about 2 gm. daily of a diet adequate in its protein content (21 per cent) showed that gastric retention was not a consequence of simple undernutrition. This is in agreement with the finding of Menville, Ané and Blackberg (7) that the gastrointestinal rate in rats is accelerated by such semi-starvation. It is also consistent with our observation that prepyloric lesions were rarely occasioned by starvation, although they frequently developed with diets low in protein (8). On the other hand, the onset or prolongation of gastric retention, when protein realimentation was attempted in the rats, suggests that severe undernutrition or prolonged protein restriction increased the irritability of the pyloric region, as was previously noted in man (9). Thus, Rat 909 (Text-fig. 2), which did not develop gastric retention during 42 days of protein restriction (2.5 per cent protein and 54 per cent fat), developed transient retention immediately after the diet was changed to one containing 63 per cent protein and 22 per cent fat. Likewise, Rat 912 (Text-fig. 3) showed transient retention with diets high in protein after periods of protein
Text-Fig. 1. Weight of Rat 916, erosion of metal (per cent of weight lost by metal) in passing through digestive tract, rate of passage and diets used during different periods. At A, only slight erosion during period of marked cecal stasis; at B, striking increase in erosion with gastric retention. Discontinuous lines connecting points at ends of curves of erosion and rate of passage indicate that part of the metal given during that period was still in the animal at death. Note that gastric retention (at B) involves a relatively slow or delayed passage of metal associated with increased erosion and occurs with diet inadequate in protein. Types of test material used indicated in curve of erosion—key to test material at right.
Text-Fig. 2. Development of gastric retention (prolongation of rate of passage associated with increased erosion of metal) under different dietary conditions in 3 rats. In Rat 797, gastric retention initiated by diet low in protein and high in fat—became fatal later with diet low in protein and high in carbohydrate. In Rat 866, gastric retention promptly produced by diet of white bread—not definitely relieved later by diet high in fat and low in protein. In Rat 909, diet low in protein and high in fat did not give rise to gastric retention but transient retention was produced by diet high in protein after period of protein restriction. For key to types of test material used and indicated in curve of erosion see Text-fig. 1.
Text-Fig. 3. At the beginning is shown moderate gastric retention with diet low in protein; next, decreasing retention with diets high in protein; then increasing retention with diet of white bread, followed by transient prolongation of retention with diet high in protein; next, absence of gastric retention with food permitting free choice of protein, carbohydrate and fat and no retention with marked undernutrition, using diet with 21 per cent protein; then transient retention with diet high in protein, and, finally, gastric retention with alcohol added to diet. For key to test material used see Text-fig. 1.
restriction and undernutrition. In all cases in this study, the gastric retention associated with the beginning of protein realimentation was soon reduced or cleared up entirely with further realimentation. But similar or more acute gastric retention, when realimentation was attempted after prolonged fasting in an earlier study (10), evidently accounted for the deaths of a number of rats.

An investigation of the effect of alcohol, added to the diet, was also made in the present study. Dry food was soaked in solutions of alcohol (from 25 to 50 per cent) and offered as a paste (alcoholic diet) to the rats. Often the animals refused to partake of the fresh mixture and waited until more or less of the alcohol had evaporated. The higher concentrations evaporated so much faster than the weaker solutions that the amount which the animals took and the net effects were apparently the same. Gastric retention, following the giving of alcoholic solutions to rats, has already been observed by Cori, Villiaume and Cori (11). In the present tests, alcoholic diets low in protein produced greater gastric retention and correspondingly more erosion than diets in which alcohol was not used. With alcoholic diets adequate in protein, gastric retention was also produced or prolonged, in spite of substantial gains in the weight of some of the animals (Rat 912, Text-figs. 3 and 4). This again showed that gastric retention or its absence did not depend directly upon the general condition of the animals. Retentions produced by alcoholic diets promptly cleared up again when the use of alcohol was discontinued.

Text-fig. 4 indicates the results when a somewhat simpler method was tried than that used in obtaining the data concerning gastric retention upon which Text-figs. 1, 2 and 3 were based. The object at first was to give only a single injection of test material daily and to use only a single type of material throughout. As the larger and rougher pieces of test material appeared to be retained in the stomach more commonly than the smaller and smoother material, it was decided to use the shanks of 2-56 iron machine screws—about the largest and roughest material we ever gave to rats (Fig. 1). However, in the hope of also demonstrating a differential gastric retention of dissimilar materials, a small and smooth type of test material (stainless steel balls) was likewise given daily (excepting when a separation of material injected during different periods was desired). The results
Text-Fig. 4. More or less parallelism is shown in gastric retention of a large and rough type of test material (shanks of 2-56 iron machine screws) and a small and smooth type of material (1/16 inch stainless steel balls). During Period A, we gave 5 shanks of 2-56 screws (about 0.6 gm.) and 40 steel balls (about 0.6 gm.) daily, excepting as noted in curve of erosion of steel balls (key for exceptions with Text-fig. 1). During Period B, gave two-fifths as much test material as in Period A. Per cent retention means per cent of amount of test material given daily and retained more than 24 hours. Gastric retention produced mainly by 25 per cent solution of alcohol added to type of diet indicated.
confirmed what had already seemed evident; namely, that sometimes mainly the larger and rougher test material is retained while at other times all types of material, including food and fluid, seem to be retained in equal degree. With the method here used, evidence of marked erosion during the periods of gastric retention was not obtained, partly, because of the impossibility of separating material given during the different periods when the same type is given throughout and, also, because both the screw shanks and the stainless steel balls resisted erosion considerably.

The curves indicating gastric retention, particularly in Text-figs. 2 and 3, show a periodicity that suggests the introduction of an artifact by the use of the test material. That is, it seems that the accumulating test material might have stimulated motor activity, with the consequence that mass movements of material through the pylorus occurred periodically and in spite of a tendency toward retention. If this were true, a reduction of the amount of test material given daily would be expected to permit a more prolonged accumulation in the stomach and this was apparently demonstrated in the latter part of Period B, Text-fig. 4. During Period B only two-fifths as much test material was given as in Period A. The retention during Period B became more prolonged but it did not become as great absolutely. A greater reduction in the amount of test material given daily might have been still better but observations on other rats that were fed diets tending to produce gastric retention showed that considerable variations in the food intake occur, even when no metal is given. This suggests that a true periodicity, at least in the degree of gastric retention, exists. In fact, a periodicity is very likely created by the factors involved in gastric retention. Retention leads to a restricted food intake and this, as the experiments with undernutrition showed, does not favor the production of gastric retention and perhaps even helps to relieve one. When the stomach empties, food likely to cause a recurrence of gastric retention might again be eaten, and so on.

DISCUSSION

There can hardly be any doubt that data such as are represented in Text-figs. 1 to 4 serve quite well to indicate when gastric retention occurs but they tell us nothing about the state of the pylorus. The
presence of more or less pylorospasm during all periods of gastric retention in this study was nevertheless inferred from the findings at autopsy. In the first place, although the stomach was usually large, there was nothing to indicate that an atonic condition, such as might account for the retention, ever existed. In the second place, the pylorus of rats with gastric retention generally appeared to be markedly constricted (Fig. 4), and finally, when the digestive tract of such rats was filled with fixing fluid, shortly after death, the pylorus acted as if it were spastic. In our various gastrointestinal studies, we have filled the intact stomach of a large number of rats with formalin-Zenker solution, by injecting it either through the esophagus or through the duodenum. In rats that had been kept on diets that tended to produce gastric retention, the passage of the fixing fluid was often obstructed entirely at the pylorus, while in rats that had not been kept on such diets, the fluid usually passed the pylorus easily. A pyloric hypertrophy, such as sometimes occurs in human infants, was, however, never seen; nor did we ever note anything suggesting cardiopasm in a rat.

Granting then that pylorospasm was the cause of the gastric retention of metal, it remains to explain the onset of pylorospasm. Simple mechanical irritation of the pyloric region by the test material can hardly be responsible, since, in spite of continuing to give the same amounts and kinds of test material daily, it repeatedly proved possible to clear up gastric retentions entirely by making simple changes in the diets. The difficulty of producing gastrointestinal lesions by mechanical irritation has already been referred to in a previous report (5), but this might be emphasized by citing the following case from a further study.

Rat 15 (Fig. 2) was given over 50,000 pieces of gold and silver—a total of over 10 times the animal's average weight—during a period of 557 days. Beginning at the age of 21 days, the amount of metal given daily was increased from time to time until 300 pieces of silver were given daily during the last 15 days. About 90 per cent of the metal given to this rat consisted of round and square wire and over half of this was either threaded or corrugated (Figs. 1 and 2). In spite of this, Rat 15 grew to be the largest female among a colony of about 1500 rats—weighing 432 gm. net (minus metal in tract) at the time it was sacrificed. Although kept separated from males part of the time, it also had 5 litters and raised most of the young, while receiving metal daily. Gastric retention apparently never developed
and, excepting for a general hypertrophy, a digestive tract in better condition was not found in any of the other rats in our colony. Of course, an adequate diet was always supplied and the amount of metal given, although large, was never beyond the animal's capacity to pass it.

That the human stomach, under some circumstances, can bear an almost unbelievable amount of mechanical insult seems indicated by a case cited by Ewald (12), in which a sailor swallowed 35 pocket knives in the course of 10 years. At death (due to perforation of the colon by 2 blades) some 30 pieces of blades together with handles were found in the stomach, but no signs of recent or earlier ulcers! Nevertheless, the theory that mechanical irritation is an important factor in the etiology of gastritis and ulceration continues to be upheld in some quarters. In support of this view, Konjetzny and Puhl, for instance, referred to the frequent occurrence of gastric and duodenal ulceration among prematurely weaned calves (13). However, such calves are primarily undernourished because they cannot very well utilize the coarse food upon which they are forced to subsist and this undernutrition, as the results of our studies indicate, evidently renders the digestive tract susceptible to ulceration. That mechanical irritation may then assist in producing lesions is supported by some evidence also obtained in our own studies but the bulk of evidence indicates that it is a negligible factor, in the genesis of peptic ulcer, in the absence of acid gastric juice. In this connection, it is of interest that Puhl, whose work in the past largely helped to bolster the theories fostered by Konjetzny (14), more recently reported the consistent production of lesions in dogs (15) by the sham-feeding (appetite gastric secretion) technique introduced by Silbermann (16).

The data obtained in this study did not serve to show whether a change in gastric acidity, sufficient to account for the development of pylorospasm and gastric retention, ever occurred. We believe nevertheless that irritation of the pyloric region by acid gastric contents was a factor but, at the same time, we feel that an increased susceptibility of the pyloric region to irritation was a more important factor. The gastric retention which often immediately followed the use of alcohol, for instance, was very likely due to the power of alcohol to precipitate the protective mucin in the stomach. Thus, the pyloric region was evidently more directly exposed to irritation by the gastric contents.
with the result that pylorospasm promptly developed. Likewise, the
gastric retention produced by protein restriction and the transient
retention following periods of undernutrition may have been due to a
decrease in the secretion of mucin, but we are more inclined to believe
that a change in the character and/or quantity of bile secreted was
the most important factor involved here.

The importance of biliary or hepatic factors in the development of
duodenal and gastric lesions has been emphasized by the work of
Kapšinow and others (17). These investigators showed that duodenal
ulcers develop in dogs when the biliary secretion is diverted so as not
to reach this region. In contrast to this, rats apparently furnish an
illustration of a species in which duodenal ulceration is largely pre-
vented by a more or less continuous flow of bile into the duodenum.
In our studies on about 1500 rats, we neither found nor were able to
produce duodenal ulceration in a single case, although severe erosion
sometimes occurred. (Bullock and Rohdenburg published gross
illustrations (but not sections) of "spontaneous" duodenal ulcers in
two rats (18) but we never saw anything like this.) On the other
hand, in the course of a preliminary investigation on mice, we found
or produced duodenal lesions in at least 5 out of 60 animals. Mice
differ from rats in having a gall bladder, while rats, without a gall
bladder, apparently have a more continuous flow of bile into the duo-
denum (19). If, then, Whipple’s conclusion concerning the relation
of protein metabolism to bile secretion (20) is applicable to rats and
mice, protein restriction might be expected to have reduced the bile
flow in rats only enough to permit an irritable pyloric condition and
prepyloric lesions to develop but not duodenal ulcers, while inade-
quate diets and undernutrition in some mice permitted the develop-
ment of duodenal lesions also. Again, applying Whipple’s conclu-
sions, the transient gastric retention that generally developed in rats
when a diet high in protein was used after a period of undernutrition
would be due to the lag in the increase of bile flow that occurs with
protein realimentation. In apparent conflict with this explanation is
McMaster’s failure to observe any difference between the effect of a
vegetable diet and a meat diet on the secretion of bile in rats (21).
However, assuming that no error was introduced by the special tech-
nique used by McMaster in collecting bile, his observation on the
effect of a vegetable diet (presumably grains and milk) does not apply directly to our use of diets lower in protein. Undoubtedly further study is here needed.

Diametrically opposed to the view that a deficiency of bile might account for an increase in the sensibility of the pyloric region and thus lead to pylorospasm and gastric retention is the theory propounded by Spira; namely, that bile is the cause of pylorospasm, as well as of gastric and duodenal ulceration (22). According to Spira, fat in the diet, by giving rise to biliary regurgitation, is mainly responsible for ulceration. Experiments are said to be under way to prove this theory but positive results are not likely to be secured if the observations made in our studies have significance. We fed rats various diets containing large proportions of fat (23). We could agree with Spira that fat, and particularly oil, may have no protective value against ulceration when the protein content of the diet is inadequate. But with diets adequate in protein, our results showed that fat in the diet tended to help heal, rather than produce, ulcers. Possibly Spira's therapeutic claims for diets low in fat can be explained by the protein-sparing effect of such diets.

The results of our studies appear to justify the procedure followed at Bier's clinic, where a preparation consisting mainly of bile acids is used in gastritis and ulcer therapy (24). Nevertheless, the possibility remains that bile may be highly toxic to the gastric and duodenal mucosa under some conditions, although protective under other conditions. Perhaps further work like that referred to above (17) and that of Draper and Touraine (who find constitutional peculiarities in ulcer patients) (25), McClure and Huntsinger (who found hepatic dysfunction associated with duodenal ulcer) (26) and Tashiro and his assistants (who regard bile salt retention in the blood as responsible for ulcer) (27) will eventually settle this question.

Independent of the precise rôle of bile, however, it seems of interest that, although carbohydrates tend to leave the stomach rapidly and protein more slowly in brief tests (28), the reverse proved to be the case in our more prolonged experiments. Also, diets high in fat and low in protein, which ordinarily remain longer in the stomach than diets high in carbohydrate, did not lead to gastric retention quite as readily as the latter. Furthermore, although coarse particles often
remain in the stomach longer than finely divided material, it has long been known that coarse (Graham) bread leaves the stomach faster than white bread (29). Our work confirmed this by showing no definite gastric retention when diets consisting mainly of bran or other roughage were used while diets of white bread led to the most acute retention. Taken together, these results make it obvious that some factors of importance in pyloric function and gastric evacuation have not been taken into consideration in earlier studies.

As pylorospasm and gastric retention have been regarded as important factors in the genesis of peptic ulcers in man, it seemed of interest to note whether such a relationship also existed in the rats. The appearance of the normal stomach of the rat is indicated in Fig. 3 and the gastric conditions and types of lesions found in the present study are illustrated in Fig. 4. All rats, including those that never developed a gastric retention in this study, showed evidence that more or less ulceration occurred in the prostomach at some time. This and earlier observations indicate that, although gastric retention may intensify ulceration in the prostomach, ulceration in this region can occur independently of retention. Seven of the 10 rats showed some crater or ulcer formation in the prepyloric region. The exceptions were the only 2 rats that never developed gastric retention in this study and 1 rat (Rat 911) that developed retention while fed a diet of white bread and was then relieved of the retention with an adequate diet (which might also have led to the healing of prepyloric lesions) and finally died while fed only small amounts of food, without retention. These results suggest that a definite relation existed between the occurrence of gastric retention and the presence or production of prepyloric lesions but the precise relation can only be determined by further study.

Rat 797 (Text-fig. 2 and Fig. 4), which was the only rat in this group that died with a marked retention of fluid in the stomach, developed the most severe ulceration in the prostomach. A number of small shallow craters or beginning ulcers appeared in the antrum. Craters or ulcers usually develop much more slowly in the antrum than in the prostomach of rats; and a high fat, low protein diet, such as was used to initiate gastric retention in this rat, generally did not give rise to as marked crater formation or ulceration in the prepyloric region as low protein diets with a high carbohydrate (starch) content. Rat 912 (Text-figs. 3 and 4 and Fig. 4) had only one small ulcer in its prostomach and only one small (non-bleeding)
crater in the antrum. The lack of more ulceration in the stomach of this rat is, in part, consistent with the fact that gastric retention never became very great in this case without a "spontaneous remission." Excepting for a little fluid (probably water), the stomach was entirely empty at the time this animal was sacrificed. That more severe ulceration did not develop in this rat, which was given the largest amount of the roughest pieces of metal for the longest time in this study, again demonstrates that mechanical irritation is not an important factor in ulcer production in rats. Rat 916 (Text-fig. 1 and Fig. 4) had a marked epithelial overgrowth in the prostomach and a number of small bleeding ulcers or craters in the antrum. The bleeding prepyloric lesions in this rat, after a prolonged low protein diet poor in fat, contrast with the relatively inactive prepyloric craters in Rats 797 and 912 above.

Rat 916 (Fig. 4, N) and two other rats in this study also had one or more nodules apparent on the outer or inner surface of the prostomach. Such nodules were previously found to be consequences of ulceration in the prostomach of rats (10).

In earlier studies in which rats were not given pieces of metal but were fed inadequate diets such as were used in this study, gastric ulceration, epithelial overgrowth and nodule formation also occurred (8, 10, 23). In fact, more marked lesions than any seen in the present study were not uncommon. This further indicates that the lesions found in this study were mainly consequences of nutritional disturbances and not of irritation by the test material employed.

To what extent the findings on rats are transferable to man has become something of a question in view of our observation that differences already exist between rats and mice. However, both rats and mice are omnivores like man; both species develop lesions with inadequate diets and it is our belief that further studies on these and other omnivores would best serve to bring to light those factors in the development of peptic ulcer that apply alike to the lower animals and to man.

SUMMARY

1. A method was found whereby the development of gastric retention could be studied in intact animals without the necessity of recourse to the use of x-rays.

2. Gastric retention was found to develop as a result of protein restriction in 7 out of 10 rats studied. Such retention could again be cleared up with protein realimentation or by allowing the animals free choice of protein, fat and carbohydrate.

3. A diet high in protein following periods of undernutrition or
prolonged protein restriction usually gave rise to a transient gastric retention.

4. Diets with a solution of 25 per cent or more of alcohol added promptly gave rise to gastric retention in rats even when the protein content of the diet was adequate.

5. Evidence is given indicating that the gastric retention which occurred in this study involved more or less pylorospasm and the possible influence of mechanical and chemical irritation and of changes in gastric mucin and bile flow upon the development of pylorospasm are discussed.

6. Spira's theory that fat in the diet gives rise to pylorospasm and ulceration is not supported by the results of our experiments.

BIBLIOGRAPHY


**EXPLANATION OF PLATES**

**PLATE 40**

**FIG. 1.** Photograph and roentgenogram of test material. Groups A and B used in intestinal rate study; Group A used on rats; Group B, on larger animals (5). Groups C and D used for mechanical irritation of digestive tract. Part of Groups A, C and D used in the present study. Group A (from left to right)—glass beads, glass balls, gold balls, silver balls and 1/16 inch steel balls (used in this study). Group B—knots made of colored cotton thread, glass beads, glass balls, steel ball (above) and gold ball (below), marked gold discs and marked silver discs. Group C—steel, iron, aluminum, silver and gold wire; at left, round wire; at right, square wire. Of this group, used in present study, No. 15 soft iron wire (fourth from left); No. 18 aluminum wire (fifth from left), and No. 16 aluminum wire (sixth from left). Group D—gold, silver, aluminum and iron test material; at left, corrugated; at right, threaded material. Used in this study, shanks of 2–56 iron machine screws (fifth row from right). Scale in centimeters and inches.

**FIG. 2. A**, roentgenogram of Rat 15, during period when it was given 300 pieces of metal daily, showing 182 pieces of threaded and corrugated silver wire in digestive tract. *S*, about 125 pieces of metal in stomach (150 pieces were given earlier in day); *Ce*, mass in cecum; *Co*, large pellet with metal in colon; scattered single pieces are in small intestine. *B*, photograph, and *C*, roentgenogram of 24 hour collection of fecal pellets from Rat 15 during same period, showing distribution of metal (305 pieces) in pellets.
PLATE 41

Fig. 3. Appearance of normal stomach of rat. At left, ventral or anterior half of an empty stomach (Rat 700); at right, dorsal or posterior half of a full stomach (Rat X-228). Es, esophagus; PS, prostomach—lined with squamous epithelium like esophagus; R, ridge or fold between prostomach and main stomach; MS, main stomach or ventriculus—acid-secreting part of stomach; An, antrum or prepyloric region, and Py, Pylorus. Rat 700 weighed 200 gm. when sacrificed and had been kept on a high fat (30 to 45 per cent) diet, with cut up dog hair included, during the preceding 4 months. Rat X-228 weighed 195 gm. when sacrificed and had previously been on a stock diet of meat, milk, bread, cracked corn and greens.

Fig. 4. Gastric conditions and types of lesions found in present study; Rat 797 (above), Rat 912 (middle), and Rat 916 (below). Pylorus constricted and stomach enlarged in each case. C, sites of small craters or ulcers in prepyloric regions (both halves of stomach of Rat 916 with prepyloric lesions). U (Rat 912), ulcer in prostomach at ridge. N (Rat 916), nodule or small tumor-like prominence evident on outer surface of prostomach.
Fig. 1

Fig. 2

(Hoelzel and Da Costa: Pylorospasm and gastric retention)