Archives of Disease in Childhood, 1975, **50**, 467.

Plasma gastrin in congenital hypertrophic pyloric stenosis

A hypothesis disproved?

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Rogers, I. M., Drainer, I. K., Moore, M. R., and Buchanan, K. D. (1975). *Archives of Disease in Childhood*, **50**, 467. **Plasma gastrin in congenital hypertrophic pyloric stenosis: a hypothesis disproved?** Fasting plasma gastrin levels were measured in babies with pyloric stenosis and in normal babies of similar age. There was no difference in gastrin levels either before or after operation between the babies with pyloric stenosis and normal babies. Similarly, neither the fasting blood glucose nor the fasting gastric *p*H of the babies with pyloric stenosis differed significantly from the values obtained in normal babies.

Our findings do not support the hypothesis that gastrin in the fasting baby has an aetiological role in the development of hypertrophic pyloric stenosis of infancy. An alternative hypothesis is suggested.

Hypertrophic pyloric stenosis of infancy is a curious condition of unknown aetiology. Vomiting usually begins after the second week of life and may not become persistent until the baby is aged 3 months or more (Rendle-Short and Zachary, 1955). The condition is rarely observed in the newborn baby (Meeker and DeNicola, 1948) and prospective barium meal studies suggest that babies who develop the condition do not have pyloric obstruction from birth (Wallgren, 1941). These observations suggest that the condition is, at least in part, acquired after birth and may possibly be due to an abnormal physiological response by the pylorus to intermittent milk feeding. Pyloromyotomy cures the condition and there is a gradual softening of the 'tumour' so that it is of normal size and consistency about 2 years later (Wollstein, 1922). When gastroenterostomy was used to bypass the obstruction however, the 'tumour' was noted to persist (Swenson, 1969).

Such intriguing observations led us to suppose that pyloric hold-up with associated gastric distension might be a self-perpetuating condition. If this hold-up is relieved by pyloromyotomy, the condition will settle and not recur. Similarly, the relief of gastric distension by daily gastric lavage supplemented by atropine derivatives by mouth may also cure the condition, albeit less satisfactorily. The untreated case usually dies.

Distension of the gastric antrum with protein, such as would occur with milk feeds accumulating behind a hypertrophied pylorus, would be a particularly potent stimulus to gastrin secretion (Debas *et al.*, 1974; Konturek, Biernat, and Oleksy, 1974). Gastrin is known to contract the antral circular muscle *in vivo* (Isenberg and Grossman, 1969) and *in vitro* (Bennett, 1965) and the synthetic analogue, pentagastrin, appears to contract the circular muscle of the primate pylorus *in vitro* (I. M. Rogers, F. MacGillion, and I. K. Drainer, unpublished). Exogenous gastrin has also been found to decrease the rate of gastric emptying in man (Hunt and Ramsbottom, 1967).

Neonatal gastrin levels rise steeply after birth (Rogers *et al.*, 1974) and may reach a peak (and may induce pyloric hold-up) within the usual age presentation of babies with pyloric stenosis. Thus, in babies who develop pyloric stenosis, a self-perpetuating sequence of pyloric hold-up, antral distension with milk, and gastrin secretion with further pyloric contraction would ensue (Fig. 1). This hypothesis would explain the persistence of

Received 19 November 1974.

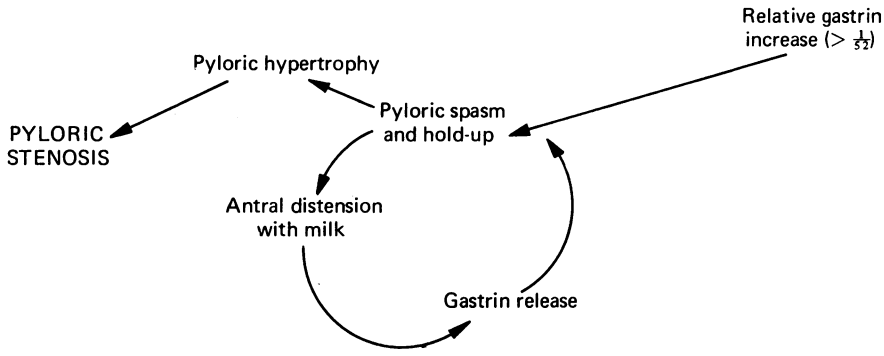

FIG. 1.—*Original hypothesis based on a relative or absolute increase in plasma gastrin level of babies with pyloric stenosis.*

the pyloric 'tumour' when the antrum is not adequately drained by a gastroenterostomy.

Furthermore, Dodge (1970) was able to produce pyloric 'tumours' in puppy dogs by injecting pentagastrin into their mothers before birth. The greatest degree of pyloric hypertrophy was observed when pentagastrin was also given to the newborn puppies. These observations have recently been confirmed (Karim, Morrison, and Parks, 1974).

If the above hypothesis were true, the untreated baby with pyloric stenosis would have higher plasma gastrin levels than normal babies. In addition to measuring plasma gastrin we also measured the true blood glucose in the same venous sample and the fasting gastric *p*H at the time of venepuncture, since both these are known to influence gastrin levels (Konturek *et al.*, 1974; Hayes, *et al.*, 1972).

Materials and methods

A 3 ml peripheral venous sample was obtained from 15 babies with untreated pyloric stenosis at least 3 hours after their last feed. The babies were all male and were aged between 4 weeks and 16 weeks. Their weights ranged from 2·01 kg to 5·25 kg. Pyloromyotomy was performed on all the babies and a further peripheral venous sample was obtained 5 days after operation after a 3-hour fast.

Fourteen babies without gastrointestinal disease were used as controls. There were 12 males and 2 females and, with one exception, their ages ranged from 3 weeks to 16 weeks, the oldest being 26 weeks of age. The age distribution within this group was similar to the pyloric group and the babies' weights ranged from 2·25 kg to 5·69 kg.

The venous sample was immediately centrifuged and the separated plasma was stored at −20°C. Gastrin assay was performed by radioimmunoassay and the antisera used was raised to synthetic human gastrin I (2–17) conjugated to ov-albumin using glutaraldehyde Synthetic human gastrin I was labelled with ^{125}Iodine (Radiochemical Centre, Amersham) and standard gastrin was obtained from the Medical Research Council. Separation of antibody bound from free hormone was achieved using dextran-coated charcoal. Cross-reaction with cholecystokinin-pancreozymin is 1 in 10 000 on a molar basis (Ardill, 1973). If enough blood had been obtained, the true blood glucose was measured from the same venous sample. Where possible, a specimen of fasting gastric juice was obtained at the time of venepuncture and the *p*H was measured using a *p*H meter.

Results

Gastrin levels. There was no difference in the fasting plasma gastrin between normal babies and preoperative ($P > 0{\cdot}4$, no. = 29) and postoperative ($P > 0{\cdot}1$, no. = 28) pyloric babies when the mean values were compared. The mean gastrin level increased after operation but this was not statistically significant ($P > 0{\cdot}2$, no. = 29) (Table I). Gastrin levels were not influenced by age (Fig. 2) and there was no correlation between the weight and the gastrin level in the pyloric

TABLE I

Mean gastrin levels (pg/ml ± SEM) of 15 preoperative and 14 postoperative pyloric babies, and of 14 normal babies

Preoperative pyloric 163 ± 26	Normals 193 ± 28	Significance NS ($P > 0{\cdot}4$)
Postoperative pyloric 205·0 ± 19	Normals 193 ± 28	NS ($P > 0{\cdot}1$)
Preoperative pyloric 163 ± 26	Postoperative pyloric 205·0 ± 19	NS ($P > 0{\cdot}2$)

Mean values of groups compared by Student's 't' test.

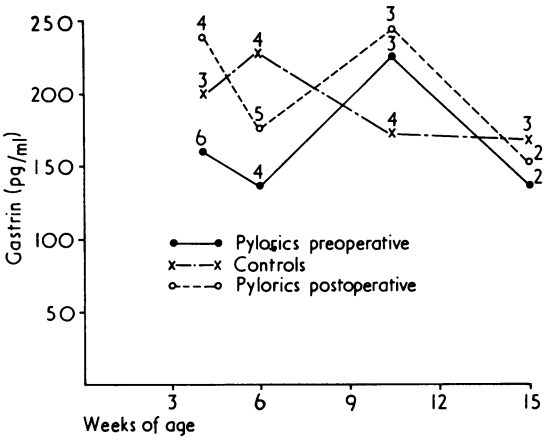

FIG. 2.—*Mean gastrin level of prepyloric, postpyloric, and control babies related to their age in weeks. The number of babies within each age group is shown and the babies have been grouped within the nearest 2-week period.*

($P > 0{\cdot}3$, no. = 14) or normal group ($P > 0{\cdot}3$, no. = 10).

Gastric pH. The mean *p*H of the preoperative pyloric group did not differ from the *p*H of the normal group ($P > 0{\cdot}8$, no. = 24) nor from the postoperative group ($P > 0{\cdot}1$, no. = 23).

Blood glucose. There was no difference in blood glucose between the preoperative pyloric group and the normal group ($P > 0{\cdot}5$, no. = 21). After operation, the blood glucose tended to rise but this was not significant ($P > 0{\cdot}6$, no. = 22) (Table II).

TABLE II

Mean fasting blood glucose (mg/100 ml ± SEM) of 12 preoperative and 10 postoperative pyloric babies, and of 9 normal babies

Preoperative pyloric	68·2±15
Postoperative pyloric	78·1±13
Normal	81·3±15

Gastrin/pH ratio. No difference could be found between the preoperative pyloric group and normal group within the early age range of 3 to 4 weeks ($P > 0{\cdot}6$, no. = 9).

Discussion

Our findings do not support the hypothesis that increased fasting gastrin levels may promote or maintain hypertrophic pyloric stenosis of infancy. Indeed, there was a tendency for the fasting gastrin to be lower in the preoperative pyloric baby, though this did not reach statistical significance. Since we did not measure gastrin levels in response to a feed, we can not exclude the possibility that the pyloric baby may have an exaggerated gastrin response to a feed.

The mean gastrin level of the pyloric and normal babies (Table I) was higher than that expected in the fasting adult (<90 pg/ml) with this assay.

Some recent *in vitro* experiments with the pyloric sphincter of animals have shown that it contracts in response to cholecystokinin and secretin (Isenberg and Csendes, 1972) and that gastrin inhibits this contraction (Fisher, Lipshutz, and Cohen, 1973). These observations have been confirmed by sphincter pressure measurements in human volunteers (Fisher, *et al.*, 1973).

It is possible to interpret Dodge's model for the production of canine hypertrophic stenosis in two ways. Firstly, one might suppose that pentagastrin had an intrinsic ability to produce pyloric contraction and pyloric hypertrophy. Our hypothesis was based on this premise but our findings do not support it.

The second interpretation is that pentagastrin would produce pyloric hypertrophy through its action in stimulating gastric acid secretion. Cholecystokinin and secretin are released from the duodenal mucosa in response to acid stimulation and would be expected to reach high levels in the blood when the gastric acidity was high (Meyer, Way, and Grossman, 1970). Thus the pylorus would be subject to an increased hormonal drive to contraction and pyloric hypertrophy would ensue.

Our preoperative pyloric babies differed from the normal controls in that the 'fasting' gastric content was great in quantity and was almost always heavily contaminated with milk. Despite this, the mean *p*H of the preoperative pyloric babies was lower than that of the normal controls, though not significantly so (Table III). It would not be unreasonable to suppose, therefore, that the 'early' pyloric baby would have a significantly higher

TABLE III

Mean fasting gastric pH (±SEM) of 13 preoperative pyloric and 10 postoperative pyloric babies, and of 11 normal babies

Preoperative pyloric	3·17±0·4
Postoperative pyloric	3·12±0·37
Normal	3·32±0·5

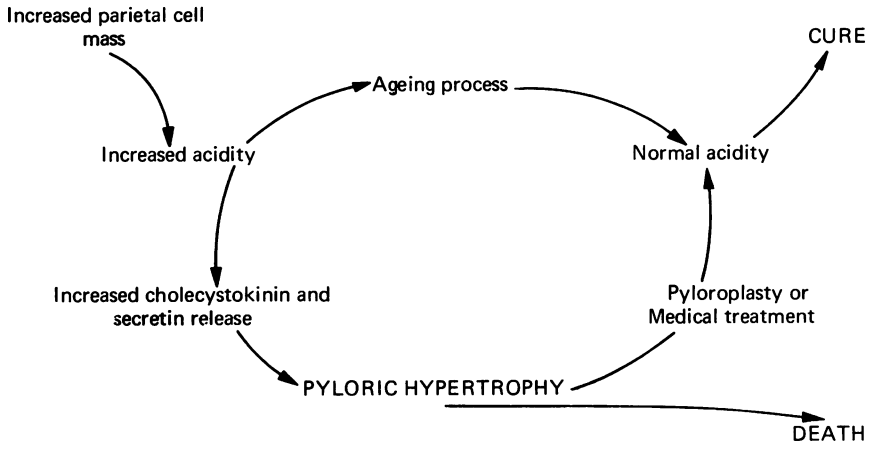

FIG. 3.—*Alternative hypothesis to that of Fig. 1, based on the presumed increased gastric acidity of babies who will develop pyloric stenosis.*

acidity than normal before persistent pyloric obstruction obscured this fact. It is known that the gastric acidity in normal babies is particularly high in the first few days of life (Miller, 1941) and subsequently resolves (Levinson and MacFate, 1937). Pyloromyotomy obviously eliminates pyloric obstruction since the tight pyloric muscular ring is divided. It may also be successful, however, in the long term by reducing gastric acidity by promoting gastric drainage and/or alkaline duodenal reflux until this temporary hyperacidity is naturally resolved. Daily gastric lavage and atropine therapy may be effective through a similar mechanism (Fig. 3).

If this alternative hypothesis is true, then congenital hypertrophic pyloric stenosis may be comparable with chronic duodenal ulcer in adults. Both would be (and are) conditions with a hereditary basis predominantly affecting the male and presumably due to a greater parietal cell mass than normal (MacKeown, MacMahon, and Record, 1951). Indeed, many of the puppies with pyloric stenosis described by Dodge (1970) had an associated pyloric ulcer. Perhaps the adult develops the ulcer because of a decreased mucosal tolerance to peptic digestion with age.

We thank Mr. John Grant, Consultant Paediatric Surgeon, Stobhill General Hospital for his helpful encouragement and the physicians and surgeons of Stobhill Hospital and the Royal Hospital for Sick Children, Glasgow, for allowing us to study babies under their care.

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