



*Point of View*

## **The Cause of Infantile Hypertrophic Pyloric Stenosis: one man's journey.**

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It is an adage oft repeated and certainly true. Listen to the patient; he is telling you the diagnosis. So must it be with the cause of infantile hypertrophic pyloric stenosis (IHPS). The infant is certainly very generous with his clues. The presentation at 3 weeks of age, the 5/1 male predominance, the natural cure with time with temporary medical treatment, the strong familial tendency, the complete disappearance of the tumor after simply dividing the hypertrophied sphincter, the persistence of the tumor in the thriving baby after gastroenterostomy, <sup>[1]</sup> and the repeated observation of primogeniture all should combine to make the process easy. Many medical and surgical detectives have no doubt pondered the problem and yet the cause remains completely unknown.

In the beginning, in this, the most common cause of neonatal upper GI obstruction, pylorospasm and indeed work hypertrophy was the favored explanation. <sup>[2]</sup> This theory silently lapsed presumably for want of corroborative data. 37 years ago as a young surgical trainee, I came across the 1941 paper by Miller in which he documented the phenomenon of neonatal hyperacidity. He reported that the immediate post-partum gastric neutrality became quickly hyperacid after a few hours and remained so for several days. Miller proposed the trans-placental passage of a gastric secretagogue as an explanation, 10 years before the discovery of gastrin. <sup>[3]</sup>

Our attempts to prove gastrin transfer as a cause, while non-confirmatory, showed for the first time that fasting gastrin levels rise from birth to very high levels at 4 days of life. <sup>[4]</sup> Rising gastrin at a time of rising acidity strongly suggests that gastrin is the cause of the acidity. <sup>[5]</sup> The entry of acid into the duodenum is well known to be a potent stimulus to pyloric sphincter contraction in adults. The most potent cause of pyloric muscle contraction in dogs is the entry of acid into the duodenum. <sup>[6,7]</sup> When gastrin 11 is given intravenously to adults, the first consequence is pyloric delay, presumably from pyloric contraction. <sup>[8]</sup> In adults with hyperacid disease, the early symptom of post-prandial bloating (pyloric delay), is quickly relieved when acid secretion is abolished by timely antacid therapy. Indeed, selected cases of pyloric stenosis in adults may be successfully managed by antacid therapy. <sup>[9]</sup>

Milk feeds accumulating behind a closed sphincter would stimulate further gastrin secretion by combining temporary alkalinity with antral distension. <sup>[5]</sup> Such an acid-producing positive feedback would lead to repeated sphincter contraction, work hypertrophy and IHPS. Pyloric stenosis artificially induced in

rats has also been shown to be a potent trophic stimulus to gastric (and parietal cell) hyperplasia with associated hyperacidity.<sup>[10, 11]</sup>

This early gastrin theory was investigated by measuring fasting gastrin levels in babies with IHPS and matching controls. We established that fasting gastrin levels were statistically no different in the babies with IHPS<sup>[12]</sup> while basal acid secretion was greatly increased.<sup>[13]</sup> The hypersecretion of acid in IHPS has been confirmed using histamine stimulated acid studies both before and, most importantly, 1 week after pyloromyotomy.<sup>[14]</sup>

Soon after these papers were published, the papers of Professor John Dodge came to light. He had been able to produce pyloric stenosis in new-born puppy dogs by giving injections of pentagastrin to their mothers before birth. More than 60% of puppies were affected and 16% were found at post mortem examination to have superficial pyloric ulceration.<sup>[15]</sup> Even more puppies were affected if pentagastrin was continued after birth. An explicit interpretation was not given but pentagastrin-induced acid secretion in the puppy appears the most likely cause particularly since it is known that gastrin crosses the mammalian placenta.<sup>[16]</sup>

Personal career considerations then intervened and I rejoined my pilgrimage many years later and revisited the problem anew. The following persistent questions all prompted by the clinical features, still remained unanswered.

1. What makes some babies develop IHPS when normal babies do not?
2. Why does IHPS occur more frequently in male babies?
3. How does self-cure occur with the passage of time?
4. Why is IHPS more frequent in the first born?
5. How does pyloromyotomy, and not gastro-enterostomy, cause the tumor to disappear?<sup>[1]</sup>

The only certain observed abnormality up till this time was hyperacidity. What if an inherited primary **hyperacidity**, that is acidity at the top of the normal distribution curve, were the primary cause? Indeed, when viewed from the perspective of a primary hyperacidity, the answers suddenly came thick and fast.

1. For example one need no longer ponder on the relatively normal fasting gastrin levels. Indeed if negative feedback control of gastrin release by hydrochloric acid is functioning at this age and this is by no means certain, gastrin level should be lower in IHPS. Their normality would be consistent with a relatively insensitivity of this feedback mechanism at this age (vide infra). Any baby in the pyloric age group who persistently vomits and who is alkalotic is invariably found to have IHPS.<sup>[17]</sup> The obvious implication is that babies with IHPS are hypersecretors of acid.

Adults who have had IHPS have been shown repeatedly to suffer from the adult consequences of hyperacidity such as duodenal ulcer with high volume acid secretion and are subjected more often to peptic ulcer surgery.<sup>[18]</sup>

Such hyperacid babies would provoke the cycle of sphincter work hypertrophy earlier and more persistently, and progress to a self-sustaining work hypertrophy. The presence of normal fasting gastrins would be expected. Such babies would be genetically selected and the condition would consequently be familial. Normal babies would have insufficient acid to trigger the process. The importance of a functioning sphincter and work hypertrophy, is clearly integral to the cause. Divide the sphincter - the tumour disappears. Bypass it and it remains. Work hypertrophy is also supported by the erythromycin phenomenon; a 7-fold increase in the incidence of IHPS has been reported among newborn infants who received erythromycin in antibiotic doses for post-exposure pertussis prophylaxis. <sup>[19]</sup>

Erythromycin, a macrolide antibiotic, specifically increases antral motility <sup>[20]</sup> and contraction of the pyloric bulb <sup>[21, 22]</sup> by binding to motilin receptors. These receptors not only exist in cholinergic nerves but also are thought to exist directly on smooth muscle. The strongest antral contractions induced by large doses of erythromycin are not blocked by atropine and direct muscle stimulation is likely. <sup>[23]</sup> Indeed the authors of the pertussis report <sup>[19]</sup> specifically speculate that that the marked gastric motility leads to (work) hypertrophy of the pylorus.

The gastrointestinal hormone motilin is responsible for the mass emptying movements of the stomach. It is classically secreted from the duodenal mucosa when the duodenum is empty or alkalinized. <sup>[24-27]</sup> The voltage-tension curves for the antral-pyloric region coupled with the narrow pyloric diameter mean that the interdigestive phase 11 first contractions will regularly encounter a closed pylorus consistent with sieving function of phase 2 contractions. <sup>[26]</sup>

Further enquiries have shown that duodenal pH does not influence endogenous motilin release if the pH is between 2 and 8.5, <sup>[26]</sup> a range well within the pH range in IHPS. <sup>[12]</sup> Nutrients in the duodenal cap strongly suppress the typical pulsed interdigestive motilin release, <sup>[27]</sup> and there is one report of acid in the duodenum stimulating motilin release <sup>[28]</sup>

Hence the empty duodenum in IHPS may provide a means whereby motilin maintains the stimulus for pyloric sphincter contraction. Studies in adults with an active duodenal ulcer (and presumed hyperacidity) have shown that Phase 2 gastric contractions, rhythmic and phase-locked but not expulsive, occur in the interdigestive phase. Phase 3 expulsive contractions which empty the stomach require acid-blocking drugs to alkalinize the antral contents. <sup>[25, 29]</sup>

Antral contractions in the fed state also increasingly meet with a closed pylorus as the condition develops, a scene well known to those who have felt the contracting tumor in the classical test feed. It is of further interest to record that plasma levels of motilin rise steeply after birth in normal infants reaching levels greater than those in fasting adults by day 24 and that the post-natal increase in motilin and gastrin require that the infant be fed. <sup>[30]</sup>

The one report of motilin levels in IHPS records low levels, <sup>[31]</sup> and further corroborative analyses are clearly required. An analysis of the motilin (MLN) gene has compared normal controls with babies with IHPS and no mutations or differences have been detected. <sup>[32]</sup> The repeated finding of a tenfold increase in

IHPS in babies with esophageal atresia <sup>[33]</sup> may reflect an early exposure to maternal gastrin-induced acidity which would be undiluted and unbuffered by amniotic fluid. The subsequent delayed postnatal introduction of milk feeds would complete the pathogenetic process.

1. A recent decline in the incidence of IHPS that parallels the decline of sudden infant death syndrome (SIDS) has been observed in Sweden, coinciding with the implementation of the Back to Sleep Campaign. <sup>[34]</sup> Gastric emptying is likely to be increased in the supine position compared to the prone position since duodenal emptying in the prone position requires nutrients to move against gravity. The reduced incidence of IHPS in babies sleeping on their backs has a physiological basis, and may tip the balance to self-cure with time.

2. The male predominance is also explained. The male / female ratio of 5-6: 1 continues to be reported <sup>[35]</sup> and parallels gender differences in incidence of duodenal ulcer in adult males, a condition known to depend on hyperacidity. Preterm male babies have been clearly shown to have more acid than matched females <sup>[36]</sup>. This report published in 1959 remains unchallenged and ethical considerations may prevent further nasogastric studies in normally fed term babies.

3. Important analyses of the relationship between neonatal gastrin and acid secretion in normal babies provide a credible explanation of the phenomenon of self-cure. Sequential studies of fasting and post-prandial gastrin were performed up to 6 weeks of life in normally developing infants. When fasting gastrin level is high at around 60 hours of age, there is no postprandial gastrin response. At around 3 weeks of age, fasting gastrin level is a little lower and a post-prandial gastrin response can be detected. <sup>[37]</sup> The authors explain these findings on the basis of a *relative insensitivity* of the negative feedback relationship between circulating gastrin and gastric acid in the first few weeks of life. By this they mean that it has not matured sufficiently to respond inversely to antral acidity.

Hence, between birth and 3 weeks, the *normal* baby exhibits some of the biochemical findings of a temporary Zollinger-Ellison syndrome (ZES). <sup>[38]</sup> Gastrin is being maximally secreted commensurate with development and cannot be further increased by food. This phenomenon is the presumed explanation for peak acidity in normal development at between 10-17 days reported and graphically outlined by Agunod. <sup>[39]</sup> Hence the baby inheriting hyperacidity is especially liable to trigger IHPS within the first few weeks of life. These infants essentially have a mini ZE syndrome with a hyperacidity unfettered by an adequate negative gastrin feedback. Left untreated, the condition usually leads to a fatal outcome. Pyloromyotomy will provide a quick long-lasting cure by stopping work hypertrophy and allowing acidity to be naturally expelled by peristalsis.

Temporary medical treatment using atropine and gastric wash-outs will reduce acid secretion and antral distension and will allow time for a natural self-cure when a normal mature feedback is established. The natural widening of the lumen with age combined with gastrin control will allow medical treatment to be safely stopped.

4. The first born child is fed by a first-time mother. Babies that vomit, especially babies with IHPS, are typically hungry and vigorous babies. The inexperienced mother is more likely to continue to feed the baby who vomits and the stomach will be seldom allowed to be empty. Hence the process of feed-promoted acid-induced work hypertrophy would continue. A more experienced mother is likely to give the stomach a rest. The work of Jacoby is of particular interest in this matter. Although a pediatrician, he treated IHPS both surgically and medically. A similar mortality of 1% in 100 surgical and 100 medically treated babies was reported. Great stress was put on the need for relative under nutrition as part of the well controlled titrated atropine therapy in the medically treated group.<sup>[40]</sup> The very low reported incidence of IHPS in underdeveloped countries such as Africa and Asia<sup>[41]</sup> may reflect infrequent overfeeding either from poor maternal nutrition or from a different pattern of infant feeding such as an infrequent desire to feed the vomiting baby.

5. Pyloromyotomy renders the sphincter incompetent and widens the lumen. Hence further contraction and work hypertrophy is impossible and the tumor quickly disappears. Gastroenterostomy, the earliest surgical treatment, only bypasses the obstruction. The pathogenetic processes are only partially abolished. Hence it is easy to understand why the tumor has been shown to be still present 40 years after gastroenterostomy.<sup>[1]</sup>

#### **Other contemporary lines of enquiry:**

Recent genetic analyses set up to explore the possibility of a monogenic association have simply confirmed that heterogeneous genetic inheritance is the norm.<sup>[41, 42]</sup> The concordance rate in monozygotic twins while greater than that in dizygotes, is still only between 0.25 and 0.44.<sup>[43]</sup> The basic consensus is that IHPS remains a condition which is multigenic and multifactorial- the likely acceptable pathway for the inheritance of constitutional hyperacidity.<sup>[44]</sup>

The reported abnormalities within the tumor of various growth factors as well as deficiencies of nitric oxide synthetase, although theoretically attractive, do not stand up to critical analysis.<sup>[45]</sup> First, for obvious reasons, adequate control specimens are not possible. Second, the reported accumulation of growth factors in the tumor tissue is no more than one would expect from a work-hypertrophied sphincter. When a repeatedly contracting muscle or a muscle subjected to an increasing load becomes hypertrophic, it does so through the agency of locally attracted growth factors.<sup>[46-48]</sup> There is no evidence to support genetically controlled inappropriate accumulation of growth factors as a primary process.

Third, as with the genetic studies, there is no attempt to relate genetic abnormalities to the dynamic clinical features. The search for a necessary time-sensitive environmental precipitant in pathogenesis has led to speculation about self-limiting infection. Throat swab analysis of the common nasopharyngeal viruses has shown no greater frequency in pyloric babies compared to normal matched controls.<sup>[49]</sup> *Helicobacter pylori* (*H. pylori*), the important gastric pathogen and known stimulant of gastric acid secretion has also been investigated.<sup>[50]</sup>

*H. pylori* is known to be present in some babies from 6 months in age. In a 5 year follow-up study of mother and child random amplified polymorphic DNA fingerprinting has revealed that mother to baby transmission does occur. <sup>[51]</sup>

In another study prompted by an index case suspicion of *H. pylori* organisms on histology, 16 consecutive babies with IHPS underwent gastric biopsy preoperatively. All the urease tests were negative, 4 cases had chronic gastritis, 6 had a mild gastritis and 5 were normal. No *H. pylori* were discovered on histology. <sup>[52]</sup> At the age of pyloric presentation immunological tests for *H. pylori* are unreliable since maternal transmitted immunity may last up to 6 months.

A further study using stool culture for *H. pylori* in 39 consecutive babies with IHPS failed to discover a single case. Control babies were also negative. <sup>[53]</sup>

Curiously the major consequence of *H. pylori* infection in adults- namely hyperacidity - is not mentioned as a possible link between infection and the development of IHPS in any of the cited papers. In the absence of a known cause the gastritis recorded on biopsy presumably would simply be a consequence of prolonged gastric stasis. There is consequently no evidence at present to support an infectious cause.

### Conclusion

So there it is. My journey is almost complete. Constitutional hyperacidity at the right time in development begets pyloric spasm which begets work hypertrophy which begets IHPS. We are almost back where we began so many years ago when Thompson <sup>[2]</sup> first proposed pylorospasm and work hypertrophy as the cause. This theory is perfectly testable. Babies with IHPS lose lots of acid when they vomit. The associated alkalosis may cause problems with anesthesia by reducing respiratory drive. An adult similarly affected would be appropriately treated with the currently super-effective acid-blocking drugs with an immediate reduction in fluid, acid and potassium loss. Such a preoperative strategy with babies with IHPS is long overdue. It should not come as a surprise if we find that such temporary treatment promotes a lasting cure.

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