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Research Article

Why Pyloric Stenosis of Infancy Occurs-Facing the Facts

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Abstract

Background: There has been no shortage of published articles about pyloric stenosis of infancy(PS). Curiously, few have opined a cause despite a galaxy of potentially informative clues. The earliest speculative suggestion was that hyperacidity was involved. More recently the notion that there is a deficit of a relaxing agent-nitric oxide(NO) in the sphincter. Others have proposed that there is an abnormal accumulation of growth factors which leads to sphincter hypertrophy. Neither the NO nor the growth factor theories have attempted to link with the classical clinical features.

Materials and methods: The accepted physiological facts and the classical clinical features are linked in a comprehensive theory of cause. An inherited greater than average acid secretory ability is key. An important support is provided by two other normal developmental phenomena- a peak acidity in the early weeks and a temporary insensitivity of the negative feed-back between neonatal gastrin and gastric acidity soon after birth. Inappropriate overfeeding is an important stimulus for sphincter contraction. The evidence for its contribution to pathogenesis is also examined.

Results and conclusion: The Primary Hyperacidity theory has been found to expain all the clinical features.In outlining a conflict between stenosing forces and relaxing forces, it also provides and explanation for the way in which symptoms and signs may come and go.The theory is critically examined and is proposed as the cause.

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- Trans-placental transfer of gastrin
- H2 receptor blockade in neonates

INTRODUCTION

There has been no shortage of articles published about the still misunderstood condition of Pyloric Stenosis of Infancy (PS) (Figure 1).

1. The astonishing fact is that almost none, until very recent years, has proposed theories of cause. Almost all have only yet again confirmed from their own practice or from meta-analysis the classical signs, symptoms and demographics of this enigmatic disease. The few recent scientific attempts such as the alleged abnormal accumulation of growth factors in the sphincter [1], and the nitric oxide theory [2], have not stood the test of time. Neither theory has addressed the need to explain the clinical spectrum; both have reported findings that you would expect in a frequently contracting sphincter and the growth factor theory has never had any adequate controls. The real cause has remained a mystery. The elephant in the room has been studiously ignored.

2. Possible reasons for this antipathy towards a comprehensive cause, no doubt relate to the ease of modern ultrasound diagnosis and surgical cure. However, multiple support groups exist online such as *pyloric stenosis support group* which frequently reveal frustration and worry-largely about delayed and mistaken diagnosis. Pediatricians wisely have confined themselves to diagnosis and rapid referral given that medical cures are less certain, do have side effects and take much longer.

For a medical detective seeking the cause, the clues are not in short supply. What happens when you face the facts?

MATERIALS AND METHODS-THE THEORY

There are several facts concerning pyloric stenosis of infancy (PS) , which are beyond dispute.

1. The tumor is caused by hypertrophy of the circular muscle fibers of the sphincter [3].
2. Repeated contraction will cause sphincter work hypertrophy especially under the trophic influence of neonatal hypergastrinaemia [4]. Hypertrophy occurs naturally when growth factors are attracted by repeated contraction.
3. Pyloric stenosis (PS) babies are hypersecretors of acid even after successful pyloromyotomy [5,6], and

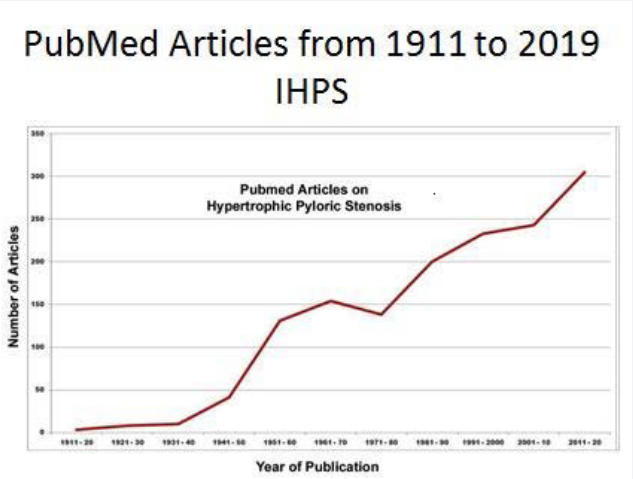

Figure 1 Frequency of PubMed reported articles between 1911 and 2011.

hyperacidity is a potent cause of sphincter contraction [7,8]. The mechanism of acid induced sphincter contraction is not yet conclusively established. Duodenal acidity stimulates cholecystokinin and secretin, both of which cause sphincter contraction [8], and prostaglandin, released locally from the stomach in response to gastric hyperacidity, has a similar effect.

4. H2 receptor blockade rapidly reduces alkalosis and allows same day surgery. Hence an active real time hypersecretion of acid **must** be present rather than retention of acid behind a closed pylorus [9].

This statement is further strengthened by the observations that any vomiting baby in the PS age range with an alkalosis, will have PS [10], and that hyperacidity problems more frequently supervene in adult life [11].

The strong family history adds weight to the working hypothesis. PS babies will inherit an acid secreting ability above normal; the pylorus will contract more often and the subsequent sphincter work hypertrophy will produce PS. These simple theory, detective-like, needs to be tested in relation to the classical clinical features.

Male predominance

Male premature infants secrete more acid than females [12]. There are no comparative studies in term babies. The classical ratio of 4-5/1 parallels the sex-ratio of adult duodenal ulcer (DU), patients-a condition known to depend on hyperacidity. PS babies like DU adults also have a greater frequency of blood group O [13,14].

The presentation at 4 weeks: Fasting gastrin levels rise quickly after birth *in all normal babies* and do not fall despite the rising gastric acidity in the first few weeks of life. When both gastrin and acid secretion rise together (such as in the Zollinger-Ellison syndrome) the negative feedback between gastrin and antral acidity is not working [4,15,16]. There is evidence which suggests this applies also to the PS baby.

Support for an initial immaturity of the negative feed-back also comes from other sources. There is a reduced or absent post-feed gastrin response in the first few weeks of life [17]. During this time gastrin is being maximally secreted without restraint from acidity, and feeding cannot increase it further.

Moreover, in normal development, the maximally stimulated acid secretion and fasting acid secretion are the same [18], during the first day of life. The stimulus for gastrin secretion is unrestrained from day 1.

Neither acid nor gastrin, at this time, inhibits the other as they do in adult life. When negative feed-back is established at around 3 weeks a temporary peak acidity is predicted on this physiological basis and it has been shown to occur at around 2-3 weeks of life just when negative feed-back is being established [19] (Figure 2).

In *normal* babies an early rise in acidity from a temporary maternal gastrin boost and peak acidity (from a maturing feed-back) protects against enteric infections and does not harm (19). In babies already with an inherited hyperacidity, the hyperacidity will cause frequent sphincter contractions, hypertrophy and Pyloric Stenosis. It is not surprising that vomiting will begin around 4 weeks-soon after the time of peak acidity.

The condition self-cures if the babies can be kept alive for long enough: When the feed-back matures, gastrin will be expected to fall and, for the first-time since birth, a post-prandial gastrin response will occur. This phenomenon has already been confirmed [17]. The reporting authors described their findings as being best explained by an early insensitivity of the negative feedback. The maturing negative-feedback will also explain the known reduction in acidity at that time.

The reduced acid drive to pyloric contraction coupled with age -related widening of the lumen will combine to produce self-cure.

This sequence of events finds support in the acid studies of Agunod and also of Hyman which reveal that, in normal

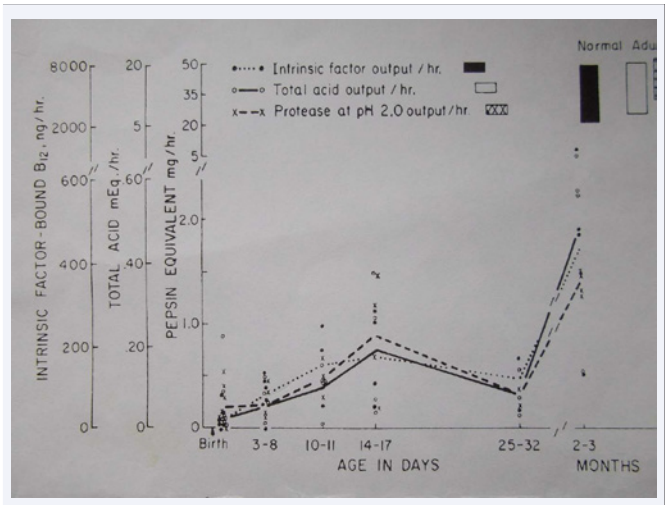

Figure 2 Total acid, pepsin and intrinsic factor secretion from birth to 25 days reported by Agunod (Ref.19). A temporary peak secretion is clear in all three groups.

development, acid secretion rises to a peak at around 2-3 weeks of age before slowly falling within the next few weeks [16,19] (Figure 2).

Why does pyloromyotomy produce a long-term cure?

Sphincter division makes contraction impossible. Work hypertrophy can no longer occur. In any event, by this time the time for peak hyperacidity will have passed.

Why the family history in 25% of PS babies?

Constitutional hyperacidity is inherited on a multifactorial basis both by PS babies and DU patients and is also the pattern of inheritance of PS [20].

The first- born and the feeding phenomenon.

First born babies are born to novice mothers. In two consecutive studies from Birmingham U.K. involving 1059 PS babies from 1940-1951, it was concluded that the earlier presentation of home-fed babies was caused by 3 hourly home feeds compared to 4 hourly hospital feeds [21,22]. Sphincter contractions are most frequent and most powerful after a feed when the feed is being mixed against a frequently closing pylorus [23].

In this huge series the first-born predominance was only apparent from week 3 onwards. There was a clear environmental factor which acts after birth and takes 2 weeks to have an effect. That factor was over frequent feeding-a practice more likely to be associated with an anxious novice mother [21,22].

The bigger picture-acid defence versus acid attack

Neonatal gastric acid protects against enteric infections. Hence a system to kick-start acidity soon after birth and to maintain acidity in the first few days before it rises naturally with rising gastrin, would have a survival advantage. An early wave of acidity occurring a few hours after birth was first described in 1947 [24]. The phenomenon was thought to be due to a maternal hormone transmitted from mother to baby during labour which would cause gastric acid secretion. There is much evidence now to support trans-placental gastrin transfer during labour as the cause.

Maternal plasma gastrin rises progressively during pregnancy and peaks at birth [25]. Within 30 minutes of delivery the levels fall. The maternal placenta is rich in gastrin [26], and at birth the fasting foetal gastrin levels are significantly higher than in the fasting maternal venous samples [2]. Gastrin is known to cross from mother to baby in dogs and to actively cause acid secretion [27].

All of this point to trans-placental transfer of gastrin in humans which would cover the acid gap before progressive acidity generated by the temporary negative feed-back begins. These developmental mechanisms give a survival advantage to normal babies. One disadvantage is the development of PS in the baby with inherited hyperacidity.

Professor Dodge and the canine model

Puppy dogs born to mothers who had received injections just before labour develop sphincter hypertrophy identical to PS. [28]. Even more puppies developed PS when they receive the injections after birth. These experiments are crucial to our understanding of pathogenesis since gastric outlet stenosis itself leads to increased acid secretion [29].

The puppy experiment in producing PS from an otherwise normal development shows that the prime mover is indeed hyperacidity. While gastric outlet stenosis increases acid secretion it occurs only after the event-it does not initiate it.

The classical and effective conventional medical treatment originally designed in the hope of reducing pyloric "spasm" [30], may do so by removing acidity directly by gastric washouts and indirectly by reducing vagal- induced acid secretion through atropine. Relatively underfeeding is also important in any successful medical treatment, since it removes another important driver of sphincter contraction [23].

RESULTS

This theory is supported by the observation that pre-operative cimetidine therapy in early cases of PS with a sphincter diameter of 4 mm. or less [31], will produce a long-term cure in 17/18 babies.

In 1921 Dr. John Thompson after an analysis of 100 PS babies in the preceding 25 years proposed pylorospasm and work hypertrophy as the cause although no primary cause was defined [32].

He divided the presentation of PS into 3 groups –

A) an acute form with violent symptoms-

B) an ordinary form-and most importantly-

C) the mild cases.

The mild cases were *not at all uncommon*-they slipped in and out of PS. No doubt this would be a reflection of the conflict between factors increasing acidity or pyloric contraction (emerging gastric hold up and inappropriate feeding) and factors favoring natural cure such as the time related reduction in acidity and widening of the pyloric lumen with age. Most experienced medical or surgical observers will have had cause to reflect that, in the words of MacKeown after an experience of analyzing 1059 PS babies from Birmingham U.K.-the presentation is "rarely sharp" [21].

CONCLUSIONS

Nothing has really changed. We all continue to stand on the shoulders of those who have gone before. One such worthy was Dr.W. Freund who in 1903, untrammelled by sophisticated science, found the hydro-chloric acid content to be in excess of normal. He concluded that acid was the cause of "spasm" of the pylorus [33]. In observing hyperacidity, he joined forces who were using alkalis in the treatment and with the American Hezekiah Beardsly (1788), and the later opinion of the Australian Austin Lendon (1912) [34,35]. It was however Freund who specifically related hyperacidity to the pathogenesis.

Despite the many articles about chemical growth mediators, nitric oxide abnormalities with knock-out mice etc., none of these

theories addresses the need to explain the clinical features. None has stood the test of time.

The hyperacidity theory explains all of them.

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