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Why pyloric stenosis of infancy occurs-simple echos from the past

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Ian Munro Rogers
Sunderland, UK

Correspondence: Ian Munro Rogers, Mb.,Ch.B., FRCS,FRCP,PGCMed.Edu, 46 Whitburn Road, Cleadon, Sunderland SR67QS, UK, Tel 0044(0)1915367944, Email irogers2000@hotmail.com

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Introduction

"to put your mind into accordance with things as they really are- "after James Clerk Maxwell in a letter of encouragement to a fellow Physicist (circa 1850).

The hyperacidity theory of the cause of pyloric stenosis is here reviewed. The combination of a trans-placental gastrin transfer with an initially non-functioning negative feedback between gastrin and antral acidity, ensures the maintenance of an effective acid barrier to neonatal gut infection. Such a developmental acidity while an advantage to the great majority of normal babies, will precipitate sufficient hyperacidity in babies with an already inherited capacity for hyperacidity, to provoke work hypertrophy of the pyloric sphincter and pyloric stenosis. The proposed pathogenesis relies on already established facts.

There are several facts which are beyond dispute.

a. The classical tumour is caused by hyperplasia and hypertrophy of the circular muscle fibres of the sphincter.[1]

b. Repeated contraction of the sphincter will cause hypertrophy/ hyperplasia especially under the influence of the high gastrin levels present in the first few weeks of life.[2] Gastrin, is a gastric trophic hormone responsible for gastric development and enlargement.

c. Acid entering the duodenum causes the pyloric sphincter to contract.[3,4]

d. Neonates with PS are hypersecretors of acid even after successful pyloromyotomy.[5,6]

Indeed, cimetidine treatment preoperatively rapidly reduces alkalosis sufficiently to allow same day surgery indicating an active real time acid secretion rather than retention of acid behind a closed pylorus.[7] Any vomiting baby in the PS age range with an alkalosis, will have PS.[8] When adult, these babies suffer not surprisingly with hyperacidity problems.[9]

Hence it is easy to construct a model for the development of PS. The babies will have an acid secreting ability above the average- the pylorus will contract more often and the subsequent sphincter enlargement will produce PS. The frequently documented clinical features are similarly not in dispute and, naturally, any theory of cause, such as this, requires to explain them.

For example-

i. Male babies are affected more often.

Male premature infants secrete more acid than females.[10] There are no comparative studies in term babies. The classical ratio of 4-5/1 parallels the sex-ratio of adult duodenal ulcer patients-a condition known to depend on hyperacidity. PS babies have a preponderance of blood group O like classically hyperacid duodenal ulcer patients.[11,12]

A. The condition classically presents at 4 weeks of life

Fasting gastrin levels rise steeply to levels exceeding adult fasting values after birth 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.[2,13,14] During this time there is no post-prandial gastrin response since gastrin is maximally secreted without the constraint of an acid negative feed-back. In normal babies this early peak acidity does not trigger PS. It will simply confer a survival advantage by an increased resistance to enteric infections at that time.[14] In babies with an increased acid secreting ability, pyloric stenosis due to critical hyperacidity will be the natural result -and will present 2-3 weeks after birth.

B. The condition self-cures if the babies can be kept alive for long enough

At some time after birth, the negative feed-back between gastrin and acidity must be established. At around 2 months of age the fasting gastrins are lower and for the first-time since birth, a post-prandial gastrin response can be detected.[15] The authors who first described this phenomenon proposed that there was a temporary insensitivity of the negative relationship between gastrin and antral acidity, which took some weeks to mature. This maturation of the negative feed-back between acid and gastrin at 2 months means that acid secretion becomes controlled and the frequency of pyloric contraction is reduced.[15] The normal increase in size of the pyloric lumen with time is obviously an important additional factor in achieving a time related self-cure. This sequence of events finds support in the acid studies of Agunod and also of Hyman which reveal that , in normal development, acid secretion rises to a peak at around 2-3 weeks of age before slowly falling up to 4 weeks late.[16,14]

C. Why does pyloromyotomy produce a long term cure?

Sphincter division makes contraction impossible. Work hypertrophy can no longer occur.

D. Why the family history in 25% of PS babies?

Constitutional hyperacidity is inherited presumably on a multifactorial basis. The genetics of the control of parietal cell mass and acidity has not yet been revealed.

Other supporting evidence

When puppy dogs are born after pentagastrin injections have been given to their mother shortly before birth, PS similar to the human variety is created. Even more puppies suffer from the disease if they too receive pentagastrin.[17] The classical medical treatment designed to reduce pyloric "spasm" which has a success rate not much less than surgery,[18] will in reality remove acidity by gastric washouts and reduce vagal acid secretion by atropine therapy.

The frequency and amplitude of pyloric sphincter contractions in adults, is best increased by feeding.Pyloric hunger contractions are much less frequent and are of smaller amplitude. The sphincter contracts repeatedly in response to feeding and only relaxes when the feed has been sufficiently mechanically mixed.[19] Indeed the effect of erythromycin medication in the first few weeks of life in promoting PS is likely to be based on the drug promoting more frequent sphincter contractions.[20] Relatively underfeeding is consequently an important part of successful medical treatment.[18]

The classical first-born presentation of PS may simply reflect increased anxiety of the first-born mother which leads to repeated and inappropriate attempts to re-feed her vomiting child. Once PS is established, gastric hold-up itself will produce further hypersecretion of acid and gastric hyperplasia. Such consequences develop when the pylorus of rats is experimentally constricted.[21] When pyloric stenosis develops in adults with a duodenal ulcer- a further increase in acid secretion follows.[22] The post-prandial bloating so commonly found in hyperacid adults is presumably due to pronounced sphincter contraction. The main tenets of this theory gains further support by the knowledge that pre-operative cimetidine therapy will produce a long term cure in 17/18 babies who have a sphincter diameter of 4 mm. or less.[23]

The bigger picture

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 weeks 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 at or around labour which would cause gastric acid secretion. There is much evidence now to support gastrin being this hormone. Maternal plasma gastrin rises progressively during pregnancy and peaks at labour.[25] Within 30 minutes of delivery the levels fall.[26] The maternal placenta is rich in gastrin[25] and at birth the fasting foetal gastrin levels are significantly higher than in the maternal venous samples.[27] Gastrin is known to cross from mother to baby in dogs and to actively cause acid secretion.[28] In the sheep foetal gastrin secretion continues to rise from 2 weeks before birth onwards.[29]

All of this points to the probability of trans-placental transfer of gastrin in humans which would kick-start gastric acidity. The mechanism of an initially immature negative feed-back between gastrin and acidy would ensure that acidity is maintained until the negative feed-back matures. These developmental mechanisms for maintain an acid barrier, are good for the great majority of normal babies. For the baby who inherits too great a potential for acid secretion, these developmental mechanisms will produce hyperacidity sufficient to produce pyloric stenosis of infancy.

Overview

Despite all the many articles about chemical mediators, nitric oxide abnormalities with knock-out mice etc. over very many years, none of these observations begins to explain the clinical features. The hyperacidity theory explains all of them. Writing in 1903 Freund declared that a hydrochloric acid content in excess of normal was a causative factor. For some reason this theory was never properly investigated presumably because retained acid was assumed to cause the high acidity in these babies, not an active hypersecretion of acid.[30] In 1921 Thompson proposed pylorospasm and work hypertrophy as the cause although no primary cause was defined. He further divided the presentation of PS into 3 groups – an acute form with violent symptoms-an ordinary form-and most importantly-the mild cases. The mild cases were *not at all uncommon*-appeared to slip in and out of PS.[31] These cases may well reflect the dynamic conflict between factors increasing acidity and pyloric contraction (emerging gastric hold up and inappropriate feeding) and factors favouring natural cure such as the time related reduction in acidity and widening of the pyloric lumen. Nothing has really changed. We all continue to stand on the shoulders of those who have gone before.

A more comprehensive account of the development of the ideas behind this theory may be obtained in *The Consequences and Cause of Pyloric stenosis of infancy. Fred Vanderborn and I.M.Rogers obtainable from More Books (Lambert Academic Publishing) ISBN 978-3-659-52125-6.*

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Conflicts of interest

Author declares that there is no conflict of interest.

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