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Induction of pyloric hypertrophy by pentagastrin

An animal model for infantile hypertrophic pyloric stenosis

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SUMMARY Administration of pentagastrin in depot form to 20 pregnant bitches produced pyloric hypertrophy in about 28% and gastroduodenal ulceration in about 16% of their pups. The two lesions were not necessarily found in the same individuals. Histological appearances of the pylorus in affected pups closely resembled those of human infantile pyloric stenosis.

Attempts to reproduce infantile hypertrophic pyloric stenosis in experimental animals have mostly been unsuccessful. An exception was an experiment in which foreign bodies were sutured into the fundus of rabbits' stomachs, and hypertrophy of the pylorus followed as a 'compensatory mechanism' (Heinisch, 1967). This paper reports a method in which administration of Pentagastrin to pregnant bitches has produced typical pyloric tumours in some of their offspring.

Methods

PENTAGASTRIN PREPARATIONS

Two depot forms of pentagastrin were prepared. In one, pure pentagastrin powder was suspended under aseptic conditions in an 8% or 10% mixture of beeswax in arachis oil, which had been previously sterilized in a hot air oven and cooled to about 60°C. The concentration of the final preparation was 8 mg pentagastrin in 1 ml. The second preparation used a base of 0·5% phenol and 16% gelatin, which had been sterilized by autoclaving. Pentagastrin was again added, after cooling, in a concentration of 8 mg per ml.

The preparations were liquid at room temperature, but solidified on storing in a domestic refrigerator. The amounts used each day were liquefied by warming in a water bath.

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PENTAGASTRIN ADMINISTRATION

The dogs used were a heterogeneous group of mongrels and pure breeds. They were divided into four groups as follows:

Group 1 Fourteen bitches were given prenatal injections of 2-4 mg of one or other pentagastrin preparation, and in one case 20 mg, twice daily for varying periods from one to 85 days before term.

Group 2 Eight bitches were similarly treated for five to 49 days, and further injections were given to their offspring at birth. The dosage used for the pups was in the range of 0·5 to 4 mg twice daily, and the duration of treatment was from one to 30 days.

There were two litters in the original experiments where the mothers were both treated, but only half the pups from each litter were given further treatment. Results in these two litters are therefore recorded in both groups 1 and 2, according to whether the pups concerned were exposed to pentagastrin postnatally or not.

Group 3 This consisted of six control litters, where neither the mother nor the pups were treated.

Group 4 This was a group in which the four mothers were treated with the depot vehicle only. Two were given injections of beeswax, and the other two gelatin.

There was thus considerable variation in the dosage and duration of treatment given to different animals even without taking into account the weight differences between them (Table 1). Details of the treatment given to individual animals are recorded elsewhere (Dodge, 1970; Karim, 1975). No studies of gastric function were performed.

A few pups died (from perforated ulcers), and others were killed at varying intervals after birth. Necropsies were performed and both macroscopic

Litter	*Weight of bitches (kg)*	*Injections (days)*		*Vehicle*	*Daily dose of pentagastrin (mg)*		*Litter size*	*Incidence of hypertrophy ulcer*	
		Mother	*Pups*		*Mother*	*Pups*		*Mother*	*Pups*
K4	26·6	0	0	—	—	—	5	0	0
K7	26·6	0	0	—	—	—	4	0	0
K13	11·6	0	0	—	—	—	4	0	0
K15	15·0	0	0	—	—	—	8	0	0
K17	15·0	0	0	—	—	—	6	0	0
D2	14·0	0	0	—	—	—	2	0	0
K22	17·5	1	0	G	8	—	4	2	0
K12	8·7	6	0	BW	4	—	4	2	2
K18	22·7	7	0	BW	8	—	6	0	0
K11	11·6	6	2	BW	8	4	5	0	1
K25	27·3	9	0	G	40	—	8	2	1
K2	28·5	10	0	G	4	—	3	0	1
K3	30·0	10	0	G	4	—	3	1	0
K16*	12·3	13	0	BW	8	—	6	0	0
K1	27·3	15	0	G	4	—	7	0	2
K8	22·7	5	14	BW	8	8	4	0	0
K19	31·3	13	10	BW	8	2	5	3	0
K5	33·3	32	0	BW	4	—	5	3	0
K14	14·1	33	0	BW	8	—	6	3	2
K9	22·7	5	30	G	8	4	6	1	0
K10	27·3	15	19	G	8	1	4	2	0
K6	39·0	34	19	BW	2	2	6	1	1
K21	22·7	79	0	G	8	—	1	1	0
K20	22·7	85	0	G	8	—	1	0	0
D1	18·0	21	0·30	BW	4	2†	7	2	1
D3	10·0	21	0·45	BW	4	2‡	4	2	3

Table 1 *Incidence of pyloric hypertrophy and peptic ulceration in puppies related to maternal weight and dose of pentagastrin*

* Five pups destroyed by mother. † Given to three pups from this litter. ‡ Given to two pups from this litter.

and microscopic appearances of the stomach and duodenum were noted. Some of the bitches were also killed and examined.

Results

The incidence of pyloric muscle hypertrophy, and of pyloroduodenal ulceration, is given in Table 1. The relative incidence of these lesions between the four groups is summarized in Table 2. The gross appearances of the pylorus in affected pups varied from definite thickening to typical tumours similar to those seen in human infants (Fig. 1).

GROUP 1

The 14 treated bitches in this group gave birth to 61 pups, none of which received additional injections of pentagastrin. One bitch produced six pups, but destroyed five of them. Necropsy was therefore carried out on the remaining puppy as well as the mother. The pup showed no evidence of pathological changes, but the mother had a large duodenal ulcer. A post-mortem examination of all the 56 available puppies revealed 16 instances of pyloric hypertrophy —that is, 29·1%. Nine of the 56 pups had ulcers in the pre-pyloric region, pyloric canal, or duodenum at necropsy (16·3%), and in three instances perforation occurred. It was noted on occasion that, within individual litters, some pups had pyloric hypertrophy, while the remainder were normal. Of the 16 pups with pyloric hypertrophy, four had duodenal ulcers, but the pylorus appeared normal in the other five with ulceration.

Group	*Bitches (no.)*	*Pups (no.)*	*Pathological changes in pups*	
			Hypertrophy	*Ulceration*
1	14	55	16 (29·1%)	9 (16·3%)
2	8	36	9 (25·7%)	5 (14·3%)
3 (Control)	6	29	0	0
4 (Vehicle control)	4	18	0	0

Table 2 *Incidence of pyloric hypertrophy and peptic ulceration among puppies in four experimental groups*

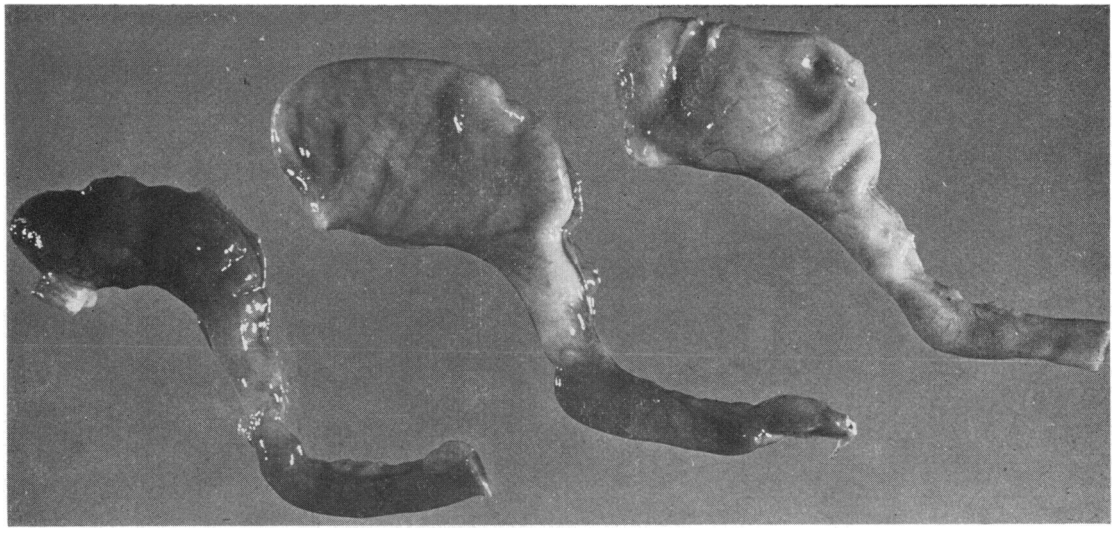


Fig. 1 *Three stomachs of puppies from same litter. The middle specimen shows the external appearance of hypertrophic pyloric stenosis.*

GROUP 2

There were eight bitches in group 2 whose 35 puppies were treated with depot pentagastrin injections. Nine of the pups had pyloric hypertrophy at necropsy (25·7%) and five had ulcers (14·3%). The ulcers were situated in the pylorus in two, in the duodenum in three, and one of the latter died from perforation of a concomitant oesophageal ulcer. In spite of the continued administration of pentagastrin daily for varying periods to the puppies, the incidence of ulceration was slightly lower in this group than in group 1, but the difference was not statistically significant. Three of the nine with hypertrophy also had ulceration.

GROUP 3

None of the six bitches or their 29 offspring in this group received any form of injection, and none showed any abnormalities on postmortem examination.

GROUP 4

In the four instances where bitches were treated with injections of beeswax or gelatin without pentagastrin, no abnormalities of the digestive tract were found in either the mothers or their 18 offspring.

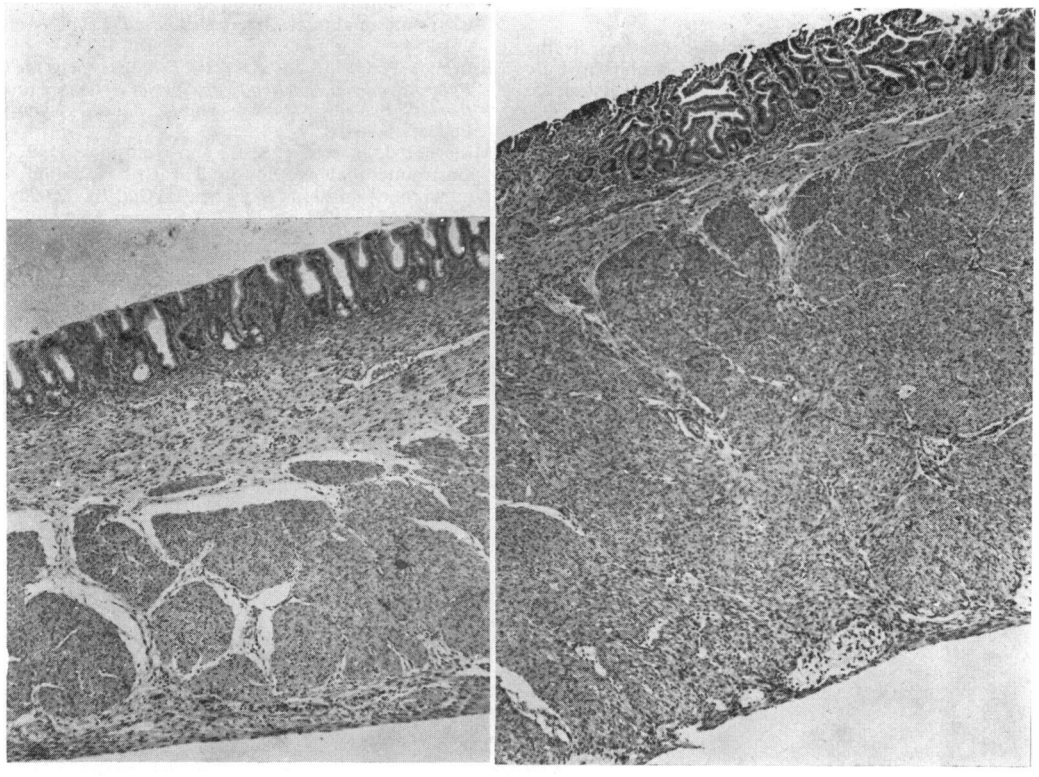
The histological features of the pylorus in pups showing hypertrophy closely resembled those of the human infant with pyloric stenosis. The circular muscle was hypertrophic (Fig. 2). Ganglion cells in the myenteric plexus showed changes in size and configuration compared with normals, and occasional vacuolation was present. Submucosal ganglion cells were absent at the pyloroduodenal junction.

Statistical analysis showed that the control groups differed significantly ($P < 0.01$) from groups 1 and 2 in respect of the incidence of both pyloric hypertrophy and ulceration. No correlation was found between the incidence of pyloric hypertrophy and either the absolute or weight-related dose of Pentagastrin given to mothers, nor did the duration of treatment appear to be directly related to the presence of pathological changes. No significant differences were found when the two pentagastrin preparations were compared for incidence of hypertrophy or ulcers, and there was no significant difference between the groups treated with beeswax and gelatin-based preparations in respect of dosage of Pentagastrin or duration of treatment ($P < 0.10$ using Fisher's exact probability test).

Discussion

Gastrin has been shown to cross the placenta in dogs (Bruckner *et al.*, 1970). In the human infant, there is evidence that secretion of gastrin is already established at birth, but it remains to be demonstrated that gastrin secretion occurs *in utero* or that maternal gastrin crosses the placenta (Rogers *et al.*, 1974).

A preliminary report that administration of pentagastrin to pregnant bitches may produce hypertrophic pyloric stenosis and gastroduodenal ulceration in their offspring (Dodge, 1970) has been con-



(a) (b)

Fig. 2 *Histological section of pylorus from (a) normal control newborn pup weighing 350 g, compared with (b) pentagastrin-treated newborn pup weighing 164 g (both sections × 10).*

firmed by the present study. As with many biological systems, there is variation in the response, with some pups showing no pathological changes, while others, sometimes from the same litter, are markedly affected. This would suggest that individual inherent susceptibilities are an important determinant of the response; and is in keeping with the situation in human infantile hypertrophic pyloric stenosis, where genetic and environmental facts apparently interact to produce the characteristic tumour (Dodge, 1973).

The detailed histological findings, as well as *in vivo* motility studies in affected pups, are similar to those encountered in human infants with pyloric stenosis and have been presented elsewhere (Karim, 1975) and will be the subject of further reports. The ganglion cell changes seen in human infantile pyloric stenosis in this study, and in affected puppies, closely resembled previous descriptions of the human disorder (Alarotu, 1956).

The exact mechanism by which the characteristic hypertrophy is brought about is still uncertain. Pentagastrin is believed to have direct somatotrophic properties (Johnson *et al.*, 1969) and, in addition, it is a potent stimulant of antral motility (Misiewicz *et al.*, 1969). It has recently been suggested that the acid secretagogue effect of pentagastrin may in turn stimulate the release of secretin and cholecystokinin, and that it is these hormones which mainly induce contraction and ultimately hypertrophy in the pylorus (Rogers *et al.*, 1975). The fact that pyloroduodenal ulceration also occurred in some of the animals was not surprising, in view of the finding of duodenal ulcers in cats subjected to stimulation with gastrin (Emås and Grossman, 1967). It is noteworthy that there is no correlation between pyloric hypertrophy and ulceration in individual animals. However, the occasional occurrence of both infantile pyloric stenosis and duodenal ulcer in the same babies has been recorded (Schärli *et al.*, 1969).

In spite of the inconsistency of response, transplacental pentagastrin stimulation of the canine fetus appears to be a valid animal model for infantile pyloric stenosis.

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