

INFANTILE HYPERTROPHIC PYLORIC STENOSIS IN PARENT AND CHILD

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In a recent report, Carter and Powell (1954) recorded 12 examples of pyloric stenosis in parent and child, and drew attention to the increased risk of the disease in offspring of parents who were themselves affected. In examining their observations we noted that the risk to the child seemed to be greater if the affected parent was the mother; but the number of cases was small, and the matter evidently required investigation in a larger series. Nielsen (1954) has since recorded nine examples of pyloric stenosis in parent and child, to which we have been able to add a further 12. The results support the conclusion that the risk is raised in children of affected parents, and suggest that it is much higher if the affected parent is the mother.

Incidence in Offspring of an Affected Parent

There were 491 patients in whom the diagnosis of pyloric stenosis was confirmed by operation at the Birmingham Children's Hospital in the period 1920-34. One hundred and twenty-eight (26.1%) died in hospital, and a further 33 lived more than 15 miles from the city. Of the remaining 330 patients, 129 were traced; 17 of them had died since discharge from hospital. Unfortunately, most of the 112 patients interviewed were treated in the later years of the period, so that the number of offspring born before the time of enquiry was small, 29 in 23 families. None of them had had pyloric stenosis.

Carter and Powell (1954) found three cases of pyloric stenosis among 46 children of 28 patients treated at The Hospital for Sick Children, Great Ormond Street, between 1920 and 1929, and Nielsen (1954) found 11 cases among 128 children of 95 patients. In the three series there are 14 affected among 203 children, an incidence of 6.9%.

Sex of Affected Parents

Although no examples of pyloric stenosis in parent and child were found by tracing Birmingham patients treated between 1920 and 1934, eight were

ascertained by inspection of recent records of children with the disease. Four of these families were previously recorded among cases treated in the period 1940-49 (McKeown, MacMahon and Record, 1951): in two (both mothers) the parent was operated on; in the other two cases (one mother and one father) the diagnosis rested on medical evidence only. Four more families were found in records of the Birmingham Children's Hospital for the years 1950-54, three in which the mother had been submitted to operation, and a fourth in which the condition was diagnosed medically in a father. Two other Birmingham families (operation on mother and child), identified by postal enquiry, are referred to below.

In an attempt to increase the number of cases, records of 2,579 recent patients were inspected in hospitals in Liverpool, Manchester, Newcastle-on-Tyne and Sheffield (see acknowledgments). Only two more examples were ascertained; in both cases the father was affected and the diagnosis was confirmed at operation.

Details of the 12 families are given in Table 1; in eight the parent affected was the mother. In

TABLE 1
12 FAMILIES WITH PYLORIC STENOSIS IN PARENT AND CHILD

Number	Parent Affected	Sex of Children
1	Mother†	M*
2	Mother*	M* M
3	Mother*	M† F*
4	Mother*	M*
5	Mother*	F M*
6	Mother*	M*
7	Mother*	M M*
8	Mother*	M*
9	Father†	a a F* M*
10	Father†	M*
11	Father*	M* M*
12	Father*	F*

* = operated, † = treated medically for pyloric stenosis, a = abortion
(Families 1, 2, 3 and 9 are Nos. 49, 337, X10 and 223, respectively, in the appendix published by McKeown *et al.*, 1951.)

TABLE 2
SEX OF AFFECTED PARENT IN FAMILIES WITH
PYLORIC STENOSIS IN PARENT AND CHILD

Source	Parent Affected*		Parent Affected†		Total	
	Mother	Father	Mother	Father	Mother	Father
Birmingham data	7	2	1	2	8	4
Carter and Powell (1954)	5	6	1	0	6	6
Nielsen (1954)	0	0	3	6	3	6
Total	12	8	5	8	17	16

* = operated, † = treated medically for pyloric stenosis

Table 2 the results are combined with those of the two previous series. In 17 of 33 families in which pyloric stenosis was diagnosed in the parent of a patient, it was the mother who was affected. The diagnosis was confirmed at operation in 20 parents, of whom 12 were mothers and eight fathers.

It will be recalled that the proportion of males among children with pyloric stenosis (about 80%) has been remarkably constant in all published series, and it would therefore be expected that the number of fathers affected would be approximately four times as great as the number of mothers. The difference between the observed (52%) and expected (20%) proportions of mothers in this rather small series is highly significant ($32 \pm 7\%$).

Before discussing the interpretation of this observation we must consider the possibility that it arises from a defect in the method of collecting the data. Most of the familial cases were derived from hospital records, provided as a rule by the mother, whose knowledge of her husband's childhood illnesses may be less complete than her knowledge of her own. In an attempt to discover whether the number of affected fathers was deficient, questionnaires were sent by post to fathers of 394 patients treated for pyloric stenosis at the Birmingham Children's Hospital in the years 1950-54. Notes of these patients had previously indicated that three mothers were certainly, and one father possibly, affected. Replies were received from 321 fathers (54 other questionnaires were returned uncompleted because of a change of address). No further examples of affected fathers were ascertained. Five fathers stated that their wives had been affected. Three of these cases had previously been identified from hospital notes; both the new cases were said to have been operated on for pyloric stenosis, although it was possible to inspect operation notes in only one of them. It is concluded that there is no reason to suppose that the number of affected fathers is deficient.

Several possible explanations can be suggested for the observation that the proportion of mothers among affected parents is much higher than the expected 20%. (a) The proportion of males among patients with pyloric stenosis may have been lower in the period 1920-30 than it is today. (b) Survival rates may have been higher for female than for male patients. (c) Fertility may be greater in affected females than in affected males.

The first two possibilities can be dismissed by examination of the sex ratio of the patients treated at the earlier period and traced. In our own series there were 89 males and 23 females; Carter and Powell (1954) traced 73 and 12, and Nielsen (1954) 73 and 22, males and females respectively. The proportion of males is approximately as would be expected if the sex ratio were the same at the earlier period and if there were no appreciable sex difference in survival rates.

There is also no reason to believe that fertility was lower in men than in women. In our own series the 89 patients had 26 children, and the 23 females had three. Carter and Powell recorded 39 children of 73 affected fathers, and seven of 12 affected mothers. (This information was not given by Nielsen.) In the two series combined, 162 males had 65 children (0.40 per father) and 35 females had 10 (0.29 per mother). On this evidence fertility is somewhat lower in women than in men, and, since mean age at marriage is probably also lower, it is possible that the difference in fertility between the sexes is a little greater than the data suggest.

It is concluded that the risk of pyloric stenosis is considerably greater (at least four times) in children of affected mothers than in children of affected fathers.

Incidence in Offspring when Parent and Child are Affected

The incidence of pyloric stenosis in children of affected parents was given above as 6.9% (14 in 203). In families where one child is affected the incidence in other children is evidently much greater than this. Eight of the 33 second-generation fraternities shown in Table 2 contained more than one affected member.

All 33 fraternities are identified by the presence of at least one affected child. In these circumstances the numbers of affected children to be expected in the fraternities on the assumption that the risk is the same as that experienced by all children of affected parents (6.9%) has been estimated (Table 3) by a method described by Hogben (1931). The number of affected children observed (42) is higher than the expected number (34.3). By the same method it is possible to show

TABLE 3

OBSERVED AND EXPECTED NUMBERS OF CHILDREN WITH PYLORIC STENOSIS IN FAMILIES WITH A PARENT AND CHILD AFFECTED

Size of Family	No. of Families	No. of Children	Number of Children Affected	
			Observed	Expected*
1	11	11	11	11.00
2	14	28	19	14.50
3	4	12	5	4.29
4	3	12	4	3.33
6	1	6	3	1.19
Total	33	69	42	34.31

* Expected proportions affected for each family size are:

$$\frac{r}{1-(1-r)^s}$$

where r is the risk to children, and s is family size (Hogben, 1931).

that in these fraternities, distinguished by the presence of pyloric stenosis in parent and child, the proportion of the children who may be expected to have the disease is 39%. Clearly the risk is not spread uniformly among all offspring of parents who have had pyloric stenosis, but is highly localized in certain families.

Discussion

Until recently it was thought that infantile hypertrophic pyloric stenosis was attributable to a recessive gene whose manifestation is influenced by sex and birth order (Cockayne and Penrose, 1943). McKeown, MacMahon and Record found no evidence to support the recessive hypothesis (1951) and showed that the post-natal environment affects both time of onset of symptoms and the increased risk experienced by first-born children (1952). Nevertheless, it is still widely believed that pyloric stenosis is an inherited condition whose aetiology can profitably be discussed in terms of a simple genetic hypothesis. Evidence from three sources has been thought to support this conclusion: investigations of familial incidence; comparison of the frequency of concordance in monozygous and dizygous twins; and examination of relative incidence in male and female children.

That the incidence of pyloric stenosis is raised in certain families is shown by the increased risk experienced by (a) brothers and sisters of an affected child (Cockayne and Penrose, 1943; McKeown *et al.*, 1951), and (b) children of affected parents (Carter and Powell, 1954; Nielsen, 1954). But it by no means follows that the familial tendency is genetically determined. Many features of the post-natal environment must be common to consecutive children of the same mother, and whether the increased risk in later sibs of an affected child is attributable mainly to a common inheritance or to

a common environment is at present an open question. Nor is it difficult to conceive that the early post-natal environment of a child is in some cases identified with that of its parents; the occasional presence of a grandmother is sufficient to ensure this. But perhaps the strongest reason for doubting whether the increased incidence of pyloric stenosis in children of affected parents is determined by inheritance is that the risk is greatly increased if the affected parent is the mother. It is also clear that the risks are by no means equal in all families in which a parent has had the disease, but are highly localized in certain families. These observations cannot be reconciled with any simple genetic hypothesis; they are readily explained if the varying risks of the disease are determined by the environment.

It has also been thought that when pyloric stenosis occurs in one twin, the other twin is almost invariably affected if the pair is monozygous and rarely affected if it is dizygous (Sheldon, 1938). A number of exceptions to this generalization have now been reported, and indeed examination of a representative series suggested that the frequency of concordance is probably about the same in monozygous and dizygous twins (MacMahon and McKeown, 1955). The previous result is apparently attributable to the unrepresentative character of twin pairs reported in the literature.

As evidence of the influence of inheritance on the origin of pyloric stenosis, we are left with the undoubted higher incidence in male than in female children. But several features of the condition are incompatible with sex-linked inheritance, and the sex difference in incidence must presumably be attributed to genetic processes whose nature cannot be specified. In this respect pyloric stenosis is characteristic of a class of diseases, of which peptic ulcer is an example, in which susceptibility is different in the two sexes, but is certainly not due to a single gene.

Summary

One hundred and twelve living patients in whom the diagnosis of pyloric stenosis was confirmed by operation at the Birmingham Children's Hospital in the period 1920-34 were traced in 1955. They had 29 children, none of whom had pyloric stenosis. By combining these results with those from two reported series, the incidence of the disease in children of affected parents is estimated as 6.9%.

Ten cases of pyloric stenosis in parent and child were obtained from current records of children treated at the Birmingham Children's Hospital. By inspection of notes of 2,579 patients treated in

hospitals in Liverpool, Manchester, Newcastle-on-Tyne and Sheffield a further two examples of the disease in parent and child were ascertained. In eight of the 12 families the affected parent was the mother. When the results are combined with those of two published series there are 33 families; in 17 the mother was affected. Since pyloric stenosis is much more common in males than in females it is concluded that the risk of the disease is considerably greater (at least four times) in children of affected mothers than in children of affected fathers.

It is also shown that the risk of pyloric stenosis is not spread uniformly among all offspring of parents who have had the disease, but is highly localized in certain families. Among children in families in which a parent and one child have been affected, the proportion exhibiting the disease is approximately 40%.

It is suggested that these results are inconsistent

with a simple genetic hypothesis, and are more plausibly attributed to the influence of the early post-natal environment.

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