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Epidemiology of congenital innervation defects of the distal colon

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Summary. Congenital colorectal innervation defects were evaluated by studying 3699 colonic mucosal biopsy specimens obtained from 773 patients over a 5-year period (1986–1991). In 358 cases (46.3%) a classifiable defect was present, with aganglionosis in 187 of these patients (52.2%) and hypoganglionosis of the colon in 18 (5.0%). Hypoplastic or aplastic sympathetic innervation (type-A neuronal intestinal dysplasia was found in 2.2% ($n=8$) and dysplasia of the parasympathetic submucous plexus (type-B neuronal intestinal dysplasia) in 40.6% ($n=145$) of the patients with classifiable defects. Identification of a specific innervation defect was not possible in 229 of the 773 patients (29.6%), 28% of whom exhibited slight dysplasia and 30% immaturity or hypogenesis of the submucous plexus. In 40% of the unclassifiable cases heterotopic nerve cells were found in the muscularis mucosae and/or lamina propria mucosae, while 2% had severe heterotopia with the cells of the myenteric plexus completely displaced into the circular and/or longitudinal muscle layers. These patients generally suffered from severe chronic constipation requiring surgical intervention. Four congenital innervation defects of the colorectum can thus be clearly differentiated at present: aganglionosis (in its various forms), hypoganglionosis, type-A neuronal intestinal dysplasia, and type-B neuronal intestinal dysplasia.

Key words: Hirschsprung's disease – Neuronal dysplasia – Hypoganglionosis – Colorectal innervation defects – Epidemiology

Introduction

More reliable diagnosis of Hirschsprung's disease using histochemical techniques to visualize acetylcholinesterase-positive structures (Meier-Ruge and Morger 1968; Meier-Ruge et al. 1972; Kreiner 1976; Chow et al. 1977; Lake et al. 1978; Dale et al. 1979; Hinkel et al. 1989) has stimulated intense interest among paediatric surgeons in the last few years in the diagnostic use of large bowel mucosal biopsies. Aganglionosis is not the only disease entity studied, as the use of these methods has permitted improved characterization of other innervation defects, such as neuronal intestinal dysplasia (Meier-Ruge 1971, 1990; Reifferscheid and Flach 1982; Fadda et al. 1983, 1987a; Heitz and Komminoth 1990), neurogenic achalasia of the anal sphincter (Müntefering et al. 1986; Fadda et al. 1987b; Welskop 1989) and ultra-short-segment Hirschsprung's disease (Meier-Ruge 1985; Meier-Ruge and Schärli 1986).

Neuronal intestinal dysplasia (NID) is a defect of autonomic neurogenesis that occurs in two forms. These are characterized, respectively, by rudimentary or absent sympathetic innervation of the gut (type A; NID A) and by dysplasia of the submucous plexus with defective neuron and nerve fibre differentiation (type B; NID B) (Fadda et al. 1983, 1987a; Meier-Ruge 1985, 1990; Heitz and Komminoth 1990).

Based on examination of colonic mucosa biopsies over the past 5 years, reliable diagnostic criteria are proposed for the various congenital colorectal innervation defects, notably NID B, which is clearly much commoner than was thought.

Materials and methods

Between 1980 and 1990 we examined a total of 4554 tissue specimens from 1012 patients comprising unfixed mucosa biopsies of the colon or resected tissue. Most of the specimens (98%) were from the distal colorectum. From this material we limited our review to 3699 biopsies from a total of 773 patients seen in the last 5 years (1986–1991). All the specimens were obtained from children who had already undergone scrupulous clinical and manometric investigation, so that the number of cases with a normal innervation pattern was relatively small.

Serial sections with a uniform thickness of 15 μm were prepared from the unfixed biopsies in a cryostat. The use of serial sections was designed to facilitate evaluation of the submucosa by avoiding errors due to the relatively uneven distribution of ganglia in the submucous plexus.

The parasympathetic nerve fibres and ganglia were visualized by acetylcholinesterase (AChE) staining according to the method

of Karnovsky and Roots (1964), while the nerve cells of the submucous and myenteric plexuses were visualized selectively by staining for lactate dehydrogenase (LDH) using the method of Hess et al. (1958). This was particularly useful in that it enabled even smaller nerve cells to be differentiated from Schwann cells. Staining for succinate dehydrogenase (SDH; Nachlas et al. 1957) enabled mature, fully developed nerve cells to be distinguished from immature or hypogenetic cells, which only stained in the LDH reaction. Haematoxylin and eosin staining was not performed, as in our view it is inferior in its diagnostic value to AChE visualization combined with haemalum counterstaining.

Immunohistochemical methods for identifying ganglion cells by staining for neuron-specific enolase and S100 protein or synaptophysin were likewise eschewed as being more difficult to perform, more time-consuming and less specific than enzyme histochemistry (Heitz and Komminoth 1990). While such methods are excellent for demonstrating histogenetically identical structures, they do not permit functional evaluation like increased AChE activity in Hirschsprung's disease.

The incubation times were 30 min for LDH and 90 min for AChE and SDH (at a temperature of 37° C). The enzyme-histochemical technique employed has been described in detail elsewhere (Meier-Ruge 1972, 1982; Borchard et al. 1991), as have the recognition and interpretation of artefacts in colonic mucosa biopsy specimens (Meier-Ruge 1982).

Results

Five diagnostic groups were identified on the basis of examination of the 3699 biopsy specimens (Table 1). In 358 cases (46.3%) a classifiable innervation defect was diagnosed, that is, aganglionosis, hypoganglionosis or

Table 1. Breakdown of case material

Classifiable dysganglionoses ($n=358$)	46.3%
Unclassifiable dysganglionoses ($n=229$)	29.6%
Biopsies unsuitable for diagnostic purposes ($n=90$)	11.6%
Repeat biopsy examinations ($n=42$)	5.5%
Normal innervation ($n=54$)	7.0%

Table 2. Classification of congenital malformations of colorectal innervation (46.3% of the investigated patients, $n=358$)

1. Aganglionosis ($n=187$)		52.2%
a) Hirschsprung's disease (isolated form)	22.9%	40.8%
b) Hirschsprung's disease with proximal NID B	17.9%	
c) Total aganglionosis of the colon	2.5%	
d) Ultrashort Hirschsprung's disease	5.0%	8.9%
e) Neurogenic achalasia of the internal sphincter	3.9	
2. Hypoganglionosis ($n=18$)		5.0%
3. Neuronal intestinal dysplasia type A (NID A) ($n=8$)		2.2%
4. Neuronal intestinal dysplasia type B (NID B, isolated form, $n=145$)		40.6%

NID (Table 2), while in a further 229 cases (29.6%) there was an abnormality of autonomic innervation which could not be assigned to any of these categories. In 90 patients (11.6%) the biopsy material had been taken too superficially, so that, apart from excluding aganglionosis, further diagnostic appraisal was not possible. In 42 cases the material was from patients undergoing repeat biopsy examination on clinical grounds, and 54 patients (6.9%) had normal findings.

Just over half (52.2%) of the 358 patients with a classifiable dysganglionosis exhibited aganglionosis. A further 40.6% had isolated NID B (Table 2) characterized by a malformation of the parasympathetic submucous plexus showing such classic features as hyperplasia (Fig. 1) and giant ganglia with 7–15 nerve cells (Fig. 2). There were also nerve cell buds along large afferent para-

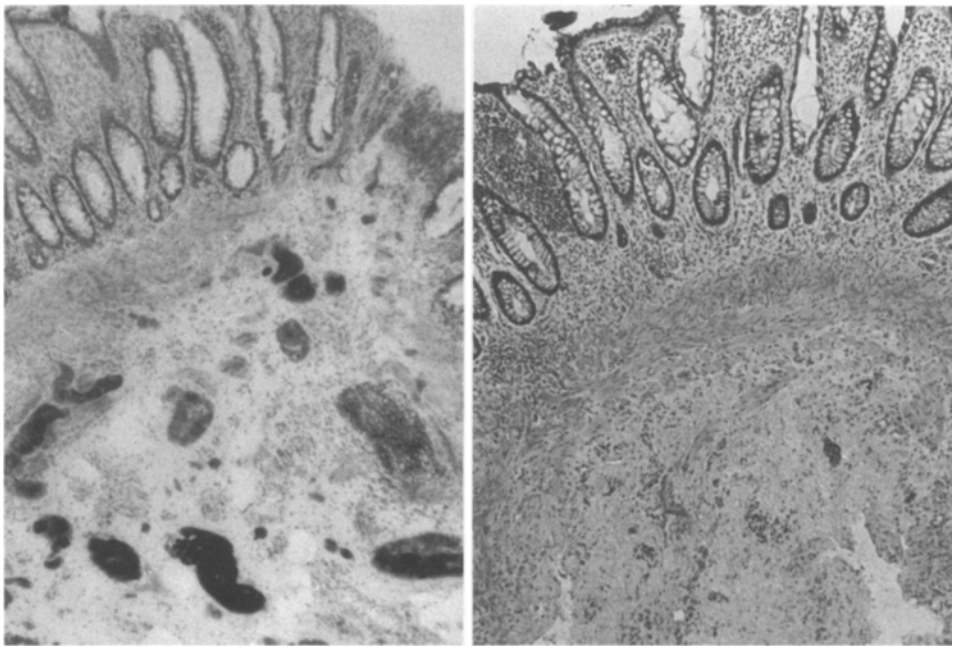

Fig. 1. a Typical picture of type-B neuronal intestinal dysplasia (NID B) with massive hyperplasia of the submucous plexus and giant ganglia. Acetylcholinesterase (AChE) with haemalum counterstain, ×35. **b** Normally innervated colonic mucosa with a small ganglion in the centre. AChE with haemalum counterstain, ×35

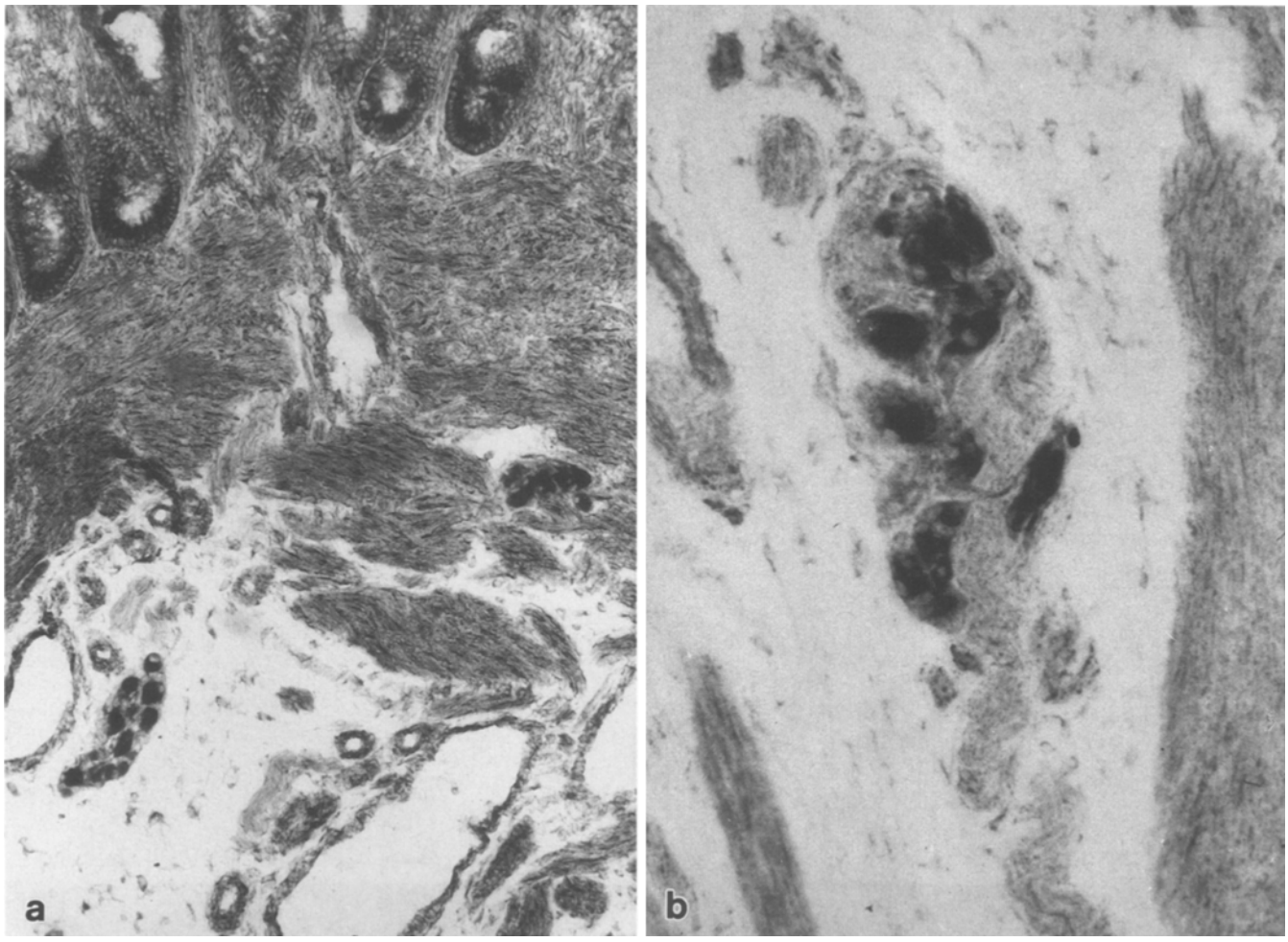

Fig. 2. **a** Colonic mucosa in NID B showing giant ganglia, some of which are located in the muscularis mucosae. Lactate dehydrogenase (LDH), ×90. **b** Single giant ganglion with nerve cells. Selective visualization by succinate dehydrogenase reaction, ×360

sympathetic fibres, and nerve cells or groups of nerve cells within afferent fibres was a common finding. These anomalies were accompanied by the presence of heterotopic submucous plexus neurons in the muscularis mucosae and/or lamina propria mucosae. NID A, which is characterized by congenital aplasia or hypoplasia of sympathetic innervation affecting the myenteric plexus, submucous arterial vessels and mucosa, was much rarer, with the lowest prevalence of all at 2.2%. Biopsy specimens from NID A patients were characterized by ulcerative colitis or inflammatory changes penetrating as far as the submucosa. There was also focal destruction of the muscularis mucosae, a result of the accompanying ulcerative colitis.

Ultrashort-segment Hirschsprung's disease (aganglionosis of the distal 3–4 cm above the pectinate line) or neurogenic achalasia of the anal sphincter was seen in 9% of the patients.

An interesting finding was that in about half the cases of Hirschsprung's disease there was associated proximal neuronal dysplasia of the submucous plexus (NID B) (Table 2) and in approximately one-third of the total number cases of NID B ($n=209$) Hirschsprung's disease was also present ($n=64$).

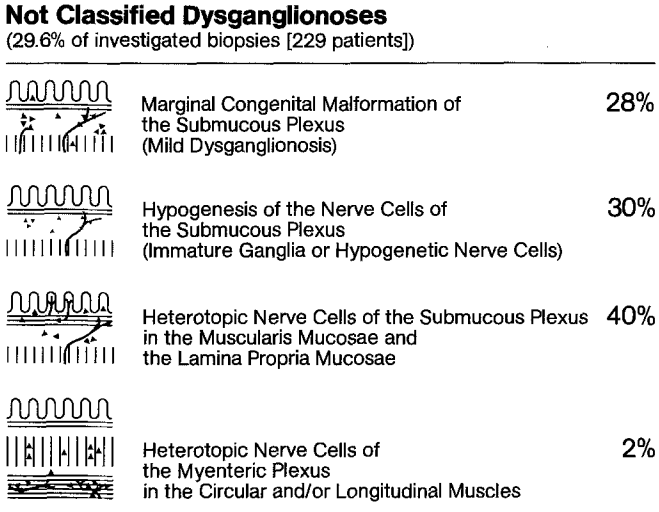

Fig. 3. The group of non-classified dysganglionoses includes mild or marginal cases of neuronal dysplasia. Heterotopic nerve cells of the submucous plexus in the muscularis mucosae and/or lamina propria mucosae is extremely common and seems to represent a normal variant. One-third of all unclassifiable dysganglionoses exhibit neuronal hypogenesis in the submucous plexus. Heterotopia of the myenteric plexus is rare and generally associated with severe impairment of propulsive intestinal activity

Table 3. Classification of 358 cases of congenital dysganglionosis of the colon by sex and age at diagnosis

	n	♂♂ *n*	Median age at diagnosis	♀♀ *n*	Median age at diagnosis	♂♂:♀♀
1. *Aganglionosis*						
a) Hirschsprung's disease (isolated form)	82	61	4.4 [4.0– 9.0 months]	21	4.1 [4.0– 5.0 months]	3:1
b) Hirschsprung's disease with NID B	64	48	13.4 [6.5–22.0 months]	16	10.7 [2.0–15.5 months]	3:1
c) Total aganglionosis of the colon	9	4	1.5 [1.5–11.2 months]	5	4.4 [4.4–11.1 months]	1:1
d) Ultrashort Hirschsprung's disease	18	17	2.0 [30% 7–34 years]	1	9.0 months	
e) Neurogenic sphincter achalasia	14	6	4.5 years [1.5–8 years]	8	4.0 years [1–8 years]	1:1
	187					
2. *Hyperganglionosis*	18	14	8.0 years [1.5–21 years]	4	26.0 years [2–52 years]	3.5:1
3. *Neuronal intestinal dysplasia type A (NID A)*	8		5 5.0 months	3	3.0 months	
4. *Neuronal intestinal dysplasia type B (NID B)*	145	72	1.5 years [50% 1–12 months] [50% 1–12 years]	73	1.5 years [50% 1–12 months] [50% 1–9 years]	1:1
	358					

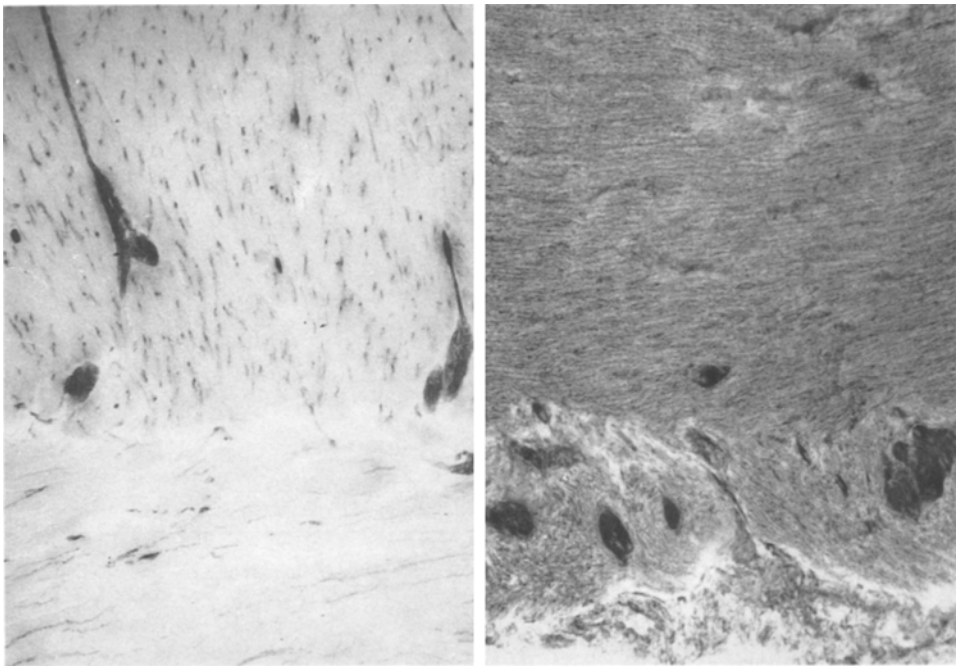

Fig. 4. a Marked heterotopia of myenteric plexus neurons with more cells in the circular muscle than in the plexus stratum itself. LDH reaction, ×90. **b** Heterotopia of myenteric plexus in the longitudinal muscle, with "rarefaction" of the plexus between the circular and longitudinal muscle layers. AChE, ×90

Hypoganglionosis is a relatively rare malformation, which accounts for only 5% of all classified congenital innervation defects of the colon. Its principal features are a very low overall level of AChE activity in the colonic mucosa, a significant deficiency of nerve cells in the myenteric plexus, and hypertrophy of the muscularis mucosae and circular muscles.

Neurogenic sphincter achalasia resembles Hirschsprung's disease as far as the internal sphincter is concerned, with increased AChE activity in parasympathetic fibres. However, there is also an increased number of fibres with a high AChE activity in the anal subcutis.

A breakdown of the findings by sex (Table 3) suggests that both Hirschsprung's disease (with and without NID B) and hypoganglionosis occur three times more frequently among male than female children. By contrast, the sex distribution of the other dysganglionoses appears to be equal, with only NID A possibly more common among males, although the number of cases was too small for any definite conclusion to be drawn. NID B is clearly evenly distributed between the sexes, but the finding that as many cases are diagnosed in the 1st year of life as in later childhood is notable.

The 229 patients with unclassifiable dysganglionosis (Fig. 3) included 91 with heterotopia of neurons of the submucous plexus in the muscularis mucosae and lamina propria mucosae, 66 with mild dysganglionosis and 5 with marked heterotopia of myenteric plexus neurons in the circular and longitudinal muscle layers (Fig. 4)

associated with severe impairment of colonic motility. The remainder (30%) had hypogenesis of nerve cells of the submucous plexus characterized by a number of very small AChE-positive ganglia showing extremely small nerve cells in the dehydrogenase reaction. An immature submucous plexus has no or very few developed nerve cells, while in the LDH reaction most or all ganglia show multinuclear cell complexes with a very low enzyme activity. Multinuclear ganglia have a higher nuclear than cytoplasmic volume and differentiation between nerve cells and Schwann cells is not possible.

Discussion

Findings based on aggregated colonic mucosa biopsy data vary enormously depending on the clinicians requesting the procedure. Some prefer to take biopsies routinely and thus submit a high proportion of normal samples to the pathologist for diagnostic evaluation, while others are more conservative and tend to resort to biopsy only when it is more or less certain that a definite abnormality or treatment-resistant constipation is present. Nevertheless, determination of the frequency distribution of the various innervation defects among the dysganglionoses provides a relatively good measure of their prevalence.

While the criteria for a diagnosis of aganglionosis based on increased AChE activity in the extramural parasympathetic nerve fibres are now generally acknowledged (Meier-Ruge 1974; Chow et al. 1977; Munakata et al. 1978; Lake et al. 1978, 1989; Causse et al. 1987; Schofield and Yunis 1991), opinion still diverges to some extent on what constitutes NID with dysplasia of the submucous plexus (NID B) (Schofield and Yunis 1991). The argument should have been virtually settled by the recent morphometric characterization of NID B (Käufeler 1991), in which ganglion density was found to be twice and ganglion size four times as great in 30 cases of NID B as in 30 normal controls. The nerve cell count in the ganglia of the submucous plexus correlated with the size of the ganglia and was generally between 7 and 13 in NID B, as against 4 ± 1 in normal cases.

Biopsy specimens from infants with NID B invariably show elevated AChE activity in nerve fibres of the lamina propria mucosae and/or muscularis mucosae, as well as in the adventitia of submucosal arteries (Meier-Ruge 1985, 1990; Lake et al. 1989). As a rule this finding disappears with advancing age, with only the increased activity in the nerve fibres of the circular muscle layer remaining detectable, sometimes even into adulthood. The same pathogenetic cause may be assumed to be responsible for NID B as Hirschsprung's disease, as documented by the frequent association of the two disorders (Gulotta and Straaten 1977; Puri et al. 1977; Kessler and Campell 1985; Heitz and Komminoth 1990); and, according to current thinking, this is assumed to lie in deficient production of trophic factors by the muscular wall of the gut (Burnstock 1981; Le Douarin 1981; Meier-Ruge 1983). The present findings provide further evidence for a common pathogenic principle, since half of all cases of Hirschsprung's disease were associated with proximal NID B (Table 2).

Assuming that the migration of neuroblasts from the myenteric plexus into the submucosa represents the final developmental step in the autonomic innervation of the gut, it is obvious that dysplasia of the submucous plexus is almost as likely to occur as aganglionosis of the Hirschsprung type. As long as the characteristics of NID B remained in dispute, however, diagnosis was far less straightforward, making it likely that the reported prevalences were considerable underestimated (Meier-Ruge 1985; Briner et al. 1986; Heitz and Komminoth 1990; Schofield and Yunis 1991). Current figures indicate that isolated forms of congenital dysplasia of the submucous plexus (NID B) occur with much greater frequency than previously thought (Meier-Ruge 1985), and in the present series association was found in only one-third of cases.

The clinical course of NID B is insidious, with progressive development of severe constipation similar to that in Hirschsprung's disease, though painful defaecation is rare. The final stage involves overflow incontinence (Schärli 1992). NID A, on the other hand, is characterized by bloody stools combined with the symptomatology of functional ileus. The course is dramatic and early surgical intervention is usually required on account of the accompanying colitis (Schärli and Meier-Ruge 1981). NID B has been reported to take a particularly unfavourable course if the condition is associated with dysgenetic heterotopia of nerve cells of the submucous plexus in the muscularis mucosae or with an increased number of immature ganglia. In cases of NID B with well-developed nerve cells, however, adequate propulsive activity of the distal gut often develops during the first 6 months of life (Schärli 1992). The mean age at diagnosis of NID B was 1.5 years (Table 3) and 50% of the children investigated were between 1 year and 12 years old. This shows that primary chronic constipation is compatible with life. It may also explain why Hirschsprung's disease associated with NID B is so often diagnosed at a much later age than the "pure" form. A possible reason might be that it is masked by the low propulsive activity of the colon due to NID B.

In conclusion, following a period of severe constipation during the first 6–12 months of life, the clinical course of NID B normally shows a spontaneous recovery of colon motility (Pistor and Hofmann-von-Kap-herr 1984; Pistor 1990; Schärli 1992) and only about 10% of patients require mechanical sphincter dilatation or invasive surgical intervention. So far it is not known how many patients showing morphological characteristics of NID B develop chronic constipation in later life. Since NID B is often characterized by extremely sluggish propulsive activity of the colon, it might be expected to occur in adults with idiopathic chronic constipation, and recent findings have confirmed this (Stoss 1990; Wiebecke and Müller-Lissner 1990). Neurogenic sphincter achalasia and hypoganglionosis are also usually diagnosed in later childhood, the reason for eventual

biopsy exploration being the more or less severe fluctuating course of constipation.

Turning to the non-classifiable innervation defects, the finding of heterotopic submucous plexus nerve cells in the muscularis mucosae and lamina propria mucosa (see Fig. 3), which is often a concomitant of NID B, is probably within the range of normal variation in cases where relatively few cells are involved. Where they are numerous, however, they must be considered pathological and the evidence of the present series suggests that this finding is normally associated with constipation, since recurrent constipation was the reason for biopsy in all the patients concerned. In some extreme forms heterotopic neurons of the myenteric plexus in the circular and longitudinal muscles contain practically no plexus in the "space" between the two layers of muscle (Fig. 4). As a rule such patients exhibit such severe impairment of colonic motility that surgical intervention is the only option.

The question of whether hypogenesis of the submucous plexus is simply a matter of immaturity or whether it represents a genuine developmental defect (Ikeda et al. 1988) remains open and further clarification must await morphometric follow-up studies. Normalization has been reported during childhood development in some cases (Pistor et al. 1987), but in others there was no change by the age of 2–4 years.

Many questions likewise remain unanswered where NID B is concerned, particularly the fact of the significant divergence between clinical course and biopsy findings (Munakata et al. 1978; Schärli and Meier-Ruge 1981; Briner et al. 1986; Pistor et al. 1987; Bussmann et al. 1990; Harms and Bertele-Harms 1990; Heiming and Glück 1990; Schmidt and Schmittenbecher 1990; Kunde et al. 1991). Here, the onus must lie on morphometric analysis to discover better correlations between biopsy and clinical features.

The milder forms of non-classifiable innervation defect include many different degrees of NID B since, from the developmental point of view, it is obvious that nerve cell migration into the submucosa may range from the definitely pathological to the almost normal. Here again, further systematic application of morphometric techniques should make it possible to define the limit between the normal and the pathological.

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