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Editorial

Intestinal neuronal dysplasia: does it exist or has it been invented?

C.L. Berry

Department of Morbid Anatomy, The Royal London Hospital, Whitechapel, London E1 1BB, UK

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Intestinal neuronal dysplasia (IND) was first used as a term to describe a clinical entity by Meier-Ruge in 1971. He reported parasympathetic hyperganglionosis in patients with symptoms of colitis or intestinal obstruction and in 1974 expanded the pathological concept to include hyperplasia of the submucosal and myenteric plexuses with the formation of giant ganglia, hypoplasia or aplasia of the sympathetic innervation of the myenteric plexus and the presence of isolated ganglion cells in the lamina propria and between the muscle fibres of the muscularis mucosa (Meier-Ruge 1974). Other workers (Munakata et al. 1985; Briner et al. 1986), as well as the original author and his co-workers, have further described this entity and suggested that it is as common as Hirschsprung's disease itself.

In a recent review of experience at the Children's Hospital of Pittsburg, Schofield and Yunis (1991) examined 498 consecutive rectal biopsies. They identified IND by the following criteria: slight to moderate increase in acetylcholinesterase-stained fibres within the lamina propria (and/or muscularis mucosa) and either greater than five submucosal ganglion cell clusters per high powered field or large (greater than ten cells) clusters of submucosal ganglion cells. There were 61 cases of Hirschsprung's disease and 38 biopsies satisfying the criteria adopted, which seem to be ones which might be adopted as the basis of reasonable comparison between pathologists; this cannot be said of the criteria used by other authors. They found no consistent clinical pattern in those affected but were able to identify an increased frequency of twin gestation and prematurity, of the meconium plug syndrome and also noted 5 cases of gastrointestinal morphological abnormality. Formula/protein-sensitive enteropathy occurred in 9 cases. As Schofield and Yunis point out, these findings have all been previously associated with changes satisfying their criteria for IND. On reading their clear paper, which discusses other factors associated with positive findings in the biopsies, it is difficult to disagree with the conclusion that the term IND "is at best a descriptive histopathological appearance rather than a unique clinicopathologic entity".

A further report from the Hospital for Sick Children, Great Ormond Street, identified only 7 cases in 2420 patients biopsied between 1975 and 1991 (Smith 1992) compared with 54 in the much smaller series of 115 patients reported by Schärli (1992), a range of 0.3–62%. What then should we make of the large study reported in our journal by Meier-Ruge (1992)? This author, after examining 3699 biopsies, describes four types of innervation defects, aganglionosis and hypoganglionosis and two types of IND. The common type of the latter (type B) resembles that described by the criteria of the Pittsburg paper and the author noted that in many (around one-third) cases of Hirschsprung's disease type B IND was also present. He also found many minor anomalies in 229 patients with what is described as unclassifiable dysganglionosis, including heterotopias of neurons and plexus.

If a common pathogenesis for these defects exists, as suggested by Meier-Ruge, it is difficult to see how it operates in terms of the newer experimental findings on the development of the innervation of the gut. Suggestions of a "deficient production of trophic factors" in the wall of the gut are vague and unhelpful and the assumption that a (non-exclusive) association of the IND type B with Hirschsprung's disease indicates a common pathogenesis is not valid. Disagreement about correlations with clinical findings can only be resolved by clinical studies, but recent fundamental findings about gut development pose some problems for any proposed generalised pathogenesis.

The new genetics has established a novel pattern of investigation of disease, rather as Koch's postulates were established in the last century – but with the additional benefit of providing pointers to therapy. The process of increasing our knowledge of abnormalities of development runs along the track of identifying a gene locus, characterising the gene products and their functions biochemically, developing animal models of the disease under study using transgenic techniques for further investigation and, ultimately, using stem cell biology to develop approaches to therapy. Not all of the steps are taken in all instances and they are not taken in a given

order but each provides intriguing data, whenever performed.

A previous editorial has commented on how ectopic expression or inhibition of expression of regional homeotic genes has profound morphogenetic effects (Berry 1992). The work of Wolgemuth et al. (1989) in inducing over-expression of the homeobox gene *Hox*-1.4 in the mouse resulted in a phenocopy of Hirschsprung's disease with failure of the innervation of the large bowel manifest as hypoganglionosis and megacolon, apparently due to failure either of neural crest cell migration or failure of gut mesenchyme to provide appropriate signals for migration (the gene is also expressed in mesenchyme). How does this finding relate to the pathogenesis of Hirschsprung's disease in Man and what does it tell us about the problem of IND – an entity whose existence is disputed by some and documented in detail by others?

The enteric nervous system (ENS) is composed of neural and glial cells derived from the neural crest, a finding now established by a wide variety of methodologies including crest ablation, isotopic tissue transplantation, immunohistochemistry and retroviral or fluorescent labelling of crest cells prior to their migration (see Kapur et al. 1992 for bibliography). Colonisation of the gut by neural crest cells occurs in a proximal to distal sequence and Serbedzija et al. (1991) have shown that sacral neural crest cells contribute to the ENS as well as those of vagal (but not truncal) origin. Within the gut, colonisation occurs in a dorsoventral sequence. In the spotted mouse, a further animal model of Hirschsprung's disease, excessive production of extracellular matrix components apparently restricts migration of neural crest cells into the post-umbilical bowel (Payette et al. 1988). Certain of the matrix changes observed are found in the outer layer of the gut, astride the probable pathway of migration of neural crest derived cells. Payette et al. (1988) provide data which suggest that there is no interference with neuronal migration directly and point out that one population of crest derived cells, the Schwann cells, appears to migrate normally. Support for an effect of mesenchyme on migration is provided by Kapur et al. (1992) who point out that the mesenchyme of the developing colon may provide different clues from the more proximal gut.

So two mechanisms of interference with development exist. One affects the cranio-caudal positioning mechanisms of developing cell populations and might result in a distal deficit. In general, such changes in homeobox expression are sharply demarcated, if developmental studies on the hind brain and upper spinal cord are representative. Hirschsprung's disease is explicable; proximal dysplastic zones are less readily explained. The second mechanism operates locally to interfere with cell migration selectively. Here hypoplastic zones before aganglionic ones are comprehensible. Since the submucosal ganglia form as a result of the migration of neurons from the original myenteric ganglia through the circular muscle (Gershon et al. 1980), changes in these structures might be associated with either failure of development as an epiphenomenon. The association of type A IND (with hypoplasia or absence of the sympathetic innervation) with colitis suggests that the change may not be primary; inflammation extending to the submucosa was described by Meier-Ruge (1992).

It is tempting to ascribe differences in incidence as large as those reported to differences in criteria for diagnosis but scrutiny of the guidelines established by a group of pathologists last year (Borchard et al. 1991) does not suggest that the differences in these series depend on this factor alone. In view of the new animal models available the detailed development of the hindgut should be studied (pre- and post-natally) before the attribution of disease status to what may be, at least in part, changes in a normal developmental framework.

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