Chapter 12
Enteric neuropathies: Yesterday, Today and Tomorrow

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Introduction

A significant proportion of people (approximately 20–30 %) in the Western population experience unexplained gastrointestinal (GI) symptoms referred to as 'functional', i.e. disturbs typically unrelated to underlying major organic diseases. Although generally mild or moderate, a small subset of cases shows GI functional symptoms, i.e. nausea, vomiting, bloating, abdominal distension, intractable constipation and chronic pain, of such severity to hamper normal feeding and compromise considerably patients' quality of life (Thompson et al. 1999). In addition, this subset of patients may also have recurrent intestinal sub-occlusive episodes, which occur in the absence of demonstrable mechanical causes, leading to numerous hospitalizations as well as useless and potentially harmful surgical interventions (Stanghellini et al. 2005). A number of diagnostic approaches, e.g. radiological and manometric tests, revealed severe abnormalities of gut transit and motor coordination

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(Stanghellini et al. 2005; De Giorgio et al. 2011) likely due to changes of the morpho-functional integrity of the enteric smooth muscle (the main effector system of gut propulsion) and/or neuromuscular systems (mainly the enteric nervous system, ENS—a collection of several million neurons that controls the vast repertoire of gut functions, including motility) (Knowles et al. 2013; Furness 2012). The possibility to investigate these severely ill patients with GI full-thickness surgical specimens opened to histopathology as a mean to actually demonstrate the type and extent of derangements occurring in the enteric neuromuscular systems. In this line, the histopathological analyses revealed degenerative or inflammatory abnormalities/loss of ganglia, neuronal cell bodies and nerve endings (and associated glial cells) of the ENS, which taken together can be labeled as 'enteric neuropathies' (ENs) (for review see Knowles et al. 2013; Furness 2012).

Despite consistent progress, the mechanisms of ENs are only partially understood and the therapeutic approaches to these patients (mainly with predominant small bowel involvement, as exemplified in the clinical phenotype referred to as chronic intestinal pseudo-obstruction—CIPO) are mainly supportive, rather than curative (Stanghellini et al. 2005; De Giorgio et al. 2011; Knowles et al. 2013). Histopathological analysis of gut full-thickness biopsies from patients with severe gut dysmotility is expected to improve the knowledge on ENs and pave the way to new management strategies and therapeutic options.

The purpose of this chapter is to review the advancements that have been done in the knowledge of ENs identified in adult patients, starting from a brief historical background, focusing on where are we and where we are headed in terms of future research and related clinical implications. The present paper will cover only adult forms of ENs and the reader is referred to excellent reviews on enteric aganglionosis, i.e. Hirschsprung disease, and other rare congenital forms of ENs (Panza et al. 2012; Laranjeira and Pachnis 2009).

'Yesterday': A Brief Historical Background on Gut Neuropathology

A synoptic view of the major milestones in ENS neuropathology has been reported in Fig. 12.1. The neuropathology of the ENS dates back to the nineteenth century (specifically 1886) when Harald Hirschsprung, a Danish pediatrician, described the disease which still carries its name. He recognized ENS abnormalities, i.e. the absence of myenteric and submucosal ganglia, in newborn babies presenting with congenital megacolon (Hirschsprung 1886). After that milestone finding most of the ENS neuropathology acquisitions revolved around the assessment of colonic tissues obtained mainly in pediatric patients undergoing surgery for megacolon. In those studies, an important advancement was obtained by the application of the Golgi's (or variations of) silver staining technique to better investigate the ENS abnormalities. In that respect, papers published by Whitehouse and Kernohan (Whitehouse and

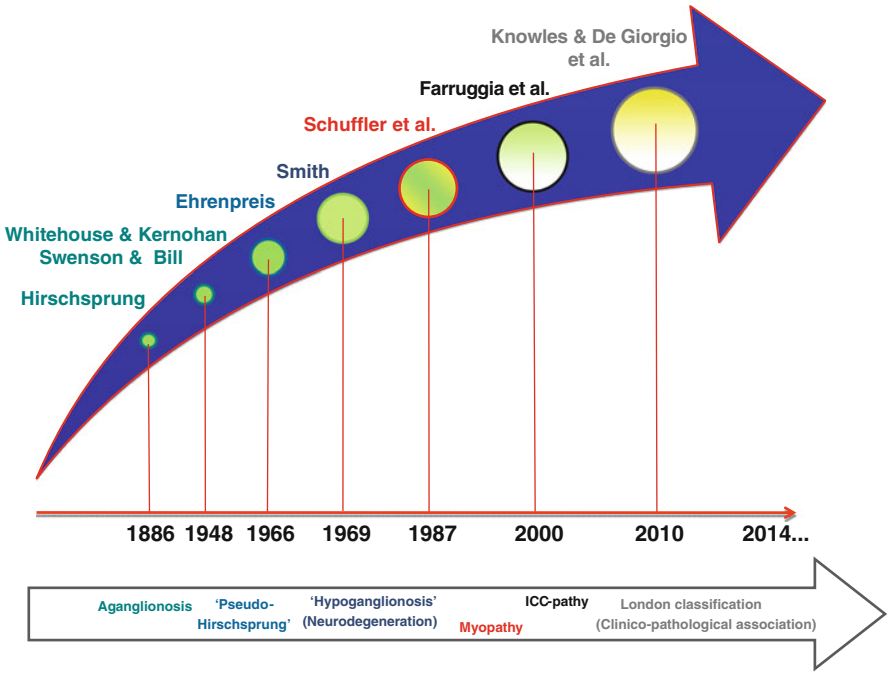

Fig. 12.1 Synopsis summarizing some of the major milestones in ENS neuropathology over the years, i.e. from Hirschsprung's seminal description of congenital aganglionosis of the colon up to the London classification. Colors shown here couple the author(s) (above the *curvilinear arrow*) with the corresponding neuropathological acquisition (reported in the *horizontal arrow*)

Kernohan 1948), Swenson and Bill (Swenson and Bill 1948), and Bodian et al. (Bodian et al. 1949) provided a better definition of the aganglionosis and associated nerve fiber abnormalities in patients with severe gut dysmotility mainly due to massive colonic (and sometimes small bowel) dilatation. Ehrenpreis was the first to introduce the term of 'pseudo-Hirschsprung' to denote the occurrence of cases with megacolon not necessarily associated with aganglionosis (Ehrenpreis 1965); Smith used tangential (not only transverse) cutting of gut specimens for a better evaluation of ENS changes in adult patients with idiopathic megacolon (Smith 1967). During the 1980s, Schuffler and collaborators used silver staining to investigate any case operated on for severe dysmotility and proposed a classification of enteric neuromuscular disorders (Krishnamurthy and Schuffler 1987). Although accurately detailed, this classification progressively lost its value as a result of the overwhelming knowledge emerging from basic studies on enteric neuromuscular structure and function (e.g., milestone work from Farrugia's group (He et al. 2000) as well as (Vanderwinden et al. 1993) and other authors on interstitial cells of Cajal and ENS abnormalities—for review also see (Knowles et al. 2013; Furness 2012; Panza et al. 2012; Laranjeira and Pachnis 2009). Finally, because of the growing knowledge on ENs and the need to provide guidelines on enteric neuropathology, a panel of experts (the

Gastro 2009 International Working Group, IWG) elaborated consensus papers regarding tissue collection, processing, staining and histopathological reporting as well as classification of gut motility disorders and related histopathological features (Knowles et al. 2009, 2010).

'Today': ENs—Where Are We?

Over the years the interest for gut histopathology in patients with suspected ENs has been challenged by the evidence that traditional surgery was commonly associated with a deterioration of the clinical picture characterized by severe impairment of gut motility and the formation of adhesions, thus introducing a mechanical component in a functional GI context. In addition, pathologists often discouraged clinicians as an 'apparently normal' neuromuscular layer was reported even in cases characterized by marked intestinal dilatation. In recent years, however, impressive technological advancements have fully regenerated the physicians' interest for gut full-thickness biopsy in ENs. Several minimally invasive procedures, including laparoscopic surgery or more recently endoscopic approaches (e.g. natural-orifice transluminal endoscopic surgery) (Song et al. 2012) showed a high diagnostic yield and safety (Knowles et al. 2008). Gut full-thickness histopathology should be considered a diagnostic 'gold-standard' as it indicates the possible abnormalities affecting the main control mechanisms regulating gut physiology, including the ENS. The demonstration of histopathological features indicative of ENs may provide not only pathophysiological information but also clinically useful insights regarding diagnosis, prognosis and possible treatment options for patients with severe gut dysmotility.

ENs can be classified as primary when the disease targets primarily the ENS or secondary if the ENS abnormalities are part of a systemic condition with multiorgan involvement (e.g. diabetes mellitus, systemic sclerosis, amyloidosis and other conditions) (Knowles et al. 2013; De Giorgio and Camilleri 2004). Most of the primary ENs are also idiopathic in origin as no evident causes can be identified. In some cases of primary ENs, however, recent data indicate that genetic abnormalities can play an aetiologic role. Herein, primary/idiopathic and genetic ENs will be reviewed, while secondary ENs lack systematic analysis based on gut full-thickness biopsy.

According to histopathological features, primary ENs can be either degenerative or immune-mediated/inflammatory. Degenerative neuropathies are still not completely understood. In fact, some cases may disclose an apparently normal ENS and therefore a quantitative analysis of enteric ganglia and neuronal cell bodies would be required (Accarino et al. 2012). However, quantitative analysis of the ENS is a complex and time-consuming approach not readily feasible in routine pathology. In addition, the lack of normative data in the human ENS contributes to increase the uncertainty experienced by pathologists facing with cases of ENs requiring a quantitative analysis. Quantitative assessment (based on control values of individual laboratories) in ENs may reveal an 'oligoneuronal hypoganglionosis', i.e. a reduced

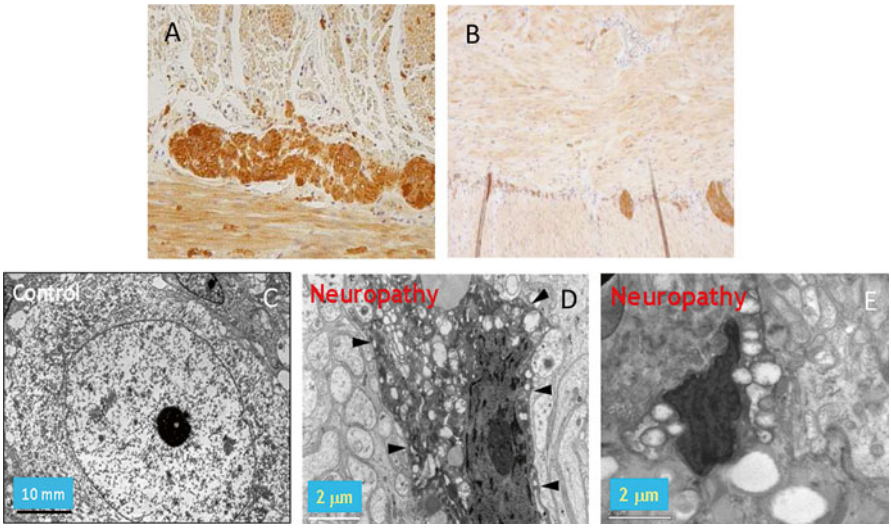

Fig. 12.2 Representative photomicrographs illustrating a small bowel section of a 21-year old female patient with a clinical diagnosis of neuropathic CIPO (**b**) compared to a control (**a**—48 year old female undergoing surgery for uncomplicated right colon cancer). Note the smaller appearance of NSE labeled myenteric ganglia as well as less intensely stained neuronal cell bodies in (**b**) (patient's section) as compared to control (**a**). Streptavidin-biotin complex peroxidase immunohistochemical technique using a specific anti-NSE mouse monoclonal antibody, to identify enteric neuronal cell bodies and processes. Original magnifications X200 in (**a**) and X100 in (**b**). (**d**) and (**e**) (Labeled as 'Neuropathy') are representative electron microscopic photomicrographs taken from the ileum of a 20-year-old man with recurrent sub-occlusive episodes related to a CIPO. Compared to a control picture (**c**), a number of ultramicroscopic abnormalities, including cytoplasmic vacuolization (*arrowheads*), mitochondrial abnormalities (*arrowheads*) and a shrunken nucleus are detectable in (**d**), while an apoptotic body is visible in (**e**). Calibration bars: 10 mm in (**c**); 2 µm in (**d**) and (**e**)

number of myenteric (usually more affected than the submucosal) ganglia and ganglion cell bodies (Wedel et al. 2002). Conversely, a neuropathic pattern may also be identified in conditions characterized by 'giant' enteric ganglia likely due to an increase in the number of neurons (and most likely glial cells) as it occurs in some peculiar disorders with a genetic origin (i.e. ganglioneuromatosis—see below) (Raue and Frank-Raue 2010). Qualitative findings in degenerative ENs include altered expression of a variety of neuronal markers (e.g. neuron specific enolase, NSE; or protein gene product 9.5, PGP9.5; or HuC/D) (Fig. 12.2b) swollen ganglion cell bodies, aberrant mitochondria, cytoplasmic vacuolization (Fig. 12.2d, e), nerve fragmentation and loss of axons (De Giorgio and Camilleri 2004; Wedel et al. 2002; Sarnelli et al. 2005). Neurodegenerative mechanisms in the ENS may include an altered calcium signaling, mitochondrial dysfunction, production of free radicals and neuronal apoptosis (Hall and Wiley 1998). Abnormalities of enteric glial cells also may play a role in enteric ENs, since consistent evidence points to a key

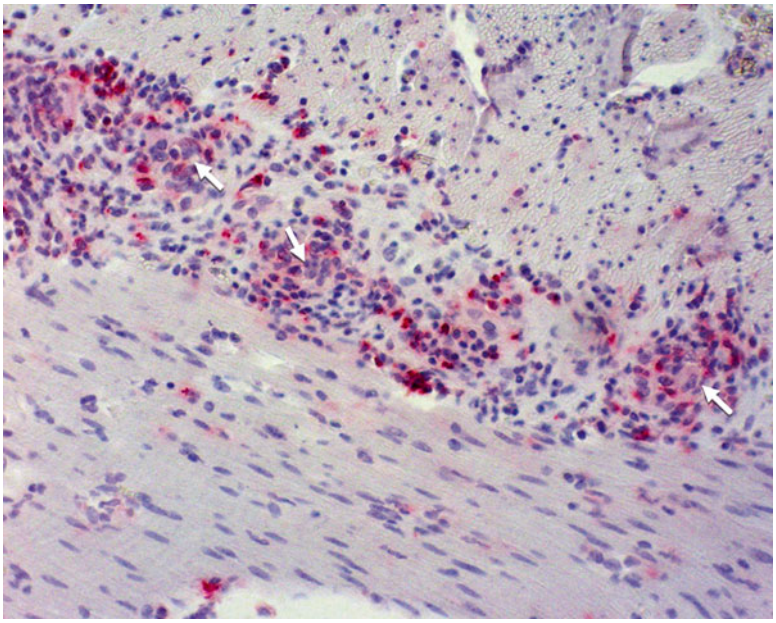

Fig. 12.3 Representative photomicrograph illustrating a small bowel section of a 32-year old male patient with a clinical diagnosis of neuropathic CIPO. The surgical specimen was obtained in the operative room and processed for histopathological analysis. Note the intense immune-mediated (lymphocytic)/inflammatory infiltrate throughout a myenteric plexus of the ileum (hence, 'myenteric ganglionitis'). The *arrows* indicate residual neuronal cell bodies surrounded or in close vicinity to CD8 positive T cells (*pink staining*). The longitudinal smooth muscle layer appears apparently not invaded by immune infiltrate. Alkaline phosphatase antialkaline phosphatase immunohistochemical technique using specific anti-CD8 monoclonal antibodies, to identify a subset of T lymphocytes. Original magnification X200

role exerted by these cells in enteric neuron maintenance and survival (De Giorgio et al. 2012).

Immune-mediated/inflammatory ENs can be due to lymphocytes (mainly CD3+ T cells), eosinophils and mast cells infiltrating the ganglionated plexuses of the ENS (hence the term 'enteric ganglionitis') (De Giorgio et al. 2004). Commonly, immune/inflammatory cells target primarily myenteric as well as axons running throughout the muscular layer of the gut. The definition of lymphocytic ganglionitis is easily applicable when a massive infiltration of lymphocytes can be detected within myenteric ganglia (Fig. 12.3); it is less easily definable in cases with a low-grade infiltrate where a quantitative assessment of the number of lymphocytes may be necessary. The Gastro 2009 IWG proposed that ≥5 lymphocytes/ganglion identify an enteric ganglionitis (Knowles et al. 2009). Overt and low-grade lymphocytic ganglionitis can be identified in severe generalized gut motility disorders (usually CIPO). In two distinct studies on CIPO the analysis of intestinal full-thickness biopsies showed lymphocytic ganglionitis in 29 % (Knowles et al. 2004) and 34 % (Lindberg et al. 2009) of patients. A lymphocytic ganglionitis may be associated

with neuronal degeneration and loss up to complete ganglion cell depletion in the most severe cases. In addition to a cell-mediated response, patients with histopathologic evidence of lymphocytic ganglionitis may develop anti-neuronal antibodies referred to as anti-HuC/D (based on the molecular target) or anti-nuclear neuronal antibodies (ANNA-1) (based on nomenclature) (De Giorgio et al. 2004). In addition to their usefulness in the diagnostic work-up, the anti-HuC/D antibodies are known to affect the ascending reflex pathway of peristalsis in vitro, evoke neuronal apoptosis and elicit autophagic mechanisms in primary culture of myenteric neurons or neuronal cell lines (De Giorgio et al. 2004). Taken together, the lymphocytic infiltrate in enteric ganglia and anti-neuronal autoantibodies provide a basis to understand the origin of severe dysmotility in patients with an inflammatory neuropathy related to generalized dysmotility.

ENs with Genetic Abnormalities

A wide array of genes are now known to regulate enteric neuron migration, development, maturation and maintenance and their mutations in animal models determine ENs often with a syndromic (multisystemic) phenotype (Laranjeira and Pachnis 2009). The genes involved in the pathogenesis of Hirschsprung disease (for review see Panza et al. 2012; De Giorgio and Camilleri 2004) do not appear to play a role in adult ENs except *SOX10*, a transcription factor exerting a key role in neuronal survival and maintenance. Sporadic patients carrying de novo *SOX10* heterozygous mutations showed a clinical phenotype of ENsS with CIPO and features of Waardenburg-Shah syndrome (i.e., pigmentary anomalies and sensorineural deafness) (Pingault et al. 2002). To our knowledge only few histopathologic pictures can suggest genetic disorders, including neuronal intranuclear inclusion disease (NIID), multiple endocrine neoplasia type 2B (MEN-2B) and mitochondrial neurogastrointestinal encephalomyopathy (MNGIE).

NIID may be considered a polyglutamine disease characterized by eosinophilic intranuclear inclusions (the hallmark of the disease) in neurons of the central, peripheral and enteric nervous systems along with progressive degeneration and neuronal loss. Molecular analysis indicates that inclusions contain expanded polyglutamine tracts, immunopositive for ubiquitin and, especially, for small ubiquitin-like modifier (SUMO)-1 (Panza et al. 2012). In cases with predominant autonomic dysfunction the GI tract is involved with a severe dysmotility affecting the esophagus (dysphagia), stomach (gastroparesis) and the whole gut (CIPO). Although most NIID cases are sporadic, occasional familial recurrence indicates a genetic basis, but the responsible gene(s) remains unidentified. NIID overlaps with familial visceral neuropathy, a heterogeneous, poorly defined group of disorders due to abnormalities of the ENS (Kimber et al. 1998).

MEN-2B is a rare autosomal-dominant syndrome characterized by the early development of medullary thyroid cancer in all affected individuals. Pheochromocytomas occur in 50 % of patients along with other features, mainly marfanoid habitus, “blub-

bery lips" (due to mucosal neuromas), and neuromas of the eyelids (Raue and Frank-Raue 2010). A diffuse ganglioneuromatosis, i.e. transmural 'giant ganglia' with increased number of neurons and (likely) glial cells, of the GI tract occurs in about 40 % of patients and is associated with severe constipation/megacolon. A specific germ-line point mutation (methionine → threonine) in *RET* in exon 16 at codon 918 (M918T) occurs in 95 % of patients. Other rarer (5 %) mutations involve exon 15 at codon 883 (A833F) in the *RET* tyrosine kinase domain (Nguyen et al. 2006).

A recessive form of CIPO is the mitochondrial neurogastrointestinal encephalopathy (MNGIE). In addition to severe gut dysmotility, patients with MNGIE manifest with cachexia, ptosis, ophthalmoparesis, peripheral neuropathy and exhibit white matter changes (leukoencephalopathy) on magnetic resonance imaging of the brain. This syndrome is caused by mutations in the thymidine phosphorylase gene (*TYMP*, also known as endothelial cell growth factor-1, *ECGF1*) or in the polymerase gamma gene (*POLG*, a form of MNGIE without leukoencephalopathy). Gut tissue analysis showed that CIPO in patients with MNGIE show a peculiar histopathologic pattern characterized by underlying enteric neuromuscular abnormalities mainly in the small bowel (Giordano et al. 2008).

Finally, in a consanguineous Turkish family, we have demonstrated an autosomal recessive idiopathic form of CIPO in addition to megaduodenum, long-segment Barrett esophagus, and different cardiac abnormalities of variable severity identifiable in the affected members (OMIM 611376; Mungan syndrome) (Mungan et al. 2003). Notably, full-thickness intestinal biopsies from two affected individuals revealed a severe reduction of the myenteric and submucosal neurons, suggesting an underlying intestinal neuro-myopathy. (Deglincerti et al. 2007). Genome-wide linkage analysis and homozygosity mapping approach identified a maximum multipoint lod score of 5.01 in a critical interval of about 13 Mb between D8S1830 and D8S1799 on the chromosome 8q23-q24 (Deglincerti et al. 2007). Using whole exome sequencing analysis we have shown a novel mutation in the *RAD21* gene, cosegregating with the disease phenotype in this family (Bonora et al. 2015). Therefore, it is clear that even severe forms of ENs show a high degree of genetic heterogeneity, hindering the identification of the molecular causes and of the deranged molecular pathways shared by the different affected individuals. Nevertheless, recent advances in omics technologies, including the massive next-generation sequencing approaches leading to the availability of entire exomes/transcriptomes will improve the identification of molecular defects leading to ENs, likewise for other highly heterogeneous diseases such as cancer (Dienstmann et al. 2014) and intellectual disability (Gilissen et al. 2014).

'Future': Where Are We Headed?

Although rare, ENs are highly disabling conditions characterized by very severe clinical phenotypes (e.g., CIPO) usually associated to a poor prognosis mainly because of the lack of available effective therapeutic strategies. Nonetheless, research

data obtained in recent years open to an optimistic view for the future. Indeed, we are now beginning to decipher molecular (genetic abnormalities; neurodegeneration) and cellular (immune-mediated) mechanisms underlying ENs (Knowles et al. 2013). Furthermore, an emerging investigational field is represented by the gut microbiota and its impact on the ENS maturation, differentiation and maintenance. Initial evidence suggests that the gut microbiota (Anitha et al. 2012) may influence the ENS maturation, chemical coding and function. Also, nutrients, alone or in combination with microbiota, have been shown to have a role in ENS neuroplasticity and gut physiology (De Giorgio and Blandizzi 2010). However, whether an altered interplay between the gut microbiota/nutrients and ENS is actually pathogenetically relevant for ENs will be matter of future study. Other challenges in the research agenda will concern: (1) a better standardization of methods in order to quantify and characterize enteric neurons; we do believe that modern medicine cannot avoid thorough (e.g., quantitative) analysis and this should be made routinely applicable in patients with ENs; (2) the acquisition of normative (control) data in each referral laboratory; (3) the combination of clinical and histopathological quali-quantitative findings in order to establish a solid relationship between clinical phenotype (for example CIPO) and the underlying morphological correlates, i.e. ENs; (4) the identification of molecular or histopathological biomarkers of ENs for improving clinical management and therapeutic option discovery.

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