A History of ESPGHAN and its Contributions to Paediatric Gastroenterology, Hepatology and Nutrition

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Introduction

Lawrence T. Weaver

In 2014 I was asked by the President and Council of ESPGHAN to convene a small group of members to put together a “History of ESPGHAN” to mark its 50th anniversary. This is the result—a supplement that aims to give an account of the origins and foundation of the Society, to record its activities, to celebrate its achievements, and to highlight its significant contributions to paediatric gastroenterology, hepatology, and nutrition (PGHAN).

Growing from a meeting in 1968 of fewer than 40 people, it is now an international organisation with hundreds of members, from all European countries and some further afield, committed to the practice of PGHN. The history of PGHN and the history of ESPGHAN are intertwined and this supplement traces them both and offers insights into how modern medicine advances and the forces that have driven and shaped it. The roots of PGHN extend back to the work of those who concerned themselves with the digestive ailments of children and wrote about them in the past, but its fame came of age as an independent clinical subspecialty in the last half century. It is now one of the foremost fields of pediatrics, as this supplement proclaims.

Chapter 1 outlines the roots of the modern clinical specialty of PGHN up to the 1950s, to put the story of ESPGHAN in a historical context. The second chapter is an account of the foundation of the Society by a small group of clinicians and scientists with a common interest in the digestive diseases of children, and how it developed, nurtured, and fostered the growth of a new clinical subspecialty in Europe. The third chapter illustrates the transition of ESPGHAN from a “family” of clinicians and researchers who gathered annually to share their personal experiences, into a large international organisation, embracing allied medical professionals, with its own journal, research, educational, and training programmes. Chapter 4 outlines the close relationship between the European and North American Societies of PGHN, marked by memorable joint meetings.

The next 3 chapters cover the contributions of ESPGHAN to paediatric gastroenterology, hepatology, and nutrition, respectively. They are not intended to be “state-of-the-art” reviews, but accounts of the involvement of ESPGHAN and its members in the development of a selection of areas of scientific research and clinical practice. Chapter 5 concentrates on 13 clinical topics that have attracted the special interests of members of ESPGHAN, and describes how the Society has been a forum for the advance of our understanding and treatment of them. Including both “common” conditions, such as coeliac disease, and rarer diseases, like congenital enteropathies, they illustrate the effectiveness of collaborations between paediatricians and scientists in elucidating their pathophysiology and underlying genetic and environmental causes. ESPGHAN has played a significant part in the birth of paediatric hepatology as a distinct branch of pediatrics, and Chapter 6 addresses some common diseases of the liver, the understanding of which, through the collaborative efforts of members of ESPGHAN, have been central to this process. Chapter 7 explores the interface of paediatric gastroenterology and nutrition and how, from the founding of ESPGHAN, interest in the nutrition of the newborn played a central role in its activities, and its committees of nutrition became influential in European affairs in formulating guidelines for feeding infants as well as defining nutritional requirements and industrial standards.

Chapter 8 is given to the past presidents of ESPGHAN, who recollect and reflect on their terms of office, recording their personal memories and professional achievements. They capture the dynamic spirit of a society that has done so much to promote PGHN in Europe. In Chapter 9, the presidents of our partner societies with which ESPGHAN shares common goals and members, pay tribute and offer congratulations at this historical milestone.

How medicine is practised, how we care for sick children, treat them and understand their diseases, has changed enormously over the last 50 years. Many members of ESPGHAN have contributed to this publication, and this is reflected in the different styles, approaches, and of course, subjects of the 9 chapters. The inclusion of many photographs brings to life the personal involvement and professional dedication of members. It is hoped that this supplement will be a record of the contributions of paediatricians and scientists, allied health professionals and industry, and significantly, European collaborations responsible for major advances in PGHN, as well as a history of a great medical Society on its 50th anniversary.

I want to acknowledge the encouragement of Birgitta Strandvik, editor of ESPGAN: 25 Years Memories 1968–1992 (Göteborg 1993), who spoke then of 25 years as being “a time of growing and finding an identity” with “an optimistic prognosis for the future.” At 50 years, ESPGHAN has truly come of age and is now a securely founded organization with a global reputation and influence. I am very grateful to my co-editors of this supplement, 5 of whom were also lead authors of chapters, to all its contributors, including past presidents of ESPGHAN, presidents of our partner societies, the European editor and managing editor of JPGN, and the host of the 51st meeting of the Society, who so willingly and energetically supported this project and brought it to fruition. It has been a truly European effort, illustrating the wonderful effects of international collaboration.
Chapter 1. The Historical Roots of Paediatric Gastroenterology, Hepatology, and Nutrition

Lawrence T. Weaver

ABSTRACT

The last 50 years have seen the establishment of paediatric gastroenterology, hepatology, and nutrition (PGHAN) as a well-recognised and thriving clinical specialty throughout most of Europe, and further afield. This has happened, in part, through the existence of the European Society for Paediatric Gastroenterology and Nutrition (ESPGHAN) as a forum for those interested in this branch of children’s medicine. To illustrate the pan-European roots of PGHAN, some key scientific and medical events, discoveries, and inventions relevant to 3 common clinical problems—diarrhoea, jaundice, and infant-feeding—have been chosen to survey the historical development of the ways in which each was understood and treated within the changing thinking and practice of past times. Together they are used to trace the prehistory of ESPGHAN and provide a background against which to explain the genesis of the Society and how its spheres of clinical and scientific interest came to be defined.

Key Words: gastroenterology, hepatology, history, nutrition

The purpose of this opening chapter is to provide the historical context within which ESPGHAN’s contributions to PGHAN can be appreciated. Some key scientific and medical events, discoveries, and inventions—the historical roots of ESPGHAN—are listed alongside the venues of its annual meetings in Table 1. Together with the text and figures, the table aims to give an idea of the origin, diffusion, and adoption of clinical and scientific advances within and around Europe, and how new ideas spread from one centre of medical innovation and were shared or developed in others. From the Ancient World, to Southern Europe and then northwestwards, this was not an orderly process, but reflects major historical events that provoked step changes in how medicine was conceived, taught and practised, such as the Black Death, the invention of the printing press, voyages of discovery, the French Revolution, the germ theory, and so on. Such “events” mark transitions from one mode of thinking to another: from humoralism to experimentalism, from alchemy to chemistry, from miasmatism to microbiology, from phenotypic to genotypic descriptions of disease, for instance. To illustrate the pan-European roots of PGHAN, this account is biographical, as well as thematic, and records the present-day countries of the people mentioned, highlighted in bold. Three common clinical problems—diarrhoea, jaundice, and milk-feeding—each from 1 of the 3 branches of PGHAN, have been chosen to survey the development of the ways in which each was understood and treated within the changing thinking and practice of past times.

Ancient, Medieval, and Renaissance Medicine

The deep roots of PGHAN, as we now know it, can be discerned in the writings and practice of the Ancients of the Greco-Roman worlds, whose medicine was holistic, treating the whole patient and seeking to prevent disease. Their approach to the care of children was empirical, based on observation and informed by humoralism (Fig. 2). Children were regarded as moist and warm, and their diseases caused by disturbance in the balance of the humours. Hippocrates (460–370 BC) [Greece] taught that “the growing organism has the most innate heat and therefore requires more nourishment.” Galen (130–200 AD) [Turkey] regarded milk as the ideal food for infants “since they have a moister constitution than those of other ages” (1). Relaxation or contraction of pores in the body increased or diminished secretion leading to greater moisture or dryness. Diarrhoea and vomiting were due to the flux (flow) of the humours downwards and upwards. Advice on childbirth and the care of the young, particularly infant feeding and the treatment of common intestinal ailments such as stomatitis, thrush, and umbilical hernia, was practical.

Galen formulated a physiology derived from the dissection of animals and the actions of vital spirits, or pneuma. Food was taken into the stomach where it was turned into chyle and passed to the liver via the portal vein. There it was converted into blood suffused
with natural pneuma, which went to the heart where it passed through “invisible pores” from right to left ventricle and was mixed with vital pneuma from the lungs. This vital blood went via the aorta and carotid arteries to the brain, and thence by the nerves to the head to foot. When children were mentioned it was usually in relation to infant care and feeding, with remedies such as “cooling herbs” like mallow and plantain, rhubarb for constipation, and white vegetables, such as fennel, to stimulate mother’s milk. The aim of herbs’ like mallow and plantain, rhubarb for constipation, and white vegetables, such as fennel, to stimulate mother’s milk. The aim of herbal remedies involved the use of natural products to treat illnesses, often based on empirical observations and traditional knowledge. The development of herbal medicine continued throughout the Middle Ages, with many texts preserved in Arabic, Latin, and Greek, which were later translated into European languages. These texts were the basis for the establishment of universities and medical schools.

**TABLE 1. Some significant people, scientific and medical events, discoveries, and inventions in the prehistory of PGHAN before the 1960s when ESPGHAN was founded**

<table>
<thead>
<tr>
<th>Year</th>
<th>Meeting</th>
<th>Venue</th>
<th>Country</th>
<th>Significant people, scientific or medical events, discoveries or inventions of that country</th>
</tr>
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With the decline of the ancient Greek and Roman civilisations, many medical texts were preserved in Arabic translations and fused with the works of Islamic scholars. Their rediscovery in the late Middle Ages became the core of the teaching of newly founded universities and medical schools. In Salerno (11th Century), Bologna (1088), Paris (1150), Oxford (1167), Cambridge (1209), Montpellier (1299), Padua (1222) **[Italy, France, England]**, these writings, elaborated by commentators, were the basis of a bedside medicine, taught from books that dealt with diseases.
During the Renaissance humoural thinking continued to inform conceptions of the causes of disease and approaches to treatment, but “new” medicines, reaching Europe from “voyages of discovery” to Africa, the Orient and New World, and along trade routes, such as the Silk Road, introduced cinchona (Peruvian bark), and spices and herbs with supposed therapeutic properties, like cinnamon, pepper, cloves, and ginger. The “Black Death,” or bubonic plague, also reached Europe from the east and reduced its population by around a third.

Medical knowledge was disseminated throughout Europe in the common *lingua franca* of Latin, and the invention of the printing press in the 1450s facilitated the circulation of copies of the works of ancient writers, and also new treatises on the diseases of children, such as *Libellus de Egritudinibus Infantum* (3) by Paulo Bagellardo (c 1450–1494) [Italy] and *Ein Regiment de Jungen Kinder* (1473) (4) by Batholomew Metlinger (c 1450–1492) [Germany]. Such texts generally restated the teachings of the Ancients, broadly under 3 headings—pregnancy, the care, rearing and feeding of infants, and the diseases of children. Their focus was on treatment, rather than diagnosis or pathology, with plant-based remedies, along with observance of rules of hygiene, healthy living, and the healing power of nature. Texts took the form of aphorisms—short, pithy statements: on “flux of the belly” (de fluxi and de vomitu) and on “stopping of the belly” (constipation) (5). Hippocrates (c 460–270 BC) [Greece], for instance:

*They that have their belly much moved and good digestion are the healthier; they that have scant movement, and being gross feeders are not nourished in proportion, are sickly.*

*They that often pass bloody and undigested stools from the belly are especially liable, amongst the symptoms of fever, to drowsiness.*

The humanism of the Renaissance rejected medieval scholasticism and stressed the significance of the individual. A spirit of enquiry informed many spheres of practical activity, including chemistry. The processes of distillation and evaporation were used by Paracelsus (1492–1541) [Switzerland] to extract, concentrate, and purify the “essences” of plants and mineral ores (including arsenic, lead, and mercury) to produce medicines. While he also sought the elixir of life using alchemical methods, he taught that many diseases came from the outside and that specific medicines were indicated for specific diseases, such as mercury for syphilis.

Didactic poems, such as *Paeidotrophia* (6), the *Art of Nursing and Rearing Children*, written in Latin by Scevole de St Marthe (1536–1623) [France], and later translated into French and English, circulated and were “read in the most famous universities of Europe with the same veneration as the works of the Ancients.” Combining practical advice with humoural theory, the treatment of constipation, for instance, was “to mix liquid honey with his food; for of the laxatives that art bestows, none has been so fitted to expel bad humours and to make the infant well.” For diarrhoea; “to brace the bowels the infant needs Cyperus brown, mixed with poppy seeds and myrtle berries that warm the stomach. Pound these together and when fitly bruised, in milk infuse the grateful loquor, which will new health produce and o’er his slender body strength diffuse.”

With the foundation of printing houses in Venice, Antwerp, Paris, Amsterdam, London, and other cities, texts translated into vernacular languages circulated around Europe, such as Thomas Phayre’s *Boke of Chyldren* (7) [England] that deals with “feeble-ness of the stomacke and vomiting,” teaching that “colyke and

**FIGURE 2.** The 4 humours, with their characteristic properties and associated elements.

**FIGURE 3.** Galen’s “physiological system.”
rumblings of the guttes cause the child restlessness. He crieth and frettish himself and many times also makes urine by reason of wind that oppresseth the neck of the bladder.”

Scientific Revolution and Enlightenment (1550–1800)

The “new anatomy” of Andreas Vesalius (1514–1564) [Belgium] “corrected ancient errors” and challenged received ideas of how the body was formed, but offered few insights into the causes of disease. Humoral physiology still served to explain physiological processes, such as digestion, absorption, excretion and lactation. Bartholomew Mettinger (c 1450–1492) [Germany] taught that human milk was produced from the blood of the mother flowing through the veins into the breast (4). “Children’s physic” continued to regard children as “wet” and “warm,” and that their medicines should sooth and cool them, and be gentle, innocent and simple. “Strong medicines,” bleeding and purging, were to be avoided. Walter Harris (1647–1742) [England], wrote in De Morbis Acutis Infantium (8), that “together with their thin diet, their redundancy of humours, and almost mucous state of solids, everybody will allow that the constitution of infants is of the moistest kind. . . moist and soft bodies are far more susceptible of any kind of impression than those endowed with the contrary qualities.” He noted the seasonal incidence of acute diarrhoea: “From the middle of July to the middle of September the epidemical gripes of children are so rife every year that more of them usually die in one month than in three of four at any other time.” The “seasonal flux” was viewed as due to deficient quality or quantity of milk, or as Sylvius Francisco (1614–1672) [France] wrote, “gripes of the belly [are] due to wind or from sour and sharp humours.”

Children were deemed worthy of care, protection, and education in accord with humanistic and enlightenment thinking. The babies of the well-to-do were often reared by wet nurses. Sick babies of the well-to-do were often reared by wet nurses. Sick

The teachings of Christianity inspired the foundation of foundling hospitals and other charitable institutions for the abandoned, sick, and infirm. Run by holy orders, they provided nursing care, refuge, and protection, but were not the locus of medical teaching or professional development. There were no children’s hospitals, nor paediatricians, in the modern sense. Physical examination was rudimentary, but “stool-watching” was keen. Jean Astruc (1684–1776) [France] wrote that “as to the nature of the evacuations, diarrhoea is of four species: stercoral (whitish, greenish, yellowish or bilious, viscid), coeliac ("milky whitish humour – chyle that could not enter the lacteals"), lenteric (undigested food), and dysenteric (bloody) (8). Extern agents, especially worms, were found in the stool. Hippocrates had taught that they were generated by putrefaction in the bowel, and “are produced in the child yet in utero” (1). The transition from scholastic, bookish medicine to clinical practice based on observational and experimental evidence involved a shift from a physiology of “vital spirits,” “invisible pores,” and alchemy, to one of mechanism, materialism, and chemistry. “Number, weight, and measure” became the watchwords of the new Natural Philosophy. The adoption of technology and experiment to investigate how the body worked generated mechanical, chemical, and haemodynamic explanations of muscle contraction (Giovanni Borelli 1608–1679) [Italy], cardiac function (William Harvey 1578–1657) [England], respiration (Robert Boyle 1627–1691) [Ireland], metabolism (Santorio Santorio 1561–1636) [Italy], digestion (Jean-Baptiste Helmont 1577–1644) [Belgium] and reproduction (François Mauriceau 1637–1709) [France]. With the assistance of the microscope, single and multicellular organisms, muscle fibres, spermatozoa, and blood cells were observed (Robert Hooke 1635–1703) [England], Antoine van Leeuwenhoek (1632–1723) [Holland], Marcello Malpighi 1628–1694) [Italy], and by human dissection the cerebral, placental and foetal circulations (Thomas Willis 1621–1675) [England], (Frederik Ruyssch 1638–1731) [Netherlands] were demonstrated (Fig. 4). This iatrophysical and chemical conception of the living body as a machine made up of smaller machines operating according to scientific laws, informed a “new” physiology, that was shared by many in Europe who wrote about children’s diseases. But therapies remained dominated by humoral thinking, with emetics, cathartics and aperients. Nils Rosen von Rosenstein (1706–1773) [Sweden], for instance, wrote in his Diseases of Children and their Remedies (10): Diarrhoea (“flux of yellow humours downwards”) may arise from whatever occasions a greater quantity to remain in the bowels than normal, or by anything causing the humours to be discharged in too great a variety of species (or anything preventing the vasa biformia (absorptive pores) from absorbing these liquids, and by whatever increases the peristaltic action. . . By eating and drinking in too great quantities, the stomach and intestines are unable to digest the food and from thence will arise indigestions and crudities, which by their activity, irritate in part and increase the motus peristalticus, and in part occasion a greater flux of humours.

While medical thinking remained imbued with humoral language and concepts, the idea that disease was an independent entity, separable from the patient, permitted the compilation of descriptions of cases of disease and taxonomies that included “causes” as well as “symptoms.” “The saliva which is swallowed promotes peristalsis and prevents the excrements from becoming hard.” “The gall is diluted by that humour (saliva) which the sweetbread (pancreas) separates from the blood, promotes the
digestions and stools.” Von Rosenstein classified diarrhoea into fourteen species; the twelfth was *Fluxus Coeliacus*:

Children are subject to another kind of diarrhoea, which physicians have termed *fluxus coeliacus*. Those who have this disease are affected with gripes and violent purging, which is not continued, but comes on now and then. Sometimes the excrements have an insupportable stench, and at other times are void of any; their colour is various, as grey, yellow, red, brown, and sometimes tinged with blood. The appetite at times is very great, and sometimes changes into disgust for food. The patient looks pale, is lean, pines away, and loses his strength; his hands and feet swell, the stomach is puffed up and feverish symptoms come on; the child is troubled with wind; the mesenteric glands are obstructed, and when the humours become more corrupt, the liver, spleen and the large gland lying behind the stomach [pancreas] swells and grows hard. The cause of this disease seems therefore to consist of a corruption of the whole mass of blood, but more especially the digestive humours, because when they are vitiated, they injure the support in the intestines and make the stomach and bowels lose their strength.

Setting aside exactly what the diagnosis was, the description combines observation on the course of the disease with inspection of the stools, examination of the abdomen, and post-mortem findings. The effects of mechanical obstruction of the biliary system on the flux of yellow bile was also understood by Von Rosenstein, who wrote: “As to the causes of jaundice, we shall find them to be such which effect the stoppage in the channels that carry the gall or bile from the liver, the ductus hepaticus, ductus choledocus, so that the bile is prevented from being freely discharged in the duodenum… Stones in the gall bladder do not cause a jaundice unless they are retained in the ductus choledocus and shut up that passage” (10).

Such assertions were corroborated by the dissection of animals: “stones are bred in the gall bladder, not only of human bodies, but in other animals, several of which I have seen from an ox,” observed an unknown 18th-century English physician, who reported that “a certain woman complains of weariness and itching of the skin. Her urine is like dark beer, the faeces ash coloured. The white of her eyes, skin and nails are tinged yellow.” Seeking to understand the causes, or seats, of disease George Armstrong (1719–1789) [England] performed an autopsy and reported in his *Account of the Diseases Most Incident to Children* (11) that:

In a child which I opened a few years ago, that died at the age of ten months, of obstructions in its bowels, which occasioned want of digestion and in consequence thereof a marasmus; the gall in the vesica fellea [gall-bladder] was as thick and ropy as a strong mucilage of quince feeds, and of a deep saffron colour. The child was never thriving from birth, had been ill a month before I saw him and was very much reduced. He had a slow fever almost constantly upon him, and his complexion was very sallow, like a person’s in the beginning of the jaundice. His urine was high coloured, his stools whitish, very tenacious and offensive to the smell; and he was generally inclined to be costive [constipated], except when laxatives were given him. When opened, the abdominal visceræ appeared very sound, nor could anything be discovered to account for his complaints, except the above viscous quality of the bile in the gall-bladder, which had tinged the neighbouring parts of a deep orange colour.

Such a clear account of the pathological findings post-mortem and the symptoms and signs of the child before he died represents an advance from purely humoural thinking. Careful observation and dissection located “morbid matter” in particular organs, rather than viewing it as due to an imbalance of the humours. Scrutiny of urine, stools, vomit, and bile from a purely humoral point of view was giving way to careful descriptions of their colour and nature. Comparison of the colour of urine with that of wines, beers and spirits (by “piss-prophets”), and minute
observation of stools ("stool watching") informed diagnosis and treatment. Armstrong recorded many cases of sick children with diarrhoeal diseases, writing: "As to vomiting and green stools, there are few infants that are not subject to them at times. The disease has been called the wetary grips, from the stools being as thin as water, attended by violent gripes. Sometimes they are colourless, sometime mixed with little streaks of blood, and sometimes of a brownish cast, like a kind of purtid sanities, of a very strong and offensive smell, but always very thin." The character of the stools was a guide treatment, as Michael Underwood (1737–1820) [England, taught in his Treatise of Diseases of Children (12):

Regard is to be paid to the kind of stools that come away, which are seldom healthy and natural, and are usually distinguished into the sour and curdled, slimy, mucous, green, pale, clayey, watery, over-tenacious, and bloody, some of which are at times fetid. Under some of these, and particularly the latter two, some powerful purgative, such as senna tea, is generally necessary, if the child is not very young. True, bloody stools are less common in infants than adults, and seldom occur but in the last stage of disease; but a few streaks of blood may sometimes be mixed with the faeces, which arising only from the haemorrhoidal veins is a matter of no consequence.

Rejecting bookish aphorisms in favour of direct inspection, remedies composed from many sources; herbs, minerals, and animals, chosen to transform the stools to normal, were recommended.

When the stools appear very slimy, and more especially sour or curdled, or when the child is much disposed to the cough, the magnesia and other absorbent powders, are calculated to afford peculiar assistance, and may be warmed by any suitable aromatic. When the stools are very green, or white or clayey; a drop or two of the aqua kali [alkali] may be occasionally put into the other medicines, or a little almond soap be dissolved in the clysters [enemas], which are essentially necessary when much griping attends this complaint. Some light cordial is also frequently useful, and the child’s belly may be rubbed with a little warm brandy, or be fomented with a decoction of chamomile flowers or white poppy heads (12).

Such remedies, and foods and drinks, were classified into those that were hot, cold, wet, and dry, chosen to redress humoral imbalance, and also to alter the chemistry of the gut. Rather than regarding foods as "unitary" substances with humoral qualities practitioners sought to define their character and to distinguish the properties of vegetable matter and animal flesh. Flowerly and sugary foods derived from plants were observed to be subject to digestion and fermentation, while animal foods tended towards putrefaction. The former were described as "gelatinous" and the latter "mucilaginous." Digestion was thought to be a form of decomposition, akin to the fate of kept foods, which tended to become "spirituous," "acetous," or "putrefactive." Milk was regarded as an intermediate substance, which combined both gelatinous and mucilaginous properties. Moreover, as a fluid, it was high in a hierarchy of other humours or fluids—blood, semen, urine, bile, saliva, and so on. Milk was also high in the hierarchy of plant—animals—man: as a substance elaborated by man (woman) and close to a perfect food, it promoted health and defended against disease.

Adopting the methods used in the manufacture of alcoholic drinks, the techniques of distillation, fermentation, and so on were used to analyse the composition of fluids and food, including milk. The processes that regulated their transformation, combination, and separation, and that combated acidity or promoted digestion, drove the search for the essence of substances, and their demonstrable or supposed effects in promoting health and well-being. Foods made up of a single substance, such as gelatine (derived from animal bones) led to the marketing of proprietary foods, which claimed health benefits. Such substances were recommended for the nourishment of children. The inferiority of plant sources for infants (in accordance with the hierarchy of food substances) was confirmed by the observation of the indigestibility of "vegetable aliment." Cereals with a lot of starch (representing respiratory or combustible ingredients) were noted to lack the "plastic ingredients" and to be associated with the accumulation of starchy deposits along the lining of the infant gut.

The production and marketing of "special foods," mineral waters, alcoholic spirits, and nutritious beverages with purported health benefits, was accompanied by the promotion of spas, cures, regimen, and diets for the sick. A convergence of gastroenterology and gastronomy, and of commerce and chemistry, informed the recommendations of medical men, replacing humoural classification of foods and their purported health-promoting properties and therapeutic effects with dietary advice based on "scientific principles." Handbooks of childcare, texts on the physiology of digestion, and articles in scientific and medical journals reported the chemical analysis of foods, the percentages of different nutrients within them, and made recommendations for their choice and use—such as Antoine Fourcroy’s (1755–1809) [France] Encyclopédie Méthodique Médecine (13), and William Buchan’s (14) [England] Domestic Medicine (1769).

Late Modern Period (1800–1900)

Founding Hospitals had been established in many European towns as early as the 15th century: in Florence, Rome, Paris, Montpellier, and Nuremburg, they provided for the care of children whose parents had died, had abandoned, or disowned them. But they were places of refuge and confinement, rather than of medical treatment and care (Fig. 5). Although a few children’s hospitals were founded earlier in some European cities, these were small, charitable institutions which, responding to a local concern for the plight of sick children, were neither long-lasting nor influential in shaping the way paediatrics came to be practised and sick children were cared for.

The taking of the great Paris hospitals of the ancien régime into public ownership after the French Revolution, in 1794, the appointment of salaried staff, the allocation of hospitals to specific clinical specialties, and thereby the concentration of patients with similar diseases together, led to a new and powerful opportunities to understand disease (Fig. 6). The collection of disease statistics and analysis of the outcomes of particular treatments ("méthode numérique"), and the use of diagnostic aids, such as the stethoscope by René Laennec (1781–1826), the thermometer by Carl Wunderlich...
(1822–1895) [Germany] and weighing scales by François Chausier (1746–1828) [France], all contributed to the application of this ‘clinico-anatomic method’ to the diseases of children (15).

Careful observation through dissection had demonstrated that in many cases the precise location of disease could be determined (localism), often in a solid organ (solidism). The physician and anatomist Giovanni Morgagni (1682–1771) [Italy] had proposed that most diseases were not due to disturbance of the humours, but to be found in specific organs, or metastasise between them. Based on the records of more than 600 dissections, many prefixed with symptoms, his De Sedibus et Causis Morborum per Anatomen Ingegatis (16) published in Latin in 1761 (translated into French in 1765, English in 1769, and German in 1771), deals with the anatomy of diseased organs, from head to foot. Symptoms ceased to be the core of disease classification, but were viewed as ‘the cries of suffering of diseased organs.’

In the L’Hôpital des Enfants Malades, established in 1803, this ‘new Paris medicine,’ which stressed observation, experiment, and the correlation of symptoms and signs with post-mortem pathology, was applied to children. Cases of diarrhoea, typhoid fever, and exanthemata (eruptive fevers) were common on the wards, and children with these conditions were the subject of study by Charles Michel Billard (1800–1832), physician at L’ Hôpital des Enfants Trouvés, who described in his Traité des Maladies des Enfants Nouveau-Nés et à la Manelle (17) that ‘in reading Morgagni I was particularly struck how this ‘distinguished observer’, after having enumerated the affections to which newborn children are liable,’ complained of the little progress that has been made in their pathology. Therefore ‘I availed myself of the opportunity thus afforded to examine by dissection all their organs, and ascertain the causes and seat of each disease.’

Billard argued that ‘it appears that it is not after birth only, as has been asserted by philosophers, that man for the first time experiences that set of maladies which afflicts his race, but the origin must be sought in a much more remote source; it commences with the organisation… as soon as the ovum, the embryo, the fetus, and the adult become more perfect in their organisation, their functions undergo a peculiar change in a state of health, and whence present corresponding peculiarities of symptoms in disease, the forms of which will change according to the different phases of organisation. The alterations of the functions, or the diseases resulting from any disturbance in the organs, vary equally according to the different subjects [organs] affected, and according to the different epoch [stage] in the life of the same subject.’

The conception of disease as due to derangement of the organisation of the growing child was a development from Xavier Bichat’s (1771–1802) [France] assertion in his Recherches Physiologiques sur la Vie et la Mort (18) that ‘Life is that set of functions which resist death,’ which he elaborated further as ‘there is a superabundance of life in the child. In the child the reaction of the system is superior to the action, which is made upon it from without. … In living bodies, such in fact is the mode of existence; that whatever surrounds them tends to their destruction.’ By the 1830s the new clinico-anatomic method recognised tissues and membranes as ‘seats of disease,’ and embryology and development as shaping their expression in children. Billard’s book was succeeded by a more substantial text by 2 physicians, Frédéric Rilliet (1814–1861) and Antoine Barthez (1811–1891) [France],
whose *Traité Clinique et Pratique de Maladies des Enfants* (19) constructed a nosology of children’s disease based primarily on the nature of the pathological lesions discovered at autopsy.

The *Tableau Synoptique du Plan de L’Ouvrage* of the first edition (1843) summarises how Rilliet and Barthez chose to classify children’s diseases: by organ and nature. Internal “organs” are chest (encompassing bronchi, lungs and heart); mouth, nose, and throat; abdomen (encompassing stomach and intestines, liver, and kidneys); brain and spinal cord; and external organs; joints, skin, and genitalia. These 5 “divisions by organ” are cross-tabulated by 8 “divisions by nature.” The first 4 have labels that echo humoral categories—phlegmasies, hydropsies, hémorrhagies, gangrènes, and are followed by névroses, fièvers, tuberculisations (occupying the whole of volume 3), and entozoaires (gut parasites) (Fig. 7) (19).

Diarrhoeal diseases (catarrhales), with and without fever, and non-diarrhoeal disease of the stomach and intestines, were classified without indication of pathological causes—“inconnue” or “irritants locaux” (Fig. 8) (19). The second edition of Rilliet et Barthez (1853) reflects developments in physiology and experimental medicine, by François Magendie (1783–1855) [France] and Claude Bernard (1813–1878) [France], and in the German-speaking states (Wilhelm Camerer, 1842–1909) [Germany], where the chemistry of Justus von Liebig (1803–1873) [Germany] formed the basis of physiology, auxology, and metabolism. Chapters

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**FIGURE 7. Tableau Synoptique du Plan de L’Ouvrage**, from Rilliet & Barthez’s *Traité Clinique et Pratique de Maladies des Enfants* (1843) (19).
devoted to particular diseases, such as Entéro-Colite Chronique, which has sections on anatomie pathologique, symptômes, complications, prognostic, diagnostic, étiologie, and traitement. But for the liver “hépatite est une affection fort rare chez les enfants.”

With the rise of laboratory science, the alliance of laboratories and scientific institutes alongside hospitals, the growing use of instruments such as the stethoscope, thermometer, microscope, and weighing scales to extend and deepen the “clinical gaze,” combined with measurement and quantitation, charting and tabulation, collection and preservation, illustration and reproduction generated and disseminated a mass of new information and ideas that informed medicine and were tested and exploited in the clinic (Fig. 9). Simple chemistry was applied to the analysis of bodily fluids (urine, blood) and foods (including milk) in ward side-rooms, dissection and vivisection were performed in nearby laboratories, and histopathological examination of morbid tissues undertaken with the microscope. Nevertheless, materia medica remained essentially empirical, employing remedies with specific indications, such as digitalis for the heart, calomel for the bowels and bark for fever, but with no understanding of their mechanisms of action.

Antoine Lavoisier (1743–1794) [France] had shown that animals use and reconstitute atmospheric air in the same way as a burning body: oxygen is consumed, carbon dioxide is generated and respiration produces heat. Using an ice calorimeter he showed that “animal heat” was the chemical equivalent of slow combustion (Fig. 10). His student, François Magendie (1783–1855) [France], demonstrated the requirement of the body for nitrogen, in the form of protein, and the German metabolists, Carl Voit (1831–1908) and Max Rubner (1852–1932) [Germany], using calorimetry and balance studies, later linked respiration with combustion, disposing of vitalistic explanations of life. Physiology was embracing chemistry, complementing the mechanistic concepts that had explained the circulation of the blood and alimentary functions such as peristasis, linking the properties of food with their actions within and upon the body.

The division of the ingredients of foods, including milks, into sugar, fat, and protein, based on the proportions and properties of these substances, was established by Justus von Liebig (1803–1873) [Germany] who sought to explain how food may power and nourish the body through study of the overall balance of the bodily ingesta (food), excreta (faeces), and respiratory gases (breath) and thereby the conservation of matter. “All vital activity arises from the natural action of the oxygen of the atmosphere and the elements of the food,” he argued, coining the term “metabolism” (20). Elaboration of the constituents of food resolved them into “nutrient” groups—gelatin, albumin and fibrin, sugars, and fat with specific properties—calorific or combustible matter (sugars and fats); plastic or nitrogenous matter (proteoids); and mineral matter (ash) or salts. Steggall’s Manual for Students (21) reflects this integration:

- Animal and vegetable bodies are formed by compounds, named proximate principles consisting of 4 elements, namely oxygen, hydrogen, carbon, and nitrogen.
- Organic bodies are distinguished by the impossibility of imitating them by the chemical art.
- Pancreatic juice resembles saliva, contains in addition albumin and osmazome (nitrogenous extracts), and is distinguished from saliva by not containing sulphocyanic acid.

The shift in focus of the medical gaze, from whole bodies (humoralism), to organs (solidism) (Giovanni Morgagni 1682–1771) [Italy], to tissues (Xavier Bichat 1771–1803) [France], to cells (Theodor Schwann 1810–1882) [Germany], drove the quest for a general physiology applicable to all living things, consistent with the doctrine that cells were the building blocks and functional units of plants and animals (Rudolf Virchow 1821–1902) [Germany]. Tissue growth and development were explained by cell multiplication—“omnis cellula e cellula”—and with the use of the microscope, microtome and tissue-specific stains, the new sciences of histology.
and embryology revealed, in bright colour, the fine structure of the tissues in health, development, and disease (Fig. 11).

A mechanistic and materialistic conception of the body as a machine in which the "physiological basis of life" was situated in the cells, was expanded and substantiated by experiment, spawning a chemical physiology that saw coordinated "organisation," rather than independent function of the vital organs—heart, lungs, liver, brain—as key to health. William Prout (1785–1850) [England] reported in 1823 the function of hydrochloric acid in the stomach, and Claude Bernard (1813–1878) [France] showed the role of the liver in sugar metabolism and the pancreas in digestion, arguing that "a complex organism should be viewed as an assemblage of small organisms, which are the anatomical elements that live in the liquid milieu intérieur" (22).

Location of "combustion/respiration" within the cell and the chemical reactions that generated energy and thereby mediated muscle action, for instance, became clearer with Louis Pasteur’s 1822–1895 [France] work on fermentation and moulds. The application of the microscope, laboratory study of moulds (Louis Pasteur 1822–1895) [France], the mapping of the social demography of diseases (Rudolph Virchow 1821–1902) [Germany], and identification of the tubercle bacillus by Robert Koch’s (1843–1910) [Germany] in 1882. This was followed by the characterisation of other agents, responsible for cholera (1883) and typhoid (1884), and the gradual acceptance of the "germ theory" of infectious disease, which transformed the practice of surgery (Joseph Lister 1827–1912) [England], midwifery (Ignaz Semmelweis 1818–1865) [Hungary], and paediatrics.

Efforts to understand and tackle typhoid fever and "summer diarrhoea" (cholera infantum), illustrate the ways in which the "germ theory," coupled with developments in nutritional chemistry, physiology, and public health came to be applied to the care of sick children in the clinic and community. Pierre Louis (1787–1872) [France] identified distinctive lesions in the Peyer’s patches of the small intestine in patients with "gastric fever" (typhoid), Carl Wunderlich (1822–1895) [Germany] distinguished distinctly different patterns of temperature change in patients with typhoid and typhus, and William Budd (1811–1880) [England] concluded that typhoid fever was spread by contaminated water; "the sewer is the direct continuation of the intestine."

This new understanding of the microbiology and epidemiology of infectious diseases had little immediate impact on the sustained high mortality rates of infants (150 or more per 1000 live births) that had persisted throughout Europe for centuries. The link between diarrhoeal diseases and "improper feeding" kindled a "clean milk movement" that sought to address the stubbornly high and well-documented death rates of young children. In 1858, *The Lancet* championed the cause with an editorial entitled "The Murder of the Innocents" (23):
FIGURE 11. Histological sections of the intestinal mucosa.

Meat, potatoes, often gin; scant nourishment drawn from the breasts whose secretive power cannot eliminate milk from a half-starved frame, and the unwholesome diluted milk of unhealthy badly-fed cows; such is the nourishment afforded to thousands of children on this day of an enlightened age, in this capital city of a civilised country [England].

An alliance of social reformers (Louis-Rene Villermé 1782–1863) [France], Edwin Chadwick 1800–1890 [England] and Rudolf Virchow 1821–1902) [Germany] with philanthropists, politicians, social reformers, and public health authorities, concerned with the high premature death rates of children, their exploitation in mines, and their mothers in textile mills, inspired by an atmosphere of social justice, liberal nationalism, and municipal charity, and at the end of the century by a fear for the strength of the armed forces of the imperial powers through the unfitness of recruits, led to the development of childcare in dispensaries, clinics and hospitals, and the social, or public health care of children (Fig. 12) (24). Obstetrics, the medicalisation of antenatal and postnatal care, infant-feeding (so critical for infant survival), crèches, and legislation to protect children from dangerous employment, recognised the importance of maternal and child health. International congresses in Europe’s capital cities, on infantile mortality, malnutrition, rickets, tuberculosis and syphilis, brought together paediatricians, public health physicians and scientists, and forged networks of like-minded professionals who shared their clinical discoveries, discussed new treatments, and strategies for preventing disease.

The massively higher mortality of artificially fed infants during epidemics of summer diarrhoea (cholera infantum, a frequently lethal disease of bottle-fed babies), was depicted graphically by Pierre Budin (1846–1907) [France] in the 1890s (Fig. 13) (25). There was a shift from a primary concern for mothers, to infants and children, who became recognised as patients. Among a range of welfare services initiated for babies, consultations de nourrisons, Gouttes de Lait and infant milk depots, designed to provide “pure, clean milk for babies” were promoted. Breast-feeding was (and always had been) the dominant way in which mothers have fed their babies. Nevertheless, alternatives for mother’s milk were badly needed and sought.

Justus von Liebig’s (1803–1873) [Germany] baby food, composed of wheat flour, cow’s milk, malt flour, and potassium bicarbonate, was launched in 1867, setting in motion an infant food industry that was to become global within 2 decades. Henri Nestlé (1844–1906) [Switzerland] developed “farine lactée” — “a wholesome Swiss milk and cereal component baked by a special process of my invention” — in 1868. Varying in composition, but designed to mimic human milk or meet the special nutritional needs of babies, these milk formulas were seen as the answer to the high infant mortality rates. Recipes for graduated mixtures of cow’s milk, cream, sugar and water, developed by Philippe Biedert (1847–1916) [Germany] were popularised throughout Europe by both physicians and commercial entrepreneurs in efforts to “humanise” cow’s milk, culminating in Thomas Rotch’s (1849–1914) [USA] absurdly complex “percentage feeding method” (26). Franz von Soxhlet (1848–1926) [Germany] invented a means for “pasteurising” cow’s milk for babies and the provision of clean, sterilised, modified formulae for babies (Fig. 14).

The mother and child welfare movements were an impetus for the collection of data on infant growth. Mothers were encouraged to bring their babies for weekly weighing, with out which artificial feeds were not supplied (Fig. 15). Growth standards were pioneered by statisticians, such as Adolph Quetelet (1796–1874) [Belgium] in the 1830s, who argued that “the study of diseases and of the deformities to which they give place, has shown the benefits derivable from corporeal measurements; but in order to recognise whatever is an anomaly, it is essentially necessary to have established the type constituting the normal or healthy condition” (27). The growth standard, just like the temperature chart, became an essential tool of clinical research as well as medical care, in the hospital ward and welfare clinic.

Coming of Age of Paediatrics (1900–1950)

The alliance of hospitals with universities, and the application of science and technology to clinical practice stimulated clinical specialisation. This was the birth-time of paediatrics as an independent medical specialty, first in Germany and France, and then in other European countries and North America. The foundation of university departments, of children’s hospitals, of journals and textbooks, and of national societies of paediatrics, all contributed to the creation of clinical specialists with the dedicated interest in the diseases of children (Fig. 16). This
professionalisation of paediatrics is well illustrated by an image of Theodore Escherich (1856–1911) [Germany] who is represented as the “chief” of a team of clinicians, scientists and teachers. He stands beside a sick child lying on the trolley. On his left is Meinhard von Pfaundler (1872–1947) [Germany], his assistant and soon to be professor of paediatrics in Munich, who listens to the heart of the child, wielding that potent symbol of the modern clinician, the stethoscope. On the right of the chief stands Ernst Moro (1874–1951) [Germany] injecting a rabbit held by a technician, symbolising “medical experimentation.” The scene is set in a lecture theatre where 3 attentive students signify the integration of clinical teaching with scientific research and medical care (Fig. 17).

Escherich and Moro took special interests in the colonic bacteria of children. The “species of diarrhoea” formerly classified according to the character of the stools, were to be better distinguished using the new sciences of histopathology and microbiology. Samuel Gee (1839–1911) [England] had noted in 1888 that the coeliac affection “is met with in persons of all ages, yet it is especially apt to affect children between one and five years old,” and is marked by the postmortem finding of “atrophy of the glandular crypts of the intestine” (28). Henry Koplik (1858–1927) [USA], in his Diseases of Infancy and Childhood (29), stated that “the various forms of acute gastroenteritis may be divided into “those whose source of infection lies outside the body (‘ectogenous’), and those in which the

**FIGURE 12.** Maps showing locations of children’s hospitals in Europe, 1802 to 1847 (24).
elements of infection are pre-existent in the body (‘endogenous’),
...which, in the opinion of Theodore Escherich (1856–1911)
[Germany] and Antoine Marfan (1858–1942) [France], may
under favourable conditions increase to enormous numbers and
become virulent."

The magisterial 4 volume, multi-author Handbuch der Kin-
derheilkunde (30) edited by Meinhard von Pfaundler (1872–1947)
and Arthur Schlossmann (1867–1932) [Germany] (translated into
English in 1908), based on physiological and developmental princi-
ples, represented the state-of-the-art of paediatrics at the start of the
20th century. The integration of the sciences of microbiology,
immunology, serology, biochemistry, and radiology signal the close
alliance of laboratory with clinic, as exemplified by the ways in which
diseases of the gastrointestinal tract were understood and investi-
gated. However, although the chemist and pharmacist were replacing
the apothecary, therapeutics still comprised recipes primarily
designed to relieve symptoms. For instance “Acute Catarrh (dior-
hoea) of the Small Intestine generally occurs as a result of marked
indiscretions in diet. ...The treatment is relatively simple and
generally successful, ...with a strict diet of weak, sweetened tea, a
hot pack to the abdomen, and an astringent medicine, for example”:

![Figure 13](image_url)

**FIGURE 13.** The mortality of breast-fed and artificially fed infants in Paris during an epidemic of summer diarrhoea (cholera infantum) in 1898 (25).
gr.) and syrup althaea 10 Gm. (2 dr.), teaspoonful every two hours; or extract haematoxylin 5 Gm. (1 1/4 dr.) to 100 c.c (3 oz.) water, tinct. catechu 3 Gm. (45 gr.), tinct. opii 20 to 25 drops, syrup cinnamomi 15 Gm. (1/2 oz.); a teaspoonful every two hours; or extract Colombo 2.5 to 3.5 Gm. (2/3 to 1 dr.) to 100 c.c (3 oz.) water with tinct. opii 20 to 25 drops in equal doses, tannigen 0.25 to 0.4 Gm. (4 to 6 gr.) three times a day; tannalabin in equal doses or in the form of tannalabin chocolate, bismuthose, and similar preparations.

"After the intestines have become quiet, diluted milk is given, best added to the tea; later to cereal waters, slowly, with constant regard to the condition of the tongue, the previous normal diet is again resumed." Such complicated and carefully compounded prescriptions, containing tinct. opii and syrup cinnamomi were hardly changed from those recommended by Michael Underwood (1737–1820) [England] a century before (12).

Treatment was directed at prevention—"nursing bottles when emptied by the infant should be filled with a saturated solution of sodium bicarbonate, allowed to stand for a few hours and then carefully washed inside and out with a bristle brush"—but if diarrhoea is persistent or progressive, rectal enemas were indicated to "remove any residue of faeces that may have collected and to stimulate peristalsis and thereby favour evacuation, and to stimulate the heart and add to the body an amount of normal solution [saline] to compensate for the drain caused by the diarrhoea. . . . The injection of normal salt solution under the skin (hyperdermoclysis) is indicated only in severe cases in which the course of the disease is rapid and prostration extreme," wrote Henry Koplik (1858–1927) [USA] (29).

The search for pathogenic microorganisms was paramount, especially in cases of summer diarrhoea or cholera infantum. Streptococcus enteritidis attracted the greatest attention. However "the treatment of chronic disturbances of digestion requires much patience." In tackling colitides and dysenteries, determination of the microorganisms involved employed the new science of immunology. Gaston Variot (1855–1930) [France] in his Traité Pratique des Maladies des Enfants du Premier Age (31) says "avec Rilliet et Barthez nous reservons le terme de dysenterie, à une maladie sporadique ou epidemique caracterisee cliniquement par des selles frequents, muco-purulentes et sanguinolentes, et anatomiquement par des lesions ulcerueuses, siegeant dans le gros intestin. . . . Pour etablir le diagnostic, il faudra tenir compte des conditions etiologiques, et recourir surtout aux procedes de laboratoire. . . . L’agglutination due bacilli dysenterique par le seurum du malade a ete utilise pour le diagnostic."
FIGURE 16. Cover of *Jahrbuch für Kinderheilkunde* (1909) showing international European editors, including Biedert, Escherich, Finkelstein, Jacobi, Henoch, Hirschprung, and von Pirquet.

FIGURE 17. Theodore Escherich with his colleagues and students in Graz in 1902.
Serology was required to identify and distinguish between species of "bacille typhique" (George Widal 1862–1929) [France] (test 1896), and "l'examen microscopique des selles" for amoeba. A vaccine for typhoid fever had been developed in 1896 by Almroth Wright (1861–1947) [England], and "le sérum antidysentérique (polyvalent)," along with "les purgatifs – huile de ricin, calomel, sulfate de soude ou magnesia, ... et 'lavages de l'intestin avec de l'eau de guimauve ou des solutions antiseptiques' were recommended as treatment. In Maladies du Tube Digestif, de La Pratique des Maladies des Enfants (32) edited by René Cruchet (1875–1959) [France], Colite Muco-Membraneuse "est caractérisée par l'émission de selles glaireuses, contenant en proportion variable des fausses membranes formée de mucin et de divers éléments épithéliaux et microbiens," identified by microscopical examination of the mucus membrane. The same year the use of barium sulphate as a radio-opaque contrast medium to outline the luminal structure of the gut was pioneered by Paul Krause (1871–1934) [Germany] (Fig. 18) (33).

Biochemistry, microbiology, and radiology made the pipette, Petri dish and photo-plate essential tools of paediatrics. Describing chronic interstitial enteritis in children for the first time in 1913, Kennedy Dalziel (1861–1924) [Scotland] suspected it to be due to tuberculosis; but "a careful search has failed to reveal microorganisms of any kind" (34). He drew attention of "chronic bacterial enteritis of cattle, called pseudotuberculosis, in which the histological characters and naked-eye appearances are as similar as may be those we have found in man." The tuberculin test (1906), invented by Clemens von Pirquet (1874–1929) [Austria] helped to detect exposure to the tubercle bacillus, but 40 years on from its identification, the debate between Robert Koch (1843–1910) [Germany] and Leon Calmette (1863–1933) [France] on the portal of its entry to the body (via respiratory or gastrointestinal tract) remained unresolved.

Efforts to understand the metabolic disturbances associated with chronic diarrhoea and malnutrition—variously termed atrophy, dystrophy, decomposition, atrepsia, intestinal intoxication—through competitive and collaborative research during the 1920s and 1930s. In Pfaundler and Schlossmann's expanded 5-volume edition of the Diseases of Children of 1935, the "theories of the origin of dystrophy" were summarised under the headings of Ferment Deficiency Theory, Intoxication Theory, Demineralisation Theory, Inanition Theory, focusing on disturbances of milk digestion, "alimentary-toxic or infectious-toxic injury," salt and water losses, and malabsorption and mal digestion. Heinrich Finkelstein's (1865–1942) [Germany] in his Lehrbuch der Säuglingskrankheiten (35), promoted eiweissmilch (casein-enriched milk). This was used to treat coeliac disease, also known as intestinal infantilism, which was distinguished from pancreatic infantilism (cystic fibrosis) by microscopy of the stool: the excess of fat or its derivatives in the former, and of unaltered starch in the latter. In 1936 Guido Fanconi (1892–1927) [Switzerland] drew together the clinical features and presentation of meconium ileus (Carl von Rokitansky 1804–1878) [Austria], bronchiectasis and chronic diarrhoea into the diagnosis of cystic fibrosis.

The diseases of the liver in children are allocated only 8 out of more than 600 pages in Henry Koplik's Diseases of Infancy and Childhood (29): jaundice and congenital obstruction of the bile

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**FIGURE 18.** Radiogram of barium meal in 3-week-old infant with congenital stenosis of the duodenum (33).

**FIGURE 19.** Method of palpating the projection of the liver below the ribs (29).
DUCTS, CIRRHOSIS, FATTY DEGENERATION, SYPHILIS, ABSCESS, AND TUMOURS, TO WHICH ARE ADDED 25 YEARS LATER, IN WILFRID SHELDON’S DISEASES OF INFANCY AND CHILDHOOD (1936), VON GIERKE’S DISEASE (FIG. 19).

APART FROM THE BIOCHEMISTRY OF JAUNDICE (JARMO YLPPÖ 1887–1992) [FINLAND] AND THE TREATMENT OF ICCERUS, WITH CALOMEL, ENEMAS FRESH AIR AND DAILY ALKALINE BATHS, NO TREATMENTS OF CHILDREN’S LIVER DISEASES WERE SPECIFIED.

THE AETIOLOGY OF CHILDHOOD RICKETS, LONG RECOGNISED AS A DISEASE OF CHILDREN (FRANCIS GLISSON 1599–1677) [ENGLAND], AND PARTICULARLY PREVALENT IN NORTHERN EUROPEAN CITIES, APPEARED UNRESPONSIVE TO SCIENTIFICALLY FORMULATED DIETARY THERAPY, UNTIL, AS A RESULT OF ANIMAL EXPERIMENTATION (EDWARD MELLANBY 1884–1955 [ENGLAND]), CLINICAL TRIALS (HARRIETTE CHICK 1875–1977 [ENGLAND], CLEMENS VON PIRquet 1874–1929 [AUSTRIA], KURT HULDSCHINSKY 1833–1940) [GERMANY]), AND BIOCHEMISTRY (FREDERICK GOWLAND HOPKINS 1861–1947 [ENGLAND], IT WAS SHOWN TO BE DUE TO VITAMIN D DEFICIENCY (FIG. 20). THIS DISCOVERY WAS FOLLOWED BY THE IDENTIFICATION OF A SERIES OF OTHER “ACCESSORY FOOD FACTORS” AND THE CHARACTERISATION OF A NUMBER OF VITAMIN-DEFICIENCY DISEASES.

CONCLUSIONS


THE DISCOVERY AND CLINICAL USE OF ANTIBIOTICS, CORTICOSTEROIDS, VITAMINS, NEW ANAESTHETICS, AND RATIONAL FLUID MANAGEMENT TRANSFORMED THE FORTUNES OF MANY SICK CHILDREN IN HOSPITAL.


THE FOUNDATION OF ESPGAN IN 1968 BY A SMALL GROUP OF EUROPEAN PEDIATRICIANS AND BIOCHEMISTS SHARING THEIR PERSONAL CLINICAL KNOWLEDGE, SKILLS, AND EXPERTISE, COINCIDED WITH A TRANSITION FROM A MEDICINE BASED ON CLASSICAL PHYSIOLOGY, BIOCHEMISTRY, AND HISTOPATHOLOGY INTO ONE IN WHICH EVIDENCE-BASED MEDICINE BOLSTERED BY TECHNOLOGY, MULTIPROFESSIONAL TEAMS, NONINVASIVE IMAGING AND SYSTEMATIC REVIEWS, DISSEMINATING THE LATEST ADVANCES IN THE APPLICATION AND OUTCOMES OF CLINICAL TRIALS, MOLECULAR GENETICS,
organ transplantation, biologic therapies, and designer drugs. ESP-GHAN has been the parent, child, and midwife of a new clinical specialty, and the next chapters tell the story of its origin, growth, and development, and give accounts of the contributions of its members to the recent history of the science and practice of paediatric gastroenterology, hepatology, and nutrition.

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Chapter 2. ESPGHAN: 50 Years Memories—The Early Years

**ABSTRACT**

Thirty-six founding members from Europe were present in 1968, when the European Society of Paediatric Gastroenterology (ESGA) had its first meeting in Paris. The aim was to create a forum for presentations and discussions of research activities in paediatric gastroenterology in Europe. At the second meeting of ESGA 1969 in Interlaken, an important landmark was set for all gastroenterologists in the world. In this conference, the first ever criteria for “the Diagnosis of Coeliac Disease” (CD) were established. In 1990, the revised criteria for the diagnosis of CD were published. After the introduction of new noninvasive techniques, like tissue transglutaminase 2-antibodies and the HLA-DQ2/HLA-DQ8 determinations in blood, “new” criteria for the diagnosis of CD were published in 2012 by the European society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). Close collaboration of ESPGHAN and the North American Society of Paediatric Gastroenterology, Hepatology and Nutrition led to mutual meetings. The first combined meeting was 1978 in Paris, followed by meetings in New York, Amsterdam, Houston, and last in Toulouse. The first World Congress of Paediatric Gastroenterology took place in Boston 2000 followed by congresses in Paris, Igazu, Taiphe, and Toronto. The creation of specialised committees (Nutrition Committee, GI-Committee, and Hepatology-Committee) enabled the society to elaborate numerous guidelines for standards in the diagnosis and treatment of diseases within the subspecialties. The Journal of Paediatric Gastroenterology and Nutrition, as organ of ESPGHAN and the North American Society of Paediatric Gastroenterology, Hepatology and Nutrition since 1991, serves as the voice for these worldwide accepted guidelines. Growing educational activities with summer schools, the Young Investigator Forum and the creation of working groups have distributed our current knowledge among the younger generation and led to fruitful reports, guidelines, and syllabus. In 1992, ESPGHAN was 1 of the founding 7 members of the United European Gastroenterology Federation (UEGF), which developed into a successful organisation for gastroenterology in Europe. This year we celebrate the 50th anniversary of ESPGHAN at our annual Meeting in Geneva.

**Key Words:** ESPGHAN, early years, 50th anniversary

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Specialisation in the field of paediatrics was a much slower process after the Second World War than that in internal medicine. Organ-related subspecialties in paediatrics developed in the 1950s and 1960s, among them paediatric gastroenterology.
Although some meetings and conferences devoted to topics in paediatric gastroenterology took place in paediatric departments in Europe, the need for more regular meetings of paediatricians and researchers with common interests in paediatric gastroenterology to provide a mutual platform for the exchange of experiences and ideas, was growing. The initiative to build this platform was taken by Dolf Weijers (Fig. 2) in November 1967, by inviting Bertil Lindquist and Jean Rey to Utrecht to discuss the foundation of a society for paediatric gastroenterology. Dolf Weijers was perhaps the first paediatric gastroenterologist in Europe. The trigger for his initiative was probably the initiation of the European Society for Paediatric Nephrology by Harm Tiddens, his colleague, at the Wilhelmina Children’s Hospital in Utrecht (The Netherlands). Dolf Weijers’ colleague, Jan van de Kamer, was also present at the meeting (incidentally). He was a pharmacist of great talent and had described a method for the determination of fat in faeces named after him, working closely with Weijers on the fat absorption in the healthy and in patients with coeliac disease (Fig. 3). Jan van de Kamer was not only a pharmacist, but also a musician and “musicologist.” At the time of the meeting he was working on “The Magic Flute.”

The main item on the agenda was to agree on the aims of the proposed Society and the criteria for membership. The structure and constitution of the Society were also discussed.

**AIM OF THE SOCIETY**

The aim was to create a forum for the presentation and discussion of the research activities being pursued in paediatric gastroenterology in Europe. Because of the close relationship between research in gastroenterology and nutrition, it was agreed that the Society should concern itself with clinical nutrition as well as gastroenterology. Both disciplines were therefore included in the constitution as fields of interests of the Society from its beginning. For the sake of simplicity, however, it was decided that the name of the Society should reflect the discipline in which, at that time, research was most active: paediatric gastroenterology.

It was further agreed that the society should carry some responsibility for the dissemination of knowledge in paediatric gastroenterology and clinical nutrition throughout Europe. This objective of the society—its “missionary function”—remained a subject of debate by the membership for many years. At a council meeting in 1975, it was agreed that the selection of papers for presentation at meetings should be based solely on scientific criteria and not on its “missionary function.” In later years, however, the “missionary function” was recognised by the publications of numerous guidelines and the European society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) summer schools.

**MEMBERSHIP AND ATTENDANCE AT MEETINGS**

It was agreed that anyone working in paediatric gastroenterology and/or clinical nutrition should be allowed to attend the meetings of the Society, either as a member or their guests. It was further agreed that membership should not be strictly confined to researchers but also include those whose main interest was clinical paediatric gastroenterology. This decision was reached because, at that time, clinical and basic research in the gastroenterology and nutrition was not being pursued in all European countries. It was...
regarded as important for the Society to represent all of these countries. In this way the Society hoped to promote the extension of research and knowledge in paediatric gastroenterology and clinical nutrition throughout Europe.

**FOUNDER MEMBERS**

It was decided that letters of invitation for founder membership would be sent, by those present in Utrecht, to paediatricians recognized for their scientific contributions to paediatric gastroenterology and/or clinical nutrition. In order to avoid geographical exclusiveness, it was agreed to approach some well-known chairmen of major paediatric departments in Europe requesting proposals for membership of colleagues with excellent qualifications and a deep interest in the disciplines served by the Society.

Bertil Lindquist volunteered to do the secretarial work of setting up the new society. Thirty-four colleagues were offered founder membership and invited to the first meeting of the Society, which Jean Rey agreed to organise in Paris 1968. The 36 founder members, who all attended the first meeting in Paris in 1968, were Charlotte Anderson (England), Salvatore Auricchio (Italy), Ephraim Eggermont (Belgium), Jean Frezal (France), Rolf Grüttner (Germany), Beat Hadorn (Switzerland), Aaron Holzel (England), Pirkko Immonen-Pelkonen (Finland), Jiri Jodl (Slovakia), Joseph Jos (France), Jan van de Kamer (Netherlands), Herbert Kayden (USA), Peter Krasilnikoff (Denmark), Maurice Lamy (France), Thor Lindberg (Sweden), Bertil Lindquist (Sweden), June Lloyd (England), Helmut Loeb (Belgium), Gunnar Meeuwisse (Sweden), Sergio Nordio (Italy), Daniel Nüsslé (Switzerland), Wolfgang Plenert (DDR), Claude Polonovski (France), Andrea Prader (Switzerland), Jean Rey (France), Ettore Rossi (Switzerland), Pierre Royer (France), Armindo Rubino (Italy) Otto Saxl (Czechoslovakia), David Shmerling (Switzerland), Arne Stören (Norway), Jarno Visakorpi (Finland), Erik A.K. Wauters (Netherlands), Dolf Weijers (Netherlands), Lars Wranne (Sweden), and Giorgio Zoppri (Italy).

**FIRST EUROPEAN SOCIETY FOR PAEDIATRIC GASTROENTEROLOGY MEETING IN PARIS IN 1968**

The first meeting of the new society was planned to take place in Paris in October 1968. However, in the springtime of that year no one was sure whether it could really occur. In the middle of May the whole of France was on strike. Barricades were erected each night and the petrol pumps were dry. However, the petrol suddenly began to flow again on the eve of Whit Sunday. The French were able to leave for the weekend. The first meeting of the new society was planned to take place in Paris on October 4, 1968 by those assembled in Paris. It was agreed that the new society should be called the “European Society for Paediatric Gastroenterology” (ESPGA).

The constitution was hardly discussed at all. Not because no one was interested in discussing it, but because the organizer of the Paris meeting, Jean Rey, did not give participants time to open their mouths. “Have you any comments or questions on the constitution?” he asked. A short silence. “No?” An even shorter silence. “The constitution is adopted,” he declared, banging his fist on the table, like an auctioneer delighted to have got rid of a knick-knack. None of the members present have got over it. (Yet many feel that Jean was more democratic than Bertil.) As an addition to the rules in the constitution, it was decided that the Society’s membership would also be open to colleagues from basic sciences (biochemistry, physiology, pathology, etc) with close professional links with the clinical group.

To the first Council of ESPGA were elected Dolf Weijers (President), Bertil Lindquist (Secretary), Charlotte Anderson, Salvatore Auricchio, and Jean Rey. Gunnar Meeuwisse was appointed Assistant Secretary. The scientific part of the meeting lasted 2 days, in which 20 oral presentations were given, each 25 minutes with 5 minutes of discussions. Two of the 5 sessions were dedicated to coeliac disease, which played from the start a major role within our society. The abstracts of the first ESPGA meeting were published in Acta Paediatrica Scandinavica 1969 (1).

**THE EARLY YEARS**

In the very first years the Council meetings were held “Chez les Weijers” in Utrecht, where everyone was made to feel part of the family. It was sometimes difficult to reach majority decisions, as in general 4 Council members were present (Charlotte Anderson, Dolf Weijers, Bertil Lindquist, and Jean Rey). To resolve the problem of majority—and as a last resort—the secretary, Bertil Lindquist, said on one occasion that if the assistant secretary, Gunnar Meeuwisse, had been present at the meeting, he would certainly have voted as he (Bertil) did. It should be mentioned that at that time Gunnar Meeuwisse was an Associate Professor in Bertil Lindquist’s department (Figs. 4 and 5).

In 1969, at the second meeting of ESPGA in Interlaken, an important landmark was set for all gastroenterologists, paediatric and adult, in the world. In a round table conference, chaired by Dolf Weijers, the first ever criteria for “the Diagnosis of Coeliac Disease” were established. For the conference Jarmo Visakorpi prepared an international inquiry of 33 centres on the topic (2). The diagnostic criteria agreed at this conference have come to be referred worldwide by scientists and clinicians as the “Interlaken Criteria of Coeliac Disease” and were published 1970 (3). Since that time the topic of coeliac disease has always been a major focus of ESPGHAN. In 1977, a follow-up round table workshop, dedicated to our first President Dolf Weijers who died in 1972, was organised in Utrecht at the annual meeting. The second round table workshop consisted of David Shmerling, Karsten Harms, Sandy McNeish, Jarmo Visakorpi, and John Walker-Smith. After a survey of 51 centres in Europe, conducted by David Shmerling, a commentary was prepared by Sandy McNeish on “The Diagnosis of
Coeliac Disease.” A commentary on the current practices of members of ESPGA was published 1979 (4) with the conclusion, that the Interlaken Criteria, which stated “the only decisive criteria are an abnormal pathology of the small intestinal mucosa, its normalization on gluten withdrawal and the reaction on reintroduction of gluten,” were still useful. But not all centres were conducting the full gluten challenge procedure. In addition, the so-called “2 years rule,” which says that a normal jejunal biopsy after 2 years of a normal diet excluded coeliac disease, was in fact not correct. Some patients had been reported to relapse after that period.

These objections to the Interlaken Criteria led to the creation of a working group on coeliac disease under the presidency of Salvatore Auricchio. A third round table workshop discussion on diagnostic criteria of coeliac disease was conducted in 1989 in Budapest. The speakers were Stefano Guandalini, Luigi Greco, Tadeusz Zalewski, Isabel Polanco, Jacques Schmitz, David Shmerling, and Jarmo Viskorpi. After a subsequent committee meeting in Paris, the revised criteria for the diagnosis of coeliac disease, prepared by John Walker-Smith (Fig. 6) were published in 1990 (5).

Discussion of the diagnostic criteria for coeliac disease within the working group of ESPGHAN continued over the years, owing to new noninvasive techniques like tissue transglutaminase 2-antibodies and the HLADQ2 and HLADQ8 determinations in blood. This led to the publication of the “new” criteria by the working group of coeliac disease of ESPGHAN in 2012 (6).

In 1978, the first European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) meeting together with our American colleagues from the North American Society for Paediatric Gastroenterology (NASPG) took place in Paris. The main topic was gastroenteritis. John Fordtran, Mike Field, Henry Binder, and John Rhode were establishing the role of bacterial toxins producing massive diarrhoea. John Rhode demonstrated the application of basic GI-Physiology to the treatment of a lethal condition, that is, cholera. When John Rhode was a research fellow in Calcutta during a massive outbreak of cholera, his wife told him that, if he believed in his research, he should load an aeroplane full of oral rehydration solution and take it to those afflicted. Other eminent paediatric gastroenterologists and nutritionists from both sides of the Atlantic, including John Harries, Jean Rey, Bertil Lindquist, Margot Shiner, Dick Grand, Charlotte Anderson, Brian Wharton, Armido Rubino, and Anne Ferguson took part in the meeting (Figs. 7–11). In 1990, the Annual General Meeting (AGM) in Amsterdam decided to add the “H” for hepatology into the name of ESPGAN, since when ESPGHAN has been the official name of the Society.

NUTRITION COMMITTEE

At the annual meeting in Verona in 1974, Bertil Lindquist suggested the formation of a nutrition committee. The first Committee of Nutrition (CoN) consisted of Bertil Lindquist (chairman), Jarmo Visakorpi (secretary), Beat Hadorn, Sergio Nordio, Jean Rey, and Otto Wolff. Later Angel Balabriga, Wolfgang Plenert, and Eberhard Schmidt joined the committee and June Lloyd was appointed permanent adviser. The first task was to lay down
guidelines on infant nutrition. The CoN between 1974 and 1976 had numerous meetings throughout Europe. Altogether the committee members travelled 250,000 km.

The second major achievement during the early years of ESPGHAN was set by this Committee of Nutrition. The first part of the guidelines was almost ready in 1976 and published as “Recommendations for the Composition of an Adapted Formula” in 1977 (7). Part II: “Recommendations for the Composition of Follow-up formula and Beikost,” and Part III: “Recommendation for Infant Feeding” followed in 1981 (8) and (1982) (9). June Lloyd did the enormous work of translating the “committee” English into “standard” English. At the annual meeting in Weimar in 1976 it was agreed that the Society’s name would be changed to ESPGAN.

In 1979 during a committee meeting in Düsseldorf, a committee was appointed to prepare guidelines on the enteral feeding of low birth weight infants. The members, Hans Bremer, Oliver Brooke, Marcello Orzalesi, Guy Putet, Niels Räihä, Jacques Senterre, Jonathan Shaw, and Brian Wharton (chairman) published in 1987 an extensive review on the nutritional needs and feeding recommendations for preterm infants as a supplement in Acta Paediatrica Scandinavica (10), which had a worldwide impact.

1986 to 1989 were the years of the “Second” Nutrition Committee of ESPGAN, established during the presidency of Salvatore Auricchio (1986–1989) with Jean Rey as chairman and Peter Aggett as secretary. Since that time the CoN has continued its successful work and published up to today 48 statements and guidelines in the field of child nutrition (see Chapter 7). The concepts and scientific standards developed by the CoN over 4 decades have had a major impact on the feeding practice of infants and young children in Europe and the world.

**COMMITTEE OF GASTROENTEROLOGY AND COMMITTEE OF HEPATOLOGY**

The enormous success of the publications in nutrition and on coeliac disease led to intensive discussion on how to facilitate clinical and scientific knowledge by writing and publishing authoritative commentaries of clinical and scientific relevance to pertinent questions in paediatric gastroenterology and hepatology. In 2004, the Committees of Gastroenterology and Hepatology were formed and started their work in this direction with the promotion of high-quality research and training in paediatric gastroenterology, by organising workshops, scientific meetings, and training courses.

**FIGURE 7.** Giorgio Semenza and John Harries, Paris 1978. Photo: Jean Rey.

**FIGURE 8.** Jean Rey and Bertil Lindquist, Paris 1978. Photo: Jean Rey.

**FIGURE 9.** Margot Shiner (middle) and Dick Grand (right), Paris 1978. Photo: Jean Rey.

**FIGURE 10.** Charlotte Anderson and Brian Wharton, Paris 1978. Photo: Jean Rey.
The working group on coeliac disease created a subcommittee (John Walker-Smith, Stefano Guandalini, David Shmerling, and Jarmo Visakorpi), which published the revised criteria for the diagnosis of coeliac disease in 1990 (4) (Fig. 6). In 1993, the subcommittee (Jarmo Visakorpi, Luigi Greco, and Markku Mäki) published the results of a multicenter study on the epidemiology of coeliac disease in Europe in a book (Common Food Intolerance 1: Epidemiology of Food Intolerance, Karger). The hepatology working group discussed the status of sclerosing cholangitis in Copenhagen in 1989 with the intention of encouraging cooperative studies in different centres. This was discussed at the 1990 meeting in Amsterdam and in Brussels in 1992 there was an excellent summary of the outcome of hepatitis B infection and the efficacy of interferon therapy. Between 1989 and 1992 the number of working groups increased every year. At the annual meeting in Brussels in 1992, 7 working groups presented their work in workshops: coeliac disease (J. Visakorpi), IBD treatment (J. Taminiau), gastro-esophageal reflux (Y. Vandenplas), hepatology (A. Mowat), Helicobacter pylori (S. Cadranel), congenital transport defects (Jean-Francois Desjeux), and oral rehydration (John A. Walker-Smith). In the 24 years, thereafter the number of working groups steadily increased to 22 altogether (gastroenterology 11, hepatology 6, nutrition 5). See reference at: http://www.espghan.org/about-espghan/committees/groups/.

SUMMER SCHOOLS AND YOUNG INVESTIGATORS

Charlotte Anderson and Sandy McNeish organised a course on paediatric gastroenterology in the early 1970s on behalf of the British Council. In 1985, there was a second British Council course in Birmingham organised by Sandy McNeish. John Harries had died the year before so Sandy invited Peter Milla to be the co-organiser of that course. Already by 1988 educational and training activities of ESPGAN were discussed in council meetings. At the Council meeting in Vevey in 1988, Peter Milla proposed the first postgraduate “Summer School,” together with Sandy McNeish, which was approved enthusiastically at the AGM in Copenhagen in 1988. Held in Birmingham 1990 during the time of the football world championship in Italy, the first “Summer School” was a great success. All participants and teachers were invited to Sandy McNeish’s house for dinner on the evening of the semifinal game between England and Germany. To pay tribute to the football fans a small television set was put up in a small room. When Sandy McNeish’s mother came into the dining room asking: “Who is this crazy German Professor (Michael J. Lentze) shouting all the time,” everyone joined the “crazy” football fan in the small room watching this exciting game, which was won by Germany after a penalty shoot-out 4:3. Since the start of that summer school a large number of schools followed over the years and master classes and eLearning classes within our subspecialties were developed.

In addition to the postgraduate trainings activities at summer schools held in “Western” Europe, an Eastern European Summer School was initiated by Jacques Schmitz to bring educational ESPGAN activities to countries that were experiencing the political changes that followed the break-up of the Soviet Union. The first Eastern European Summer Schools took place in 1994 in Budapest and Białystok (Poland). Council appointed an additional member responsible for the organization of the Eastern Summer Schools. The Eastern European representatives in the early years were Andrzej Raddzikowski, Hedvig Bodansky, Tamara Yucovic, Hania Szajewska, Sanja Kolarac, Andras Arato, and Dusanka Micetic-Turk. In later years, the Eastern European Summer Schools were integrated into the
Summer Schools. These Eastern Summer Schools achieved great popularity within our Society in former Soviet countries and were followed by an increase in memberships from this part of Europe.

In 2009, the title of the portfolio of council member responsible for these teaching activities was changed by Council to “International Affairs.” Louisa Mearin and Jerney Dolinske represented it in Council, extending ESPGHAN teaching meetings in Indonesia and Africa. The vision of many presidents and council members, that teaching should not be restricted to Europe but focus on global teaching activities, has led to various international teaching activities in Asia and Africa.

**ESPGHAN PRIZES**

**John Harries Prize**

John Harries had worked successfully at The Hospital for Sick Children at Great Ormond Street and the Institute of Child Health as a paediatric gastroenterologist (Fig. 7). He had joined ESPGHAN, which he loved very much, early in his career. He inspired many young men and women within the Society, who in later years rose to the highest positions as academics, clinicians, and scientific investigators. Shortly after his premature death in 1983, the John Harries Memorial Fund was established. At the 1985 meeting in New York, the Society proposed that the most appropriate use of this memorial fund would be the endowment of a prize for the best presentation at the annual meeting by a young investigator. The first John Harries Prize was awarded at the annual meeting in Edinburgh in 1986 to Irene Axellson. Since then 31 more prizes for the best presentation in paediatric gastroenterology have been awarded.

**Alex Mowat Prize**

Alexander Parker Mowat (Fig. 12), born in Cullen, Banffshire, was proud of his Scottish ancestry. After his medical education in Aberdeen and clinical appointments in the 1960s in Aberdeen, Hong Kong, and New York, he joined the Kings College Hospital in 1970 as consultant paediatrician and paediatric hepatologist. In 1993, he became head of the Department Child Health, King’s College Hospital. Although there had previously been no sustained academic interest in liver disorders in children in Britain, Mowat developed a first-class clinical unit for children who experienced these rare conditions. He joined ESPGHAN early in his career and was “the” representative of paediatric hepatology for many years within the Society. His medical unit at Kings achieved broad international recognition and many members of the Society were trained under his supervision. He and his wife Ann enjoyed our annual meeting thoroughly and made the memories of the “Mowats” unforgettable. Alex Mowat died much too early in 1995 during a lecture tour in Chile. To remember one of the founders of paediatric hepatology the Alex Mowat Prize was initiated in 1997. Since then 20 prizes have been awarded for the best presentation in paediatric hepatology at annual meetings.

**Jean Rey Prize**

Six years after the foundation of ESPGHAN in 1968 the first Nutrition Committee was created at the seventh annual meeting in Verona 1974. Jean Rey and Bertil Lindquist, who were both founding members of our Society, joined the nutrition committee together with Jarmo Visakorpi, Beat Hadorn, Sergio Nordio, Otto Wolf, Angel Balabriga, June Lloyd, Wolfgang Plenert, and Eberhardt Schmidt, until 1986. In the same year the “new” Nutrition Committee was established with Jean Rey as chairman until 1994. Overall, Jean Rey served successfully in the nutrition committees of ESPGHAN for 20 years. To honour his long outstanding and productive work in the field of paediatric nutrition, the Jean Rey Prize was instituted in 1994. Since then 24 prizes have been awarded for the best presentation in paediatric nutrition at annual meetings.
followed over the years by Allen W. Walker (1995), Judith Sondheimer (2001), Eric Sibley (2005), and Melvin Heyman (2010) on the American side of the office and by John Walker-Smith (1995), Jehan-Francois Desjeux (2001), Alfredo Guarino (2005), David Branski (2010), Raanan Shamir (2013), and Hania Szajewska (2015) on the European side of the office. The last 26 years of JPGN as organ of ESPGHAN and NASPGHAN have been a story of success. To become the leading journal in paediatric gastroenterology, hepatology, and nutrition is the result of endless hard work by members of the 2 societies. Thanks to them and the thoughtful guiding work of all chief editors and associated editors from both sides of the Atlantic, the journal has its place in the scientific community and is firmly established. Numerous guidelines in our subspecialties published in JPGN have established highly respected standards as to diagnose and treat children in the world.

UNITED EUROPEAN GASTROENTEROLOGY FEDERATION

The foundation of UEGF, with its first scientific meeting in Athens 1992, was a big step forward to a European Gastroenterology Institution comparable to the American DDW. Seven sister societies belonged to that foundation. ESPGHAN was one of them and played an important role in the development of the UEGF. ESPGHAN is the only paediatric member association and, during the 26 years since its inception, the relationship between the 2 organisations has matured. Knowledge exchange and networking between paediatric and adult gastroenterologists has become a more vital activity due to the enhanced understanding of gastrointestinal infections, the impact of nutrient deficiencies and chronic diseases such as coeliac disease, IBD, and metabolic diseases linked with obesity. Direct exchange between the 2 organisations has developed with invitations to ESPGHAN member to present at UEGW, and UEGF members taking part in ESPGHAN Annual Meetings, ensuring an important translation of basic science and exchange of clinical expertise in the treatment of gastrointestinal-related disease (12). Today ESPGHAN is involved in numerous UEGF initiatives, with representation in the Scientific, Education, and Future Trends Committee and the General Assembly.

THE EUROPEAN SOCIETY OF PAEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION “FAMILY”

In the early years of the Society, the number of members was small and attendance for nonmembers was restricted by invitation. The constitution at that time stated: “A member wishing to introduce a guest at a meeting will submit the name of the guest and the title of his/her paper, if any, to the organizer of the next meeting at least three months prior to the meeting.” In order to become a member the candidate had to present 2 oral papers to the annual meeting of the Society. So the Society at that time was more or less a closed shop and the number of attendees at the annual meeting could always fit into one room at the farewell dinner. Everyone knew each other well and this created a close family feeling among the members and guests. Like in a big family there were often different views, always settled amicably by rigorous debate. Social events centred around the annual meetings and played an important role in the cohesion of the Society. One afternoon of the annual meeting was free and everyone was entertained somewhere outside, enjoying some typical culture of the host country. Many of these gatherings are unforgettable and should be mentioned briefly. Music performed by members played an important role in our Society. At the annual meeting in Graz 1983 Beat Hadorn, as president of the meeting, sang (he is a professional opera singer) and Bertil Lindquist played the piano. When Beat Hadorn was introducing the performance he said: “I am a lucky man today, because it is my 50th birthday and I always wanted to celebrate my birthday with so many people.” He performed again at the annual meeting in Amsterdam 1990, where he sang with the general paediatrician, Nel Beervliet from Paramaribo Dutch Guyana, some Mozart...
opera duets and 3 songs by Maurice Ravel of the Don Quichotte to Dulcinee.

At the annual meeting in Tampere, in 1984, we enjoyed the free afternoon with some Finnish customs, like Wellington boots throwing and the smoked sauna jumping with black bottoms naked into the neighbouring lake. Jarno Visakorpi opened the main farewell dinner with the words: “In Finland on occasions like this, the traditional dishes will be either cold salmon and hot reindeer or hot salmon and cold reindeer. Today you will have cold salmon and hot reindeer.”

Two years later in 1986, at the annual meeting in Edinburgh, Sandy McNeish toasted the “Haggis” with a wonderful ode by Robbie Burns, before we ate the traditional Scottish dish. In Gotenburg, when Birgitta Strandvik was president, we all remember the farewell dinner, held in a traditional old building, where we sat in the main hall and on an upper balcony. All of a sudden paper planes were flying around and people from the upper floor were throwing them down and vice versa for at least an hour enjoying the “battle” very much. In Munich at the annual meeting in 1996 Michael J. Lentze, in the clothes of a typical Bavarian, taught the whole ESPGHAN “family” to sing the traditional Munich song: “In München steht ein Hofbräu-Haus,” and let members of the Society blow into an alp-horn. In Dresden 2006, the year of the world football championship in Germany, an ESPGHAN football match took place at the farewell dinner, where Olle Hernell from Sweden won the cup (Fig. 13). These social events are a vital part of the history of our Society and will be unforgettable memories of the early years of ESPGHAN and explain that “family” like feeling, enjoyed when attending our annual meetings.

The creation of these personal contacts, especially among young scientists and clinicians in ESPGHAN, has very often been the beginning of deep friendships and a fruitful base for future scientific collaboration, helping very much the development of individual careers and the happy feeling that membership of this ESPGHAN “family” engendered.

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REFERENCES

Chapter 3. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition in Recent Years

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ABSTRACT

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition has experienced an amazing development in the 50 years of its existence. It grew from a small group of 36 friends who held an informal meeting with some 20 oral presentations to share and discuss their clinical and research work, to a large, multiprofessional society that sets widely recognized standards for clinical care and policy and hosts the world’s largest congress of Paediatric Gastroenterology, Hepatology and Nutrition with more than 4500 delegates from 100 countries. However, the Society’s mission has remained the same: to promote the health of children with special attention to the gastrointestinal tract, liver, and nutritional status, through knowledge creation, the dissemination of science based information, the promotion of best practice in the delivery of care and the provision of high-quality education. The European Society for Paediatric Gastroenterology Hepatology and Nutrition’s success is based on the enthusiasm and engagement of its membership that contribute extensive volunteer work to support child health, while maintaining a positive spirit of collaboration and friendship, which characterises this Society. This article aims at describing recent developments and the current situation of the European Society for Paediatric Gastroenterology Hepatology and Nutrition.

Key Words: child health, code of conduct, codes of ethics, digestive health, nongovernmental organization, nonprofit organization, standard of care, volunteers

(JPGN 2018;66: S29–S43)
ESPGHAN TODAY

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition is a multiprofessional nonprofit organisation seated in Geneva, Switzerland. ESPGHAN’s mission is to promote the health of children with special attention to the gastrointestinal tract, liver, and nutritional status, through knowledge creation, the dissemination of science-based information, the promotion of best practice in the delivery of care and the provision of high-quality education for paediatric gastroenterology, hepatology, and nutrition professionals in Europe and beyond. The constitution and an operational guide, the ESPGHAN Rules and Regulations document, are available on the website of the association, at www.espghan.org. ESPGHAN provides representation for all professionals involved in Paediatric Gastroenterology, Hepatology and Nutrition (PGHAN), promotes basic, translational, and clinical research; lobbies for stronger support of research and high standards of care; and offers the highest standards of education to members and all professionals involved in PGHAN. ESPGHAN dedicates particular attention to new investigators and trainees to ensure they are supported and encouraged. ESPGHAN also aims to serve as a source of competent advice for governments, international agencies, and relevant stakeholders.

The Annual General Meeting of full ESPGHAN members is the ultimate decision-making body that elects the President, General Secretary and Executive Treasurer (who together form the Executive Committee), 6 additional council members, and the chair of the Local Organizing Committee of the annual congress (Fig. 2). Table 1 presents a list of the Presidents, Secretaries, and Treasurers of ESPGHAN. The chairs of the Young ESPGHAN Committee and of the Allied Health Professionals Committee, and the President Elect or Past President (for 1 year each) also attend the council meetings. Additional volunteers serve as the Editor of the Society’s journal, The Journal of Pediatric Gastroenterology and Nutrition, the website editor, the e-learning editor, chairs of further committees, Special Interest Groups and Working Groups, and others.

ESPGHAN has 3 main standing committees focusing on PGHAN (Fig. 2). They aim at promoting child health and increasing the understanding and treatment of disease states. ESPGHAN members are also involved in a large number of currently ≈30 Special Interest Groups and Working Groups that focus on particular aspects of child care and/or disease states, for example, celiac disease, inflammatory bowel disease, endoscopy, liver transplantation, clinical malnutrition, and early nutrition research, to name just a few (Table 2). The Allied Health Professional Committee aims to enhance the multidisciplinary approach towards PGHAN in Europe. The Young ESPGHAN Committee promotes and supports specialist training and guides trainee members, within the first 5 years after entering subspecialty training, towards full membership of ESPGHAN. ESPGHAN promotes scientific exchange among research groups in Europe and among trainees, young doctors, and scientists through PGHAN Schools, Young Investigator Forums, Monothematic Meetings, Master Classes, International Schools, and Eastern European Schools.

THE ESPGHAN MEMBERSHIP

ESPGHAN is an association of members; the members are the Society. While membership was initially restricted to established academic leaders in the field, over the years the Society has become more and more inclusive. After the recent change of membership criteria, adopted in 2013, membership is now open to all health care professionals dedicated to PGHAN. Consequently, the number of members has been steadily increasing to now more than 800 active and fully paid members (Fig. 3), with an increasing...
The proportion of young members and allied health care professionals such as nurses, dieticians, psychologists and others (Fig. 4). It is particularly encouraging to see a rising proportion of young colleagues joining ESPGHAN (Fig. 5). Women comprise 40% of the members, with a particularly high proportion among younger members. While most members are from Europe, the membership has become truly global, currently representing 72 different countries (Fig. 6).

**DIGITAL INFORMATION SHARING**

With the increasing and global membership, digital sharing and exchange of information has become an important priority to serve the needs of members. Therefore in 2015 we launched a new and markedly improve website (Fig. 7) after investing 2 years of intensive work of the president, treasurer, website editor and council. We are proud of an intuitive and easy to navigate website with modern web design and much enhanced functional capabilities. Social media share buttons are integrated. The “MyESPGHAN”—section offers personalized pages and additional information for members. Since 2017, members can also post questionnaires and job posting on our website. It is encouraging to note great acceptance and high usage of our improved website. We also introduced in 2014 a new, interactive electronic newsletter, which is sent out monthly to all members and provides regular updates on news, current developments and opportunities, and upcoming events.

**STANDARDS OF PRACTICE: THE ESPGHAN CODE OF CONDUCT**

ESPGHAN is dedicated to excellence and integrity in scientific and medical clinical practice aiming at generating and consolidating trust at all levels. Therefore, we started an initiative to

<table>
<thead>
<tr>
<th>President</th>
<th>Secretary</th>
<th>Treasurer</th>
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</thead>
<tbody>
<tr>
<td>Prof Dolf Weijers</td>
<td>Prof Bertil Lindquist</td>
<td>Not nominated</td>
</tr>
<tr>
<td>Prof Bertil Lindquist</td>
<td>Prof Jarmo K. Visakorpi</td>
<td>Not nominated</td>
</tr>
<tr>
<td>Prof Jean Rey</td>
<td>Prof Alexander S. McNeish</td>
<td>Prof Helmuth Loeb</td>
</tr>
<tr>
<td>Prof Jarmo K. Visakorpi</td>
<td>Prof John Walker Smith</td>
<td>Prof Eberhard Schmidt</td>
</tr>
<tr>
<td>Prof Alexander S. McNeish</td>
<td>Prof Armindo Rubino</td>
<td>Prof Michael Lentze</td>
</tr>
<tr>
<td>Prof Salvatore Auricchio</td>
<td>Prof Jacques Schmitz</td>
<td></td>
</tr>
<tr>
<td>Prof Birgitta Strandvik</td>
<td>Prof John Walker Smith</td>
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<tr>
<td>Prof Jacques Schmitz</td>
<td>Prof Isabel Polanco</td>
<td></td>
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<tr>
<td>Prof Samy Cadranel</td>
<td>Prof Peter Milia</td>
<td>Prof Dominique Belli</td>
</tr>
<tr>
<td>Prof Stefano Guandalini</td>
<td>Prof Markku Maki</td>
<td></td>
</tr>
<tr>
<td>Prof Peter Milia</td>
<td>Dr Jan Taminau</td>
<td>Dr Jorge Amil Dias</td>
</tr>
<tr>
<td>Prof Michael Lentze</td>
<td>Prof Jean-Pierre Olives</td>
<td></td>
</tr>
<tr>
<td>(Germany) 2004–2007</td>
<td>2003–2006</td>
<td></td>
</tr>
<tr>
<td>Prof Deirdre Kelly</td>
<td>Prof Riccardo Troncone</td>
<td></td>
</tr>
<tr>
<td>Prof Riccardo Troncone</td>
<td>Prof Hania Szajewska</td>
<td></td>
</tr>
<tr>
<td>(Italy) 2010–2013</td>
<td>2009–2012</td>
<td></td>
</tr>
<tr>
<td>Prof Berthold Koletzko</td>
<td>Prof Sanja Kolacek</td>
<td>Prof Alan Phillips</td>
</tr>
<tr>
<td>Prof Raanan Shamir</td>
<td>Prof Gigi Veereman</td>
<td>Prof Annamaria Staiano</td>
</tr>
</tbody>
</table>

**TABLE 2. ESPGHAN Working Groups and Special Interest Groups 2017**

<table>
<thead>
<tr>
<th>WG / SIG</th>
<th>Chair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenterology</td>
<td>Silvia Salvatore</td>
</tr>
<tr>
<td>Motility and Neurogastroenterology</td>
<td>Dan Turner</td>
</tr>
<tr>
<td>Paediatric and Adolescent Inflammatory Bowel Diseases</td>
<td>Jorge Amil Dias</td>
</tr>
<tr>
<td>Eosinophilic Gastrointestinal Diseases</td>
<td>Patrick Bontems</td>
</tr>
<tr>
<td>Helicobacter pylori Infection</td>
<td>Michael Wilschanski</td>
</tr>
<tr>
<td>Cystic Fibrosis and Pancreatic Disease</td>
<td>Frederie Godtrande</td>
</tr>
<tr>
<td>Esophageal atresia</td>
<td>Matthias Zilbauer</td>
</tr>
<tr>
<td>Epigenetics: Epigenetics in Paediatric Gastroenterology, Hepatology And Nutrition (EPacGHAN)</td>
<td>David Malins</td>
</tr>
<tr>
<td>Paediatric Polyposis</td>
<td>Warren Hyer</td>
</tr>
<tr>
<td>GENIUS (GENetically determined ImmUne-mediated EnteropathieS)</td>
<td>Frank Ruemmele</td>
</tr>
<tr>
<td>Special Interest Group: Endoscopy</td>
<td>Mike Thomson</td>
</tr>
<tr>
<td>Special Interest Group: Coeliac Disease</td>
<td>Carmen Ribes Koninckx</td>
</tr>
<tr>
<td>Hepatology</td>
<td>Valerie McLin</td>
</tr>
<tr>
<td>Hepatology Interest Group</td>
<td>Girish Gupta/Florence Lacaille</td>
</tr>
<tr>
<td>Internat. Registry of Porto Systemic Shunts</td>
<td>Deirdre Kelly</td>
</tr>
<tr>
<td>Intestinal Failure – Associated Liver Disease Special Interest Group</td>
<td>Hania Szajewska / Zvi Weizman</td>
</tr>
<tr>
<td>GIGOLO - Graft Injury after LTx</td>
<td>Jessica Hulst</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Hana Szajewska / Zvi Weizman</td>
</tr>
<tr>
<td>Pre and Probiotics</td>
<td>Berthold Koletzko</td>
</tr>
<tr>
<td>Clinical Malnutrition</td>
<td>Hans Van Goudoever</td>
</tr>
<tr>
<td>Early Nutrition Research</td>
<td>Hana Szajewska</td>
</tr>
<tr>
<td>Working Group on Outcomes in Nutrition Trials</td>
<td>Hans Van Goudoever</td>
</tr>
<tr>
<td>NEOMUNE: Newborn immunity, gut and brain</td>
<td>Hans Van Goudoever</td>
</tr>
</tbody>
</table>

**www.jpgn.org**
develop a comprehensive document to address these important issues, which ESPGHAN adopted in 2015 as its “Code of Conduct” (see Supplementary Material 1, Supplemental Digital Content 1, http://links.lww.com/MPG/B282). The document summarizes the ethical foundations of ESPGHAN’s obligation to ensure that paediatricians and allied health care professionals acquire and maintain knowledge, skills, and values that are central to paediatrics and child health without undue bias due to financial or commercial interests. The ESPGHAN Code of Conduct analyses the ethical challenges that can be posed when ESPGHAN members who organize, teach, or serve other roles in medical education have financial relationships with companies that have a direct interest in recommendations. It also illustrates strategies for mitigating the potential of such financial relationships to influence professional education in undesired ways. ESPGHAN’s Code of Conduct also governs the relationship between ESPGHAN and industry representatives involved in the support of research and educational activities in the field of PGHAN. Besides identifying the principles of transparency, independence and accountability, the Code of Conduct provides a practical approach to how to maintain the independence and integrity of ESPGHAN’s related professional education while promoting a trustworthy relationship between ESPGHAN and commercial companies. We are conscious that the ethical conduct of our association must go beyond the sole development and adoption of this Code of Conduct, but that we also need to foster a culture of integrity, responsibility, transparency, and critical open discussion in our organisation, focussing on the interest of our patients and their families.

THE ANNUAL CONGRESS OF ESPGHAN

The ESPGHAN annual congress (Fig. 8A–F) is the largest meeting in PGHAN in the world, with an attendance in 2017 that exceeded 4500 delegates from almost 100 countries on all 5 continents. The congress offers an excellent platform for members and nonmembers to exchange new research findings in the different fields of our specialty, to hear updates on the state of the art in research, clinical practice, and policy, and to meet key opinion leaders and colleagues from all over the world. It also gives ESPGHAN members opportunities for working group meetings and postgraduate courses. The number of abstracts submitted has been steadily increasing and has now reached close to 1000 abstracts per year. To serve the interest of the large number of clinical practitioners attending the meeting, in 2014 we introduced a new Clinical Practice Track and in 2015 a new hands-on learning zone in endoscopy, which have all been highly appreciated and successful. The use of digital tools is continuously expanded, with an interactive congress app for handheld devices, ePosters, a Virtual Meeting Site, and a Website on Demand, which enhance information sharing and convenience for delegates, for example, by accessing handouts and webcasts of presentations. Since 2015 our annual congress is joined by a variety of patient and parent organisations at the congress with whom we wish to closely collaborate to achieve our goal to optimally support patients and their families. Our members can enjoy the added privileges of the ESPGHAN Members Lounge to meet or enjoy a quiet moment, and the newly introduced Young ESPGHAN Lounge. The annual Members Dinner at the congress provides a unique opportunity for meeting friends and colleagues in a relaxed atmosphere, and to enjoy a programme of great fun.

COMMITTEES, SPECIAL INTEREST GROUPS, AND WORKING GROUPS

ESPGHAN’s main Committees on Gastroenterology, Hepatology and Nutrition, and the many other Committees (Table 3) and Special Interest and Working Groups (Table 2) engage in numerous activities throughout each year, such as developing
recommendations and clinical guidelines on pertinent topics in the field, facilitation, and execution of collaborative research studies, and engagement in educational and training activities. Many ESPGHAN guidelines have set global standards for practice, clinical care, policy and regulatory decisions not only in Europe but throughout the world and are highly cited, for example, 799 citations of the guideline for the diagnosis of coeliac disease 2012 (1), 408 citations of the ESPGHAN Comment on Complementary Feeding 2008 (2), 372 citations of the guideline on enteral nutrient supply for premature infants (3), 285 citations of the comment on dietary products for infants treatment and prevention of food allergy (4), 229 citations of the global standard for infant formula composition (5), and 204 citations of the comment on breastfeeding (Web of Science, October 26, 2017).

With the increasing role of ESPGHAN in influencing research and clinical practice, the need to discuss issues of importance to child health, conditions of clinical care, and research with political decision makers particularly at the European level has become more pressing. Therefore, in 2013 we created the new Public Affairs Committee to raise awareness for themes related to paediatric digestive health, with a particular focus on the European Commission and European Parliament where repeated meetings and events were held to lobby for greater support for child health and related research (Fig. 9). The Public Affairs Committee also engages in interaction with international agencies such as the World Health Organisation, the European Medicines Agency (6), and the Codex Alimentarius where ESPGHAN has been accepted as a registered observer organisation in 2003 and ever since has proactively contributed to the development of standards for dietetic food products for infants and young children (5,7). The Public Affairs Committee coordinates the close collaboration of ESPGHAN with patient and parent associations related to paediatric digestive health, which is considered to be a key strategic priority.

The History Committee was newly formed in 2014 with the goals to compile the history of PGHN and of ESPGHAN, and to build an ESPGHAN archive with records of the foundation of the Society, annual meetings, and other activities. This very publication on the occasion of the 50th anniversary of ESPGHAN is a result of the successful work of this Committee.

**YOUNG ESPGHAN**

The Trainee Committee was formed in November 2009 during the United European Gastroenterology (UEG) Congress in London with the vision to involve and support trainees in PGHN within ESPGHAN. One of the first meeting reports concludes: “The ESPGHAN Trainee committee is currently surveying the trainees to identify how training is carried out in the member countries. From this we may be able to ascertain areas of training which need targeting, this may include practical procedures and log books, theoretic knowledge, mentoring or the identification of training leads.” The Society encouraged the Young ESPGHAN Committee to expand the group and facilitated the involvement of Trainee Members with ESPGHAN, for example, by becoming members of the other standing committees. In 2015, the name of the Committee was changed to “The Young ESPGHAN Committee: Committee for Trainees and Young Investigators” to indicate that all young members within the first 5 years after joining the society should be represented, including nonclinical scientists and early career clinicians who already finished their training. Today young ESPGHAN members comprise the fastest growing membership category within ESPGHAN. The Young ESPGHAN Committee meets face-to-face twice yearly and reaches out to its members

![Age distribution of ESPGHAN members 2017.](image1)

**FIGURE 5.** Age distribution of ESPGHAN members 2017.

![Geographical distribution of ESPGHAN members 2017.](image2)

**FIGURE 6.** Geographical distribution of ESPGHAN members 2017.

www.jpgn.org
FIGURE 7. Snapshot from the ESPGHAN website 2017.
via e-mail, LinkedIn, and Twitter, with the last one being very popular during the annual conferences. It channels its members’ concerns via surveys and round table discussions at the annual conferences. Furthermore, the committee is actively involved with e-learning, ESPGHAN summer schools, and endoscopy/motility learning zones at the annual conferences and promotes these activities to its membership. During the annual conference, Young ESPGHAN has held its own workshop on career development skills, and during the last members’ dinners the committee attracted ESPGHAN members by rewarding the “best behaving” monkey group and the “cleverest pilot”! In 2016, a group of 5 Young ESPGHAN members received the FISPGHAN expert team award at the WCPGHAN in Montreal, Canada, and produced a very instructive teaching video on treatment of acute gastroenteritis, which is now available at www.fispghan.org. The Young ESPGHAN committee has reached out to the Young NASPGHAN

![Images of ESPGHAN Congress 2015, Amsterdam.](A) Prof Marc Benninga at the opening cabaret. (B) Prof Marc Benninga at the opening cabaret. (C) Prof Bert Koletzko at the reception for Patient and Parent Organisations. (D) Prof Luigi Dall’Oglio (far right) teaching at the Endoscopy Learning Zone. (E) The abstract presentations of new results through posters, e-posters, and oral presentations are the core of ESPGHAN congresses and always draw a lot of attention. (F) Prof Raanan Shamir presenting the ESPGHAN Distinguished Service Award 2017 to Prof Olivier Goulet.)

FIGURE 8. A, 48th ESPGHAN Congress 2015, Amsterdam. B, Prof Marc Benninga at the opening cabaret, 48th ESPGHAN Congress 2015, Amsterdam. C, Prof Bert Koletzko at the reception for Patient and Parent Organisations, ESPGHAN Congress. D, Prof Luigi Dall’Oglio (far right) teaching at the Endoscopy Learning Zone, ESPGHAN Congress. E, The abstract presentations of new results through posters, e-posters, and oral presentations are the core of ESPGHAN congresses and always draw a lot of attention. F, Prof Raanan Shamir presenting the ESPGHAN Distinguished Service Award 2017 to Prof Olivier Goulet.
Committee, Young Talent Group UEG and Young ECCO. In 2017, the society and Young ESPGHAN have started a mentoring program for its new Young members. Young ESPGHAN is also working on optimizing transition from Young to Full ESPGHAN membership. The Young ESPGHAN thanks for tremendous support it has received from the ESPGHAN Presidents Deirdre Kelly, Riccardo Troncone, Berthold Koletzko, and Raanan Shamir.

Over the years, Young ESPGHAN has established itself with an important role within ESPGHAN, and its activities have been very well received and greatly appreciated. The ongoing enthusiasm and engagement of Young ESPGHAN in the ESPGHAN activities and the support from the ESPGHAN members and its Council provide an excellent basis for a bright future of ESPGHAN!

**TABLE 3. ESPGHAN Committees 2018**

<table>
<thead>
<tr>
<th>Committee</th>
<th>Chair</th>
<th>Term of Chair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Committee on Gastroenterology</td>
<td>Nikhil Thapar</td>
<td>2015–2019</td>
</tr>
<tr>
<td>Committee on Hepatology</td>
<td>Henk Jan Verkade</td>
<td>2017–2019</td>
</tr>
<tr>
<td>Committee on Nutrition</td>
<td>Mary Fewtrell</td>
<td>2015–2018</td>
</tr>
<tr>
<td>Young ESPGHAN – Trainee Committee</td>
<td>Nicolette Moes</td>
<td>2015–2018</td>
</tr>
<tr>
<td>Allied Health Professionals Committee</td>
<td>Tena Niseteo</td>
<td>2015–2018</td>
</tr>
<tr>
<td>Scientific Committee</td>
<td>Piotr Socha</td>
<td>2015–2018</td>
</tr>
<tr>
<td>Finance &amp; Investment Committee</td>
<td>Annamaria Staiano</td>
<td>2016–2019</td>
</tr>
<tr>
<td>Public Affairs Committee</td>
<td>Deirdre Kelly</td>
<td>2017–2020</td>
</tr>
<tr>
<td>Publication Committee</td>
<td>Berthold Koletzko</td>
<td>2016–2019</td>
</tr>
<tr>
<td>Ethics Committee</td>
<td>Martin Burdelski</td>
<td>2015–2018</td>
</tr>
<tr>
<td>History Committee</td>
<td>Lawrence Weaver</td>
<td>2015–2018</td>
</tr>
</tbody>
</table>

**FIGURE 9.** The ESPGHAN Public Affairs Committee meets with members of the European Parliament and representatives of the European Commission in the European Parliament building to discuss the need for stronger research funding in the area of paediatric gastroenterology, hepatology, and nutrition.
ESPGHAN working group Clinical Malnutrition to explore the prevalence and effects of undernutrition among more than 2500 hospitalised children in 12 countries, and it also studies opportunities for nutrition screening (9,10). The European Commission (EC) funded “PreventCD” project (http://www.preventcd.com) coordinated by Maria Luisa Mearin studied the natural history of coeliac disease and the effects of infant feeding on disease manifestation (11). The “Early Nutrition Project” coordinated by Berthold Koletzko and also funded by the EC (www.project-earlnutrition.eu) explores long-term effects of early nutrition on later health, with a focus on opportunities for prevention of obesity and associated disorders (12). The EC funded “Paediatric Inflammatory Bowel Disease network for Safety, Efficacy, Treatment and Quality Improvement of Care” (http://cordis.europa.eu/project/rcn/199745_en.html) coordinated by Frank Ruehmmele aims to establish a long-term inception cohort of paediatric IBD patients and to perform a randomised clinical therapeutic trial. The EU funded regional project “Focus in CD – Innovative coeliac disease learning model for health care professionals in the Danube region” (http://www.interreg-central.eu/Content/Node/Focus-in-CD.html) coordinated by Jasmina and Jernej Dolinsek aims at strengthening knowledge and awareness on coeliac disease among health care professionals and the general public. The Erasmus Plus programme in Capacity Building in Higher Education funded the “Early Nutrition eAcademy South East Asia” coordinated by Berthold Koletzko focuses on E-learning in paediatric nutrition for health care professionals in Malaysia, Thailand, and neighbouring countries, in close collaboration with ESPGHAN’s E-learning programme. Many more opportunities exist for successful research and education activities based on the strong ESPGHAN network. Following previous successes, in 2018 ESPGHAN provides 3 grants of 50,000 Euros each to support and enable the creation of more successful networks.

EDUCATION

ESPGHAN strives to develop an up-to-date, independent, high-quality educational programme for health professionals that caters to their immediate and changing needs. ESPGHAN seeks to continuously improve its educational programme and to present additional courses and educational materials that cover niches or complement existing training opportunities and products. In addition, ESPGHAN believes it has a responsibility for the education of underprivileged areas outside Europe where the needs for education and training are more urgent, although learning and research priorities may be substantially different. The ESPGHAN training activities are guided by the European Training Syllabus in Paediatric Gastroenterology, Hepatology and Nutrition that was updated in 2014 (13) and defines minimum requirements for training to support recognition as a European Specialist in paediatric gastroenterology, hepatology, and nutrition, along with a logbook on necessary achievements. The Education Task Force, established in 2017, aims to integrate all core activities within a 5-year cycle.

The ESPGHAN Summer Schools for trainees and fellows have become regular events and a huge success story ever since the inception of the first Gastroenterology School in 1990 and the first Nutrition School in 1991. The combination of high-quality training with an informal, communicative atmosphere, and the close interaction of delegates and a small resident faculty creates an unforgettable learning experience for participants, many of whom have become active ESPGHAN members. Since its beginning ESPGHAN has established close links between western, central and eastern Europe and has built bridges and strong links across Europe. After the fall of the boundary dividing former “Western Europe” and the “Warsaw Pact Countries” and the end of the Cold War, these links have been proactively strengthened and dedicated ESPGHAN summer schools were held at least once a year in Central and Eastern Europe. These courses have attracted many highly talented colleagues from this part of the world to join ESPGHAN, a number of which today are among the thought leaders of our society. Training activities have also been organized outside of Europe to support areas with special needs, for example, the ESPGHAN Update Course for colleagues from the middle east countries held in Istanbul, Turkey, in 2014 (Fig. 10), the Training Course for Rising Stars from Latin America hosted by LASPGHAN in Cancun, Mexico, in 2014 in collaboration with ESPGHAN and NASPGHAN, or the International Paediatric Nutrition School in Thailand in 2016 organized jointly by ESPGHAN and the Society of Paediatric Nutrition of Thailand (Fig. 11). Perhaps the most successful training outside of Europe has been the regular “ESPGHAN goes Africa” diploma course for African colleagues, with two 1-week courses per year held in Cape Town from to 2012 to 2015, in close collaboration with the Universities of Cape Town and of Stellenbosch, South Africa (Fig. 12). About 120 paediatricians from the whole Sub-Saharan African region received intensive training in paediatric gastroenterology, hepatology, and nutrition based on lectures, case presentations with intense discussions, e-learning, visits to local hospitals, and final examinations. ESPGHAN provided financial support to more than 20 of the participating colleagues to attend the reciprocal “Africa goes ESPGHAN” event held at the 49th Annual Congress of ESPGHAN at Athens in 2016.

EDUCATION PARTNER PROGRAMME

To further stabilize and strengthen the numerous regular education activities, we launched in 2015 the ESPGHAN Education Partner Programme that aims at ensuring the on-going development and implementation of an up-to-date, independent, high-quality educational programme for health care professionals. It is designed and implemented in full compliance with current professional and Continuing Medical Education (CME) standards and with our Code of Conduct, to promote confidence in independence, integrity and credibility of ESPGHAN and its industry partners. The key target groups include Trainee Members and other young health care professionals.
professionals (addressed primarily by the ESPGHAN Summer Schools and the Young Investigator Forum), established specialists (addressed by the new Master Classes introduced in 2015 that are offered exclusively for ESPGHAN members), as well as health care professionals from less privileged areas (Eastern European Summer Schools, International Schools). In 2017, 7 sponsors (www.espghan.org/education/) each donated 50 000 Euro to support the training courses listed in Table 4.

ESPGHAN AWARDS AND GRANTS

ESPGHAN provides numerous grants, awards, and prizes to members and nonmembers, including

- Annual Research and Networking Grants, EUR 50,000 (3 per year).
- Charlotte Anderson Travel Award, EUR 3000.
- ESPGHAN International Exchange, EUR 3000 (7 per year).
- Young Investigator Awards (YIA) for abstract presenters at the ESPGHAN, UEG and WCPGHAN conferences up to EUR 1000.
- John Harries, Alex Mowat, and Jean Rey Prizes (best abstract presentations at the ESPGHAN congress in the fields of gastroenterology, hepatology, and nutrition, respectively), EUR 2500.
- The joint ESPGHAN / NASPGHAN Travel Award, USD/ EUR 5,000.

The highest honour of the Society is the ESPGHAN Distinguished Service Award that was inaugurated in 2010 (14). It is presented annually to an individual who has made a major contribution to the development of paediatric gastroenterology, hepatology, or nutrition. The selection criteria include

- Outstanding scientific achievements related to paediatric gastroenterology and/or hepatology, and/or nutrition, usually documented by the candidate’s publication and citation record
- Outstanding contributions to the standards, practice, and training in the fields of paediatric gastroenterology and/or hepatology and/or nutrition
- Outstanding contributions to ESPGHAN as a society
- Personal integrity.

This special honour has been awarded to Profs John Walker-Smith in 2010 (14), Salvatore Auricchio in 2011, Martin Burdelski in 2012, David Branski in 2013 (15), Peter Milla in 2014 (16), Olle Hernell in 2015 (17), Deirdre Kelly in 2016 (18), and Olivier Goulet in 2017 (19).
TABLE 4. Training activities under the ESPGHAN education partnership programme in 2017

- ESPGHAN Paediatric Nutrition Summer School: Beyond the Nutrients
- ESPGHAN Danube/Balkan Summer School
- ESPGHAN Allied Health Professional Summer School
- ESPGHAN Young Investigator Forum
- ESPGHAN Paediatric Gastrointestinal Motility Hands-On Training Course
- ESPGHAN Gastroenterology Summer School
- ESPGHAN Master Class on Gastrointestinal Immunology
- ESPGHAN 3rd Paediatric Inflammatory Bowel Disease Masterclass
- ESPGHAN Monothematic Conference: Chronic Liver disease in children treatment and follow-up

COLLABORATION WITH OTHER ASSOCIATIONS

ESPGHAN has engaged in partnering with several other associations with joint interests (Table 5). For a number of years, representatives of the national PGHAN societies across Europe have met with the ESPGHAN officers at the ESPGHAN Congress to discuss issues of common interest and opportunities for harmonization. To strengthen the collaboration of the national associations across Europe among each other and with ESPGHAN, we formally established the ESPGHAN National Societies Forum in 2015 as a platform for sustained collaboration and joint activities with all Presidents of National PGHAN societies across Europe to act as a bidirectional link between ESPGHAN and the National Societies. As a first project, a joint standard for implementing training in PGHAN is supposed to be developed, based on the ESPGHAN Training Syllabus (13), aiming towards enhanced harmonization and quality assurance of subspecialty training across Europe.

COLLABORATION WITH THE NORTH AMERICAN SOCIETY OF PEDIATRIC GASTROENTEROLOGY

The most long-standing and closest collaboration of ESPGHAN probably is that with its North American sister society, which actually was established after the model of the European society by Jon Vanderhoof after he participated in the ESPGAN (then still without Hepatology in the name) conference in 1986 in Edinburgh. The close collaboration is facilitated by a number of individuals that are members of both ESPGHAN and NASPGHAN, regular participation of European and North American colleagues, respectively, in the annual congresses on the other side of the Atlantic, a series of successful joint congresses held in 1978 in Paris, 1985 in New York, 1990 in Amsterdam, 1994 in Houston, and 1998 in Toulouse, which laid the ground for the creation of the World Congresses on PGHAN held from 2000 onwards (see below), a large number of joint guidelines and position papers, and not the least joint engagement in the co-owned journal.

THE JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION

A visible manifestation of the close and trusting collaboration of ESPGHAN and NASPGHAN is the Journal of Pediatric Gastroenterology and Nutrition (JPGN; www.jpgn.org). The journal was founded by Dr Emanuel Lebenthal and became the official journal of both societies in 1991. This only journal dedicated to PGHAN today is managed jointly by an ESPGHAN editor (currently Hania Szajewska, Warsaw) and a NASPGHAN editor (currently Mel Heymans, San Francisco). The current (2016) journal Impact Factor is 2.799, after 2.298 in 2011, 2.196 in 2012, 2.873 in 2013, 2.625, in 2014 and 2.400 in 2015. Our Journal is valued as one of the top paediatric subspecialty journals and has established itself as a leading platform for publishing research articles related to PGHAN as well as guidance on clinical practices, such as the guidelines of ESPGHAN and NASPGHAN and the working group conclusions of FISPGHAN. JPGN publishes original papers and reviews dealing with all aspects of PGHAN, including normal and abnormal functions of the alimentary tract, the liver, and associated organs. Particular emphasis is devoted to developmental aspects, and to infant and childhood nutrition. JPGN offers fast-track publication available for selected articles of general scientific or public health importance. Accepted original manuscripts are posted as Publish Ahead of Print (PAP) within 3 of 5 days of acceptance and indexed in PubMed within a few days. The full text is available to all ESPGHAN and NASPGHAN members, online and in print, and to numerous institutions worldwide. Articles are open to the public 1 year after publication.

THE CREATION OF FISPGHAN AND THE WORLD CONGRESS SERIES

Building on the success of the combined NASPGHAN-ESPGHAN meetings and the attendance of colleagues from around the world, in 1998 the ESPGHAN president Stefano Guandalini initiated a discussion about expanding these into global World Congresses to address PGHAN issues and colleagues from all parts of the globe. Obviously he was very convincing, since a first World Congress was successfully held in Boston, when also the global Federation of International Societies on Paediatric Gastroenterology, Hepatology and Nutrition (FISPGHAN; www.fispghan.org) was created by the sisters in the Asian and Pacific region (APPSPGHAN), Europe (ESPGHAN), Latin America (LASPGHAN), and North America (NASPGHAN), with additional associate membership of the Commonwealth Association (CAPGAN) and since 2016 also of the Pan Arabian (PAPGHAN) societies. The Second World

TABLE 5. Close partner societies of ESPGHAN

<table>
<thead>
<tr>
<th>National Societies</th>
<th>All national paediatric gastroenterology, hepatology and nutrition societies across Europe</th>
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<tbody>
<tr>
<td>FISPGHAN</td>
<td>Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition</td>
</tr>
<tr>
<td>NASPGHAN</td>
<td>North American Society for Pediatric Gastroenterology, Hepatology and Nutrition</td>
</tr>
<tr>
<td>LASPGHAN</td>
<td>Latinamerican Society for Pediatric Gastroenterology, Hepatology and Nutrition</td>
</tr>
<tr>
<td>APPSPGHAN</td>
<td>Asian Pan Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition</td>
</tr>
<tr>
<td>CAPGHAN</td>
<td>Commonwealth Association of Paediatric Gastroenterology &amp; Nutrition</td>
</tr>
<tr>
<td>UEG</td>
<td>United European Gastroenterology</td>
</tr>
<tr>
<td>EAP</td>
<td>European Academy of Paediatrics</td>
</tr>
<tr>
<td>EPA/UNEPSA</td>
<td>European Paediatric Association, the Union of National European Paediatric Societies and Associations</td>
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</table>
Congress in Paris, France in 2004 was co-hosted by Prof Olivier Goulet and ESPGHAN. The next world congress will be jointly hosted by FISPGHAN and ESPGHAN in Copenhagen in June 2020. In addition to the World Congresses, FISPGHAN also maintains expert working groups that develop position and guideline papers with global perspectives.

UNITED EUROPEAN GASTROENTEROLOGY

ESPGHAN was 1 of the 7 sister associations that jointly discussed the idea of creating an umbrella organisation to represent all aspects of digestive health in Europe and in 1990 formally created the United European Gastroenterology (UEG). The first UEG congress, then called the UEG week, was held in 1992 at Athens. UEG has since experienced an enormous growth and success. UEG now incorporates 20 European gastroenterological subspecialty societies and 49 national gastroenterological societies. The annual UEG congress attracts more than 14,000 delegates from all over the world, including also an ever-increasing attendance of North American delegates. Many ESPGHAN members attend the UEG congress regularly not only because ESPGHAN is one of the ‘founding sisters’ of UEG, but also because it is a prime opportunity to exchange with our adult colleagues on recent trends in clinical gastroenterology and related basic science. ESPGHAN is a very active contributor to the activities of UEG through its proactive representation in the Meeting of Members, Education Committee, Scientific Committee, Public Affairs Committee, and the Research Board. ESPGHAN members held positions at the Executive level (UEG treasurer) and currently, our immediate past president Berthold Kohletzko is the UEG Council representative for the 11 Medical Gastroenterological Associations that are members in UEG. ESPGHAN benefits from the UEG collaboration in many aspects, including for example significant support for educational activities through educational grants, and added leverage in European lobbying activities through joining forces with the large and professional UEG infrastructure. For example, UEG and ESPGHAN jointly developed a brochure and performed extensive, targeted lobbying activities at the European parliament and European Commission level to raise awareness and support of key challenges in paediatric digestive health, including liver health and nutrition (Fig. 13). There are some first indications that our voices have been heard at least to some extent, given that some of the proposed opportunities have been incorporated into the work programmes of the Horizon 2020 research funding.

DISTANCE LEARNING (E-LEARNING) IN COLLABORATION WITH UNITED EUROPEAN GASTROENTEROLOGY

An example of very fruitful collaboration between ESPGHAN and UEG is the establishment of a programme for electronic distance learning, which has become a standard educational tool in medical schools around the world. e-Learning is a valuable element that helps address the gaps created by limited face-to-face, evidence-based, and applicable information of health care professionals, who are often challenged by time and budget constraints. e-Learning enables easy access from the workplace or from home or abroad, self-paced learning, no travel and onsite costs, and interactivity. Since 2012, ESPGHAN has started to build an e-learning programme that is embedded in ESPGHAN’s PGHAN specialist training syllabus (13), supported by the technical and logistic infrastructure of UEG (https://www.ueg.eu/education/online-courses/). ESPGHAN has also partnered with the Early Nutrition eAcademy to jointly develop and implement courses related to nutrition in early life (http://www.early-nutrition.org/en/enea/).

COLLABORATION WITH OTHER PAEDIATRIC ASSOCIATIONS

ESPGHAN regularly collaborates with a variety of European and national paediatric associations, for example, with joint sessions addressing paediatric digestive health at the respective congresses. ESPGHAN has a permanent representation at the European Academy of Pediatrics (EAP) to represent PGHAN at the European Union of Medical Specialists (UEMS) and currently chairs their Tertiary Care Committee. UEMS is the oldest European medical organisation created in 1958 that defines the standards of medical education and training and subspecialty accreditation in the European Union. ESPGHAN also regularly contributes to the programme planning of the biannual EAP congress. It is also partners with the European Paediatric Association – Union of European Paediatric Societies and Associations (EPA-UNEPSA) that was founded in 1976 and serves as an umbrella organisation of 49 national paediatric associations. ESPGHAN has provided the chair of the Scientific Committee coordinating the programme development of the 8th Europaeiatrics Congress in Bucharest in 2017 (Tables 6 and 7).

FUTURE OPPORTUNITIES AND CHALLENGES

As ESPGHAN has gone from strength to strength during the last 5 decades, it appears to be well prepared to looking forward to the future and to prepare for the challenges and opportunities that the years to come may bring. We continue to strive for further improving our ability to promote child health, to treat and prevent challenges to digestive health in children and adolescents, and to strengthen the knowledge base that is required to do so. Close collaboration among all health professionals involved in this area, along with patients, families, and the many involved stakeholders and decision makers, will be key to achieving our goals. ESPGHAN provides a strong platform and great opportunity for such a fruitful collaboration. The increasing number of young and trainee members in recent years is very impressive and ensures that ESPGHAN
remains a young society, but more efforts are needed to support the growth also of allied health professional members and to provide attractive offers for this important group of members, such as the first ESPGHAN allied health professional summer school held in 2017.

The ESPGHAN Strategy Plan 2016–2019 (see supplementary material 1, Supplemental Digital Content 1, http://links.lww.com/MPG/B282) has been developed based on thorough and detailed discussions amongst thought leaders of the Society gathered at the annual ESPGHAN strategy days and the ESPGHAN council, with subsequent discussion with and input from the whole membership. Our Strategy Plan defines our mission, our strategic priorities, and the actions to achieve those and provides a roadmap for the actions to be implemented by the Society in the years after its

<table>
<thead>
<tr>
<th>Year</th>
<th>Meeting</th>
<th>Location</th>
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<tr>
<td>2016</td>
<td>2016 4th FISPGHAN World Congress</td>
<td>Montreal, Canada</td>
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<tr>
<td>2017</td>
<td>50th Annual Meeting</td>
<td>Prague, Czech Republic</td>
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<td>2016</td>
<td>49th Annual Meeting</td>
<td>Athens, Greece</td>
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<tr>
<td>2015</td>
<td>48th Annual Meeting</td>
<td>Amsterdam, Netherlands</td>
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<td>2014</td>
<td>47th Annual Meeting</td>
<td>Jerusalem, Israel</td>
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<td>2013</td>
<td>46th Annual Meeting</td>
<td>London, UK</td>
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<td>2012</td>
<td>Update Meeting</td>
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<td>2011</td>
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<td>Sorrento, Italy</td>
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<td>2010</td>
<td>43rd Annual Meeting</td>
<td>Istanbul, Turkey</td>
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<td>2009</td>
<td>42nd Annual Meeting</td>
<td>Budapest, Hungary</td>
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<tr>
<td>2008</td>
<td>41st Annual Meeting and 3rd FISPGHAN World Congress</td>
<td>Iguassu Falls, Brazil</td>
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<td>2007</td>
<td>40th Annual Meeting</td>
<td>Barcelona, Spain</td>
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<td>2006</td>
<td>39th Annual Meeting</td>
<td>Dresden, Germany</td>
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<td>2005</td>
<td>38th Annual Meeting</td>
<td>Porto, Portugal</td>
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<td>2004</td>
<td>37th Annual Meeting and 2nd FISPGHAN World Congress</td>
<td>Paris 2nd World Congress</td>
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<td>2003</td>
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<td>2002</td>
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<td>2001</td>
<td>34th Annual Meeting</td>
<td>Geneva, Switzerland</td>
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<td>1999</td>
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<td>1997</td>
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<td>1995</td>
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<td>1988</td>
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<td>1987</td>
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<td>1986</td>
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<td>New York City, NY, USA</td>
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<td>1984</td>
<td>17th Annual Meeting</td>
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<td>1983</td>
<td>16th Annual Meeting</td>
<td>Graz, Austria</td>
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<td>1982</td>
<td>15th Annual Meeting</td>
<td>Madrid, Spain</td>
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<td>1981</td>
<td>14th Annual Meeting and Joint Meeting with ESPR, ESPHI, EPRS</td>
<td>Bern, Switzerland</td>
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<td>1980</td>
<td>13th Annual Meeting</td>
<td>Capri, Italy</td>
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<td>1979</td>
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<td>1978</td>
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<td>1977</td>
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<td>Utrecht, Sweden</td>
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<td>1976</td>
<td>9th Annual Meeting</td>
<td>Weimar, German Democratic Republic</td>
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<td>1975</td>
<td>8th Annual Meeting</td>
<td>Leuven-Brussels</td>
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<td>1974</td>
<td>7th Annual Meeting</td>
<td>Verona, Italy</td>
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<td>1973</td>
<td>6th Annual Meeting</td>
<td>Helsinki, Finland</td>
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<td>1972</td>
<td>5th Annual Meeting</td>
<td>Hamburg, Federal Republic of Germany</td>
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<td>1971</td>
<td>4th Annual Meeting</td>
<td>Birmingham, UK</td>
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<td>1970</td>
<td>3rd Annual Meeting</td>
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<td>1969</td>
<td>2nd Annual Meeting and Joint Meeting with ESPR</td>
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<tr>
<td>1968</td>
<td>1st Annual Meeting</td>
<td>Paris, France</td>
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adoption. Among the identified immediate key goals are that ESPGHAN should provide broad representation for all professionals involved in our field; promote basic, translational, and clinical science; lobby for stronger support of research; offer the highest standards of education to members and all professionals involved in our field; support and defend the health and interests of children, with a special emphasis on gastrointestinal, liver, and nutritional health; and serve as a source of competent advice for institutions and international agencies. Very good progress is being made in all of these areas, thanks to the enthusiastic volunteer work of many members.

ESPGHAN takes pride in its Guidelines and Position Papers. In recent years the number of these generated by Committees, SIGs and WGs has markedly increased. To enable maintenance of high quality standards of our guidelines and position papers, we established rules for a transparent process of their creation and review.

ESPGHAN has a strong tradition in empowering young colleagues and facilitating their qualification in clinical competences and research capability, and it is committed to continue to do so. However, we face challenges due to increasing economic pressures on health systems across Europe, and in particular tertiary paediatric care and academic paediatrics. The reality of tertiary and academic paediatrics is more and more dictated by the income raised from clinical services, while training and academic activities are often not adequately considered and come under pressure, which has at times endangered the quality of training and discouraged talented colleagues to pursue a career in research. Along with other paediatric and medical associations, ESPGHAN must make its voice heard and will have to continue lobbying for providing adequate resources and infrastructures subspecialty medical care, in particular for children.

Today’s medicine is based on what science has discovered before, and today’s science is tomorrow’s medicine. We cannot be satisfied with our current ability to support patients because we do not yet have satisfactory diagnostic and therapeutic strategies available for too many children; hence we must keep moving the borders of our knowledge forward. Much of the progress in our field has previously been driven by talented and dedicated physician scientists that could build a bridge from bench to bedside. The economic pressures in the medical care system make it increasingly difficult to protect time for clinicians’ work in research unless additional grant funding is available. At the same time, research methodology rapidly has become more complex and sophisticated, and it is now difficult if not impossible for a clinician to achieve major progress for her/his patients by doing research work on its own after the regular work hours. There is a real need for close interdisciplinary collaboration and for attracting outstanding basic scientists from various disciplines to get involved in the many burning questions in PGHN. ESPGHAN must strive to attract such scientists to its meeting and the Society to facilitate this essential bidirectional exchange from bench to bedside.

A major achievement of our Society in recent years has been the adoption of the ESPGHAN Code of Conduct that defines the ethical standards and resulting guidelines for the practices and dealings of ESPGHAN. A number of other European associations have looked at the ESPGHAN Code of Conduct and have started to develop similar standards. For example the BioMed-Alliance, an umbrella organisation of 26 European biomedical associations, including ESPGHAN, that aims to improve the health and well-being of all citizens of Europe through promoting excellence in European biomedical research and advocating for increased funding in favour of biomedical research, in 2016 adopted a Code of Conduct that follows very similar concepts as the one adopted by ESPGHAN in 2015. However, it does not suffice to adopt and publish a written Code of Conduct. Day by day it is of utmost importance to strongly support and defend a culture of honesty, transparency, of resistance against opportunism and against financial allurements that may conflict with our ethical goals, and to support and strengthen open debate and civil courage within ESPGHAN.

ESPGHAN has a strong tradition of tolerance and inclusion of diversity, and of applying and promoting equality. However, despite the high and rapidly growing proportion of female colleagues particularly amongst our younger members, their representation in the council and the executive council has been less than satisfactory and should be improved. In the now 50 years of ESPGHAN’s existence we had only 2 female presidents. We need to get better here.

ESPGHAN has a very strong tradition of collegial friendship, support and collaboration that has its foundation in the spirit of a small society of experts where everyone pretty much knew each other. It is a challenge to maintain this high level of identification of members with their society, which may be the reason for the very large degree of volunteer work that members commit, in a rapidly growing society with a now huge congress. The Summer Schools for young members in training provide an opportunity to create close and lasting friendships and for building strong links of young colleagues to ESPGHAN, but we probably need to keep investing in opportunities for full members to meet and interact such as the ESPGHAN working groups that are accessible for members only, the annual members dinner, and the ESPGHAN master classes. Maintaining and strengthening the high level of dedication of members to ESPGHAN will also be a prerequisite for preserving the high level of volunteer work of our members for the association, even at times when pressures at the workplace tend to increase and the challenge to achieve a work-life-balance may be greater than ever.

The prerequisites for continued importance and success of ESPGHAN are very good, not the least because our core mission is as current as ever: we aim to promote child health through increased understanding, prevention strategies and treatment of diseases. The future developments and strengths of ESPGHAN will most likely have a considerably impact on the lives of children and on their future.

REFERENCES


Chapter 4. The Relationship Between the European and North American Societies for Pediatric Gastroenterology, Hepatology and Nutrition

Carlos H. Lifschitz, Jon Vanderhoof, Harland Winter, Stefano Guandalini, William Klish, Richard Grand, Allan Walker, and Jay Perman

ABSTRACT

This chapter is based on the memories of those who shaped the relationship between the European (ESPGHAN) and the North American Societies for Pediatric Gastroenterology, Hepatology and Nutrition. The first joint meeting of the 2 Societies took place in Paris in 1978, followed by 1 in New York in 1985, 1 in Amsterdam in 1990, 1 in Houston in 1994, and the last one in Toulouse in 1998. The formation of the Federation of the International Societies for Pediatric Gastroenterology, Hepatology and Nutrition (FISP-GHAN) preceded the First World Congress of all Societies, which took place in Boston in 2000. The success of this meeting was followed by world congresses in Paris in 2004, Iguassu in 2008, Taiwan in 2012, and Montreal in 2016. NASPGHAN and ESPGHAN jointly took on the direction of the Journal of Pediatric Gastroenterology and Nutrition in 1991. Communication between the 2 Societies is extremely active, with members participating in many joint projects.

Key Words: ESPGHAN, NASPGHAN, pediatric gastroenterology

This chapter is based on the memories of those who shaped the relationship between the European (ESPGHAN) and the North American Societies for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). Of note is that neither Society had at its origins an ‘‘H’’ in its acronym, as Hepatology was not part of either; the liver at that time was not considered to be important or nobody knew enough about it as to deserve to have it included. No one remembers or will admit to knowing the reason why haepatology was omitted. That changed with time, of course, and the ‘‘H’’ was added to the name of both Societies, which is why in this chapter you may see in some places ESPGAN and in others ESPGHAN. The same is true for the ‘‘N’’ for ‘‘Nutrition’’ in the North American Society; Europeans on the other hand always knew the importance of Nutrition, at least from around 1971. However, at its beginning, the European society was known as ESPGA. NASPGHAN got all letters of its acronym in 2001.

ESPGAN as Inspiration for the North American Society of Pediatric Gastroenterology

In 1986, Dr Jon Vanderhoof, as President of what was then called the North American Society for Pediatric Gastroenterology (NASPG) attended for the first time the annual ESPGAN meeting in Edinburgh, Scotland, as the official representative from North America. Until that time, members of the NASPG met as a group (The Pediatric Gut Club) at one of the national meetings. Dr Vanderhoof, greatly impressed with the ESPGAN meeting, returned to the USA with the strong conviction that NASPG should have a similar, independent meeting in North America. Subsequently, the NASPG Council authorized the very first Society meeting in Chicago in 1989, largely patterned upon the ESPGAN meeting. Organizing such a meeting was challenging because funding was not available and the members of Digestive Disease Week (DDW) were not interested in including pediatric gastroenterology. However, the quality of the ESPGAN meetings served as the inspiration and impetus for what has become the successful annual NASPGHAN meeting.
In 1982, the *Journal of Pediatric Gastroenterology and Nutrition* was founded by Dr Emanuel Lebenthal and was run as a private journal. Also, during the time when Dr Jon Vanderhoof was president of NASPG, several members of the American Society approached him with concerns that the only journal devoted exclusively to pediatric gastroenterology and nutrition had an affiliation with neither of the major academic Societies. Despite the fact that most of the published papers were written by members of NASPG or ESPGAN, there was no editorial input from either Society to publication decisions. The issues involved in changing the status of the Journal were of concern to both NASPG and ESPGAN. Discussions were initiated with Dr Birgitta Strandvik, President of ESPGHAN, and eventually with members of the respective Society Councils, to approach the Founding Editor, Dr Lebenthal, regarding affiliations. Negotiations by the Societies’ Presidents, Dr Birgitta Strandvik and Dr Jon Vanderhoof, and subsequently Dr Jay Perman, as well as the publisher, Raven Press, and Dr Lebenthal were challenging due to competing priorities. Eventually, in 1991 an agreement was signed in Vevey, Switzerland, and *The Journal of Pediatric Gastroenterology and Nutrition* became the official journal of ESPGHAN and NASPGHAN. In 1995, the other 2 regional Societies, the Latin American (LASPGN) and Asian Pan Pacific (APPSPGN), became affiliates with representation on the editorial board. The Journal has grown steadily and now receives manuscripts from clinical and basic research physicians and scientists worldwide. The Societies publish guidelines, position papers, supplements from major meetings, abstracts from national meetings, and opinions from leaders. The quality of the articles reflected in the rising impact factor is a major reason for the establishment of pediatric gastroenterology as a distinct specialty in the international medical community.

**First Joint ESPGAN-NASPGAN Meeting**

The First Joint Meeting took place in Paris in 1978. A photo is witness of one of the moments at that meeting (Fig. 2).

**Second Joint ESPGHAN-NASPGHAN Meeting**

The Second Joint Meeting was organized in New York by Dr William Balistreri, who was Program Chairman. He worked with Drs Jean Rey, Peter Milia, and Beat Hadorn. Dr Richard Grand, from Boston, succeeded Dr Balistreri as NASPGHAN President and chaired the meeting, which took place in 1985 at the now defunct Barbizon Plaza Hotel. At that time, the rate of exchange was such that the dollar was extremely expensive for Europeans and many people complained about the high costs. That at least was not under the control of the organizers. The Farewell Dinner took place at the Essex House Hotel. The Barbizon Hotel went bankrupt shortly after the meeting and NASPGHAN never got a bill for that. That was the first time NASPGHAN’s budget showed a positive balance. Since then, NASPGHAN has tried to hold its meetings at hotels likely to go bankrupt, but so far has been unsuccessful and other sources of revenue have had to be found. The Post Graduate Course was then created which became a source of revenue.

The European view of this Joint meeting is summarized in the following paragraphs, taken from the report of the 1985 Annual General Meeting presented by Dr Sandy McNeish’s, President of ESPGAN at that time. His witiness and sense of humour are reflected. This document was provided by one of the authors (S.G.): "The (ESPGAN) Annual General Meeting (AGM) in 1985, a joint meeting with NASPGN, was certainly uniquely memorable, both in its preparation and at the meeting itself. First, the USA organizers had to dismiss the professional conference organizer for incompetence less than one year before the date of the meeting. His replacement was a fast-talking New York lady who appeared to have everything in hand. In fact, the company she represented went bankrupt during the meeting and only sterling work by the local committee saved the day. The scientific programme was of an exceptionally high standard and showed, to this biased observer at least, that European paediatric gastroenterologists can at least hold their own with their American cousins. The symposium on ‘brain-gut peptides’ gave me a headache, not only because of its very high scientific standard, but also because it took place the morning after the welcome cocktail party. At that party, held at the Asia Society on Park Avenue, our hosts had prepared 5 g of food and 1 kg of alcohol for each person. The lunches and the formal banquet on the
penultimate night confirmed that the thinking American (or at least the about-to-be bankrupt conference organizer) can eat only chicken and pasta. But the final night was superb - an informal supper in Manhattan, accompanied by 1920’s piano. It is only about good friends that you can joke. The 1985 joint meeting was such a success that we agreed unanimously at the AGM to repeat the joint meeting regularly. Amsterdam 1990 followed and, even as I write, we are all looking forward to Houston 1994.”

Although the following pertains more to ESPGHAN proper than to joint relations of the 2 Societies, this document, also transcribed from Dr McNeil’s report, was elaborated at the time of the Joint meeting in New York. Because more than 30 years have elapsed and problems have not changed, we believe it is interesting to include it. The following was adopted unanimously at the AGM in New York:

1 PREAMBLE

1.1 Paediatric gastroenterology has grown and developed well in Europe in the past decade, largely because of the efforts of members of ESPGAN. Our activities have caught the interest of young workers, and increasing numbers feel sufficiently committed to paediatric gastroenterology to wish to become members of the Society.

1.2 Superficially this can be seen to create a conflict between those who wish to keep the Society small (with the real benefits of easy communication and mutual understanding) and those who wish to allow into membership all who might benefit us.

1.3 Council believes that the guidelines for membership of ESPGHAN should be revised to take account of these trends.

2 PROPOSED OBJECTIVES

2.1 To maintain, or better to increase, the scientific standards of the Society.

2.2 To offer membership to young workers of high achievement and potential—“to catch them while they are still young.”

3 REVISED GUIDELINES

3.1 The applicant should be working in Europe.

3.2 Published evidence of active participation in research of high scientific merit. This is likely to include several papers in refereed international journals.

3.3 At least 1 personal presentation of a paper to the Society.

3.4 No lower or upper age limit will be set. However, it is unlikely that strong candidates for membership will be more than 45 years old.

3.5 Basic scientists, and those in disciplines related to paediatric gastroenterology and nutrition, will be welcomed.

4 ADVANTAGES OF THE NEW GUIDELINES

4.1 The introduction of new blood, new ideas, new science.

4.2 Some young colleagues will mature as active members of the Society to the point where they are ready to assume responsibility as Council members and officers when still young.

5 POSSIBLE DISADVANTAGES

5.1 The membership could increase to a size, which would cause the AGM to become impersonal.

5.2 This could be minimized by either (a) limiting the number of guests allowed to each member or (b) limiting guests of new members for (say) the first 3 years of membership.

The first new member admitted (by special arrangement) was Professor Rolf Zetterstrom (editor of Acta Paediatrica Scandinavica), boyish in outlook but certainly not a teenager. Nevertheless, the guidelines have become successfully adopted, as can be seen by scanning the auditorium or the dance floor during our recent annual meetings. Despite these stringent bylaws, Drs Jon Vanderhoof, Allan Walker, and Dr Carlos Lifschitz who had (and still do) enjoy ESPGHAN meetings immensely but did not work in Europe, were accepted as members.

Third Joint ESPGHAN-NASPGHAN Meeting

The site selection was summarised like this by the main organizer, Jan Taminiau: “I liked the New York meeting in 1985, went immediately with Hugo Heymans to John Vanderhoof and Dick Grand, proposed Amsterdam that was it.” The meeting took place in 1990 in downtown Amsterdam at the hotel Krasnapolsky. Three hundred people were registered but 600 participants showed up, 300 without any prior notification. According to the organizer Dr Taminiau, the reason was because the weather was nice! Instantly 2 infant milk formula companies came up with the additional budget needed. Old times!

One of the social events took place at the old Binnegasthuis (former Academic Children’s Clinic) and the Dutch Youth Orchestra and the imploding piano organized by Werner Herbers, from the Concertgebouw orchestra, performed and one of ESPGHAN members, Beat Hadorn sang opera arias with Ms Nel Biervliet, general pediatrician from Paramaribo, Dutch Guiana. One was “‘Là ci darem la mano’” from Mozart’s Don Giovanni. There was also a tour to the open aircraft museum in Enkhuizen with buses and back by boat over the Ijsselmeer to Volendam for dinner at Spanjer hotel. The final dinner took place at the 3-story restaurant at Rokin, and became a standing dinner, as the only way to accommodate the crowd.

Fourth Joint Meeting of ESPGHAN and NASPGHAN

During the period of 1992 to 1994, the relationship between NASPGHAN and ESPGHAN evolved and became closer, due in large part to the interaction of Dr Allan Walker with European colleagues. The NASPGHAN Board of Directors discussed the possibility of holding another joint meeting between the 2 Societies in the United States. Dr William Klish, who at that time was President of NASPGHAN, had offered to hold the meeting in Houston, Texas. He solicited the help of Dr Carlos Lifschitz and with the tremendous help of Margaret Stallings, who worked for the company called SLACK, they began the process of finding a hotel large enough to hold a meeting which could attract 400 to 500 participants. Five hundred and thirteen people attended.

For the 1994 Joint Meeting, there were 186 abstracts submitted by NASPGHAN members and 200 from European colleagues. Seventy-four abstracts were accepted for presentation. A nurses’ program was included. The meeting was held in October and was extremely successful, including participants from South American and Asia. The entertainment was decidedly Texan and included a live private rodeo and Texas barbeque. The rodeo opened to the delight of everyone, with the traditional parade led by Dr William Klish on horseback and Dr Jacques Schmitz, President of ESPGHAN, riding a very large Texas longhorn steer. Tequila shot girls circulated and line dance with instructors put everyone on the dance floor. A special tour and dinner at the National Aeronautic and Space Agency (NASA) was arranged for the farewell dinner.
Some people complained that the meeting was getting too large and impersonal. That meeting attracted 513 participants, today they are over 4000!

Fifth and Last Joint Meeting of ESPGHAN and NASPGHAN

This was held in Toulouse in 1998, organized by Jean Pierre Olives at the Centre de Congrès Pierre Baudis. 900 participants attended from 37 countries around the world. The Honorary President was Jean Rey, NASPGN President was Ron Sokol, and ESPGHAN President was Samy Cadranel. The highlights of the Scientific Program were lectures on “Pathogenesis of gastrointestinal and liver disease in cystic fibrosis” by Claude Roy with a presentation and award by Richard Grand, and “Coeliac disease today: new faces of an old disorder” by Jarmo Visakorpi. There were 250 original presentations, consisting of 51 oral and 199 posters. Social Events included a Welcome reception at the City Hall, a concert in the Basilique Saint Etienne, a medieval evening in the old city of Revel and a Farewell Dinner in the “Cloitre des Augustins,” where Stefano Guandalini was elected the next ESPGHAN President.

First World Congress

Building on the success of the Combined NASPGHAN-ESPGHAN meetings and the attendance of colleagues from throughout the world, the leadership of the Asian Pan Pacific Society of Pediatric Gastroenterology and Nutrition (APPSPGHAN), Latin American Society of Pediatric Gastroenterology, and Nutrition (LASPGHAN), and the Commonwealth Association of Paediatric Gastroenterology & Nutrition (CAPGAN) began discussions about organizing a World Congress. Dr Ron Sokol was President of NASPGHAN from 1996 to 1998 and Dr Harland Winter was elected President-elect in 1996. Dr Ulysses Fagundes Neto was a key figure in the development of this project. Each Society made a presentation about hosting the Congress, and at a meeting in Denver in 1997 (Fig. 3), the Presidents decided to hold the First World Congress of Pediatric Gastroenterology, Hepatology and Nutrition in Boston, to be followed every 4 years by meetings hosted by ESPGHAN (2004), LASPGHAN (2008), and APPSPGHAN (2012). The agreement between the societies was that each would cancel its annual meeting during the year of the World Congress. Although CAPGAN was not 1 of the 4 sponsoring societies, Dr Peter Sullivan, CAPGAN President, graciously agreed to cancel the already planned meeting in 2000 in order to participate in the World Congress. The Mission Statement of the First World Congress stated: “The purpose of this first World Congress of Pediatric Gastroenterology, Hepatology and Nutrition is to bring together, for the first time, physicians, scientists and other health professionals interested in child health from all over the world to share clinical advances and scientific and technologic developments in the fields of paediatric gastroenterology, hepatology and nutrition.”

Dr Guandalini became ESPGHAN President in 1998 and his vision was that the World Congresses should be the pinnacle of a larger federation that should include the 4 major International Societies for pediatric gastroenterology. He thus began working at this project first within ESPGHAN but immediately also with the NASPGHAN leadership: in 1998, Dr Richard Colletti became President-elect of NASPGHAN and joined Drs Sokol and Winter in organizing the World Congress. Thus, after much discussion that included Ulysses Fagundes Neto and Geoff Cleghorn, the bylaws of this new Federation were drawn and eventually signed in a ceremony held in 2000 in Boston during the World Congress. FISP-GHAN (The Federation of the International Societies for Pediatric Gastroenterology, Hepatology and Nutrition) was officially created, with the mission to not only be a stable organization to organize all subsequent World Congresses, but also to form international teams (“Working Groups”), to bring together investigators from each Society to work together and develop in specific areas of clinical practice, updated statements on the current state of knowledge, and needs for future research.

The organizational aspects of the World Congress were approved. The host society would retain all the revenue from the Post-Graduate Course and, in addition, 40% of the profit from the meeting. The remaining 60% would be divided among the other 3 sponsoring Societies. The meeting was organized by SLACK, a company that worked with NASPGN in the past to raise funds for the annual meeting and manage all the logistics. About a year prior to the First World Congress, the representatives of all societies agree to the First World Congress in Denver in 1997. From left to right: Drs Ron Sokol, Samy Cadranel, Ulysses Fagundes Neto, Yuichiro Yamashiro, and Harland Winter.

FIGURE 3. Representatives of all societies agree to the First World Congress in Denver in 1997. From left to right: Drs Ron Sokol, Samy Cadranel, Ulysses Fagundes Neto, Yuichiro Yamashiro, and Harland Winter.
to the meeting, unexpectedly SLACK decided to sell their meeting business. The President, Harland Winter along with NASPGN leadership negotiated with SLACK to remove NASPGN from inclusion in the sale and Peter Slack agreed to allow Margaret Stallings to get out of her ‘non-compete’ contract and leave SLACK to become NASPGN Executive Director. Jan Sharkey, who continued to be employed at SLACK, worked with Margaret Stallings to raise the funds, organize the meeting, and handle all the logistics. These 2 women did the work of an entire company and saved the First World Congress. Margaret started what has become the NASPGHAN home office, and she remains the highly valued Executive Director of NASPGHAN.

As said earlier, the meeting was organized to emphasize scientific interactions and friendships. The objectives were as follows: to improve the digestive health and nutrition of infants, children, and adolescents worldwide by:

1. creating an international forum for communication of the latest scientific, clinical, pharmacological, and technological advances;
2. initiating and promoting global collaboration, education, and communication among health professionals;
3. fostering basic and clinical research in pertinent issues that impact the paediatric patient, family, and environment;
4. encouraging young researchers to pursue scientific investigation into relevant areas.

There were 3 committees that organized the meeting. The International Executive Committee (IEC) that had responsibility for the choice of speakers, selection, and the final approval of the entire scientific program and the marketing of the meeting. The IEC was composed of the current President and President-elect of each of the Sponsoring Societies. The Host Executive Committee was composed of officers and Host Society members who worked with the IEC to organize specific programs, raise funds for the meeting, and insure that Continuing Medical Education requirements were met. In addition, the HEC was responsible to the IEC for (i) selection of meeting site and management company, (ii) budget management, and (iii) oversight of the social activities. A Local Organizing Committee was responsible for the social events and local programs at the meeting.

The 20 working groups, which included a member from each of the 5 societies, served as a mechanism for members to interact. Each group presented its conclusions during a session at the meeting. There were 1138 abstracts submitted as both oral and poster presentations that were reviewed by members from each society by a committee chaired by Dr Mitchell Cohen. Celiac disease had the highest number with 95 abstracts, followed by Helicobacter pylori with 92, oesophageal disorders with 82, inflammatory bowel disease
with 79, endoscopy with 69, hepatitis with 66, liver transplantation with 57, and cholestatic liver disease with 47. Twelve abstracts were presented at plenary sessions, 125 were oral presentations, and 971 were posters. Plenary State of the Art lectures were given by:

1. Alan Guttmacher, MD, Senior Clinical Advisor to the Director National Human Genome Research Institute, NIH The Human Genome Project on “Genetics and Gastroenterology in the 21st Century”


FIGURE 7. Editors of the publication committee of the Journal of Pediatric Gastroenterology and Nutrition at the time of the First World Congress Sitting, from left to right: Drs John Walker-Smith, Judy Sondheimer, Emanuel Lebenthal, Michael Lentze, W. Allan Walker, Jehan Francois Desjeux, William Balistreri.
2. Jay Hoofnagle, MD, Director, Division of Digestive Diseases and Nutrition, NIH on “Global View of Hepatitis in Children”


Decisions about the program were made by the officers of each society by teleconference and at meetings held in airport conference centres. Industry was a true partner in the meeting, providing financial support without requesting any influence on the program. They were acknowledged at the very successful exhibit hall which most of the over 2000 attendees from 80 countries visited. Allocating funds to bring colleagues from resource-poor countries was an important aspect of the meeting and was unanimously supported by the NASPGN Council and the IEC. Resources from the meeting provided funding for 150 young investigators and 50 International Outreach Awards to bring colleagues from Africa, Asia, Eastern Europe, and Latin America including 12 physicians from Cuba. Many of these physicians participated for the first time in a professional international meeting. There was a lunch hosted by the leadership of NASPGN at which representatives from countries...
in the Middle East met together to discuss the creation of a regional society inclusive of all countries in the region.

In addition to the scientific program, there was an entertaining social program. The Opening Ceremony featured the Boston Ballet II, the young professional arm of the parent company. A reception for organizers was held in the backyard of the home of Harland Winter and Susan Weinstein-Winter (Figs. 4 and 5), the President’s Dinner was held at the John Fitzgerald Kennedy Library (Fig. 6), and the Membership Dinner was held at the Boston Aquarium. Live fish was not part of the menu. The Farewell Dinner was at the Museum of Science where Sue, the Tyrannosaurus Rex, greeted everyone and international food stations were located throughout the museum.

The First World Congress provided an opportunity for members and leaders in pediatric gastroenterology from every continent to meet and share experiences. In addition, the editors of the Publication Committee of the Journal of Pediatric Gastroenterology and Nutrition had a meeting (Fig. 7) and the presidents of the World Societies (Fig. 8) and members (Fig. 9).

**Subsequent World Congresses**

The second World Congress, in Paris in 2004, the third in Brazil in 2008, the fourth in Taiwan in 2012, and the fifth in Montreal in 2016, complete the global cycle. Members of NASP-GHAN and ESPGHAN actively contributed with their experience to the organization of forthcoming World Congresses. Figures 10–14 are mementos of the Paris meeting.

**CONCLUSIONS**

As one (C.L.) who has attended the first ESPGAN meeting in Madrid in 1981 and all but 4 since, and comparing them to the NASPGHAN meetings, I was always particularly impressed by 4 things about the ESPGHAN meetings: (1) the large number of topics in nutrition that were presented; (2) the interesting cities where the meetings took place; (3) the social programs; and (4) the comradery that existed among members. At NASPGHAN there was only a business lunch. Unfortunately, regulatory guidelines, costs, and the large number of attendees have restricted social events and time for informal exchanges at ESPGHAN!

What started as a small project has evolved into an international meeting where colleagues from around the world can interact and learn from one another. The leadership of ESPGHAN and
FIGURE 12. Second World Congress in Paris, 2004. Farewell Dinner. Musée des Arts Forains. The Congress President, Dr Olivier Goulet (left), and the future ESPGHAN President, Dr Berthold Koletzko.

NASPGHAN continue to work with colleagues throughout the world to support global health. Unlike most long-lasting relations, this one has been relatively problem free and extremely productive. Hopefully newer generations will continue the traditions and collaboration.

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Chapter 5. Fifty Years of Paediatric Gastroenterology

Olivier Goulet, Ricardo Troncone, Marku Makki, Jacques Schmitz, Isabel Polanco, Maria Luisa Kearin, Semy Cadranel, Sibylle Kolezko, Giuseppina Oderda, Alan Phillips, Simon Murch, John Walker-Smith, Frank Ruemmele, Jorge-Amil Dias, Sanja Kolacek, Yigal Finkel, John Punitis, Antonella Diamanti, Susan Hill, Florence Lacaille, Girish Gupta, Jean Francois Mougenot, Mike Thompson, Marc Benninga, Nikhil Thapar, Yvan Vandenplas, Peter Milla, Jehan-François Desjeux, Alfredo Guarino, and Hania Szajewska

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Chapter 5.0. 50 Years of Paediatric Gastroenterology

Olivier Goulet

It is an immense pleasure and a great honour to present this chapter devoted to Pediatric Gastroenterology (PedGI). During my training in this field I was privileged to have several mentors, the ESPGHAN members Jean Rey, Claude Ricour, and Jacques Schmitz. I thank them very warmly. In addition, during my formation, I had the chance to meet wonderful ESPGHAN colleagues and friends who are, many of them, involved in these PedGI selected topics and papers. I am sorry to have been unable to involve as many colleagues as I should have wished. Editing so many different papers, with 2 to 5 authors, was not easy, but I hope it was successful. For me all the papers are excellent, fitting perfectly with the wishes of the ESPGHAN History Committee. I would like to thank, from the depth of my heart, all the authors who gave their time and energy to achieve this.

Fifty years ago, both ESPGHAN was born, and the individualisation of PedGI within Paediatrics grew. During the following years, PedGI became very diverse, as reflected by the different papers in this short historical overview. With the onset of technology (endoscopy, imaging, recording devices), microbiology, immunology, genetics and cell biology, excellence has been promoted in every field of clinical practice and medical science. Nowadays, PedGI “generalists” and PedGI “specialists” are facing. Indeed, what is common to outstanding motility specialists as the authors of the following papers, and the PedGI immunologists who deal with IBD and “immune related congenital enteropathies” (IRCE) [I do prefer this wording to the term “very early onset IBD”]. A number of centres in the world have the privilege of developing to a high level in all aspects of PedGI. This gives them the obligation to share and diffuse the knowledge acquired through their own publications and, within the ESPGHAN framework, by their investment in the formation and promotion of young people through post-graduate courses, workshops, working groups, statements etc.

Most, but not all, of the diverse faces of PedGI are covered in these papers. Much progress and many advances are stressed. Great dynamism and enthusiasm is released from these various lines, but some fundamentals deserve to be underlined. With huge clinical demands related to digestive functional disorders, together with parental pressure, clinicians, who we are first, must avoid the multiplication of investigative procedures, and for some, to fall into merchandizing attitudes, the so called “GI business.” Our medical care should be based first on clinically well-established hypotheses, or in some settings be part of a clinical research protocol. In the same way, the development of the Internet demands new attitudes and generates requests for treatments. Fortunately, Evidence Based Medicine (EBM) makes it possible to establish guidelines, as shown in a growing number of recommendations by ESPGHAN (eg, acute diarrhoea, management of functional intestinal disorders, probiotics, prebiotics, etc).

Intestinal failure (IF) has become a very distinct field within PedGI. It links clinical gastroenterology, therapeutic nutrition, immunology, genetics, and cell biology. In that field, EBM for most purpose cannot be achieved. This medicine is based on physiology, experience and common sense as well as collaborations. More than any other domain of PedGI, IF requires interdisciplinarity, involving neonatologists, pediatric surgeons and many other organ specialist, and multi-professionalism, including nurses, dieticians, pharmacists, psychologists, and social workers. Everyone who is invested in this discipline must perceive that they are not alone and that they cannot be alone. This is one of the most beautiful aspects of this medical field. IF constitutes the essence of “rare digestive diseases.” It is a topic that should not be a closed, protected field, or of the “aristocracy of the rare diseases,” but, on the contrary, to lead always to open dynamic research interactions. In addition, IF can lead to very challenging situations, such as end-stage liver disease, intestinal transplantation failure, humanly with dark horizons sometimes, even if important progress has been accomplished during the last 50 years in both diagnosis and management of these rare conditions. We must have, even more than in other field of PedGI, great empathy and ethical sensitivity, to deal effectively with chronic diseases, and moreover to cope with major human problems (shaken families, divorce, eating disorders, financial problems) emotional strength, openness, and humility are required.

Modernity and the evolution of lifestyles have their limits. The burden of IBD is a perfect illustration. Who would have predicted in 1968 that we would become submerged by this
increasing wave, which we know not where it will lead. It touches each and everyone, irrespective of age, sex, origin, social status or ethnicity. It constitutes for me a priority in public health. Outstanding research and RCTs, mostly promoted by the wonderful and very active Porto ESPGHAN working group, have been improving IBD management. Treatments are increasingly focused but expensive and not always effective, nor are they always free of dangers, both short and long term. Can we hope that the demonstrated role of the intestinal microbiota will change current therapeutic attitudes and move us back to a more “ecological” approach as is the “nutritional” management promoted a long time ago (1987) by Ian Sanderson (1). In addition, Ian was the first to provide a clinical (phenotypical) description of the, nowadays, well-recognized IRCE, well before the genetics of IL-10 receptor deficiency, which followed 18 years later! (2). Do not believe that I am reactionary, but just careful vis-à-vis this therapeutic, hopefully evidence based progress, which makes doctors shine and delights the pharmaceutical industry. I believe that classical IBD, mainly related to lifestyle, dietary habits and possible intestinal microbiota predators, requires a basic reflection on its prevention, maybe as early as birth (might Caesarean sections, antibiotics, proton pump inhibitors, breast feeding, healthy further feeding be involved?).

This retrospective review of 50 years of PedGI made me happy and very grateful with respect to its pioneers and my senior colleagues. I would like to especially recognise Professor Alan Walker, for inviting Ian Sanderson and myself to be European co-editors of the famous Walker’s Pediatric Gastrointestinal Disease textbook for the GI part and Giorgina Mieli-Vergani for Hepatology (Fig. 2). It obliges us to continue to promote constant progress as they did. Thank you, once again, my colleagues who contributed to this Journal of Pediatric Gastroenterology and Nutrition 50th anniversary special. Thank you Lawrence Weaver, who has been so confident a conductor of this Hepatology-Gastroenterology-Nutrition “concert of the century.”

My best wishes for the next ESPGHAN 50 years and my very warm regards to all my ESPGHAN friends and colleagues.

REFERENCES
Chapter 5.1.1. Coeliac Disease

Markku Maki, Maria Luisa Meerin, Isabel Polanco, Jacques Schmitz, and Riccardo Troncone

No other disease parallels the history of ESPGHAN as coeliac disease (CD) does. For a long time it has been considered ‘‘the disease’’ of ESPGHAN. This goes back to the time CD was a disease of childhood manifesting only in the first 2 years of life, mainly with chronic diarrhoea, distended belly, and failure to thrive. The Dutch paediatrician W.K. Dicke, working in Utrecht together with one of the founders of ESPGHAN, Dolf Weijers, was the first to demonstrate the harmfulness of gluten on the basis of experiments based on standardised diets and fat absorption assessment. Other ESPGHAN members posed milestones in the history of the CD; among them Margot Shiner, who, with the development of methods for peroral biopsy of the small intestinal mucosa, rendered possible to define the histological lesions, and Anne Ferguson, with her seminal studies on gut intraepithelial lymphocytes (1). It is then not surprising that until now (in recent years only IBD seems to parallel the interest among members) CD has been the disease most investigated in ESPGHAN, as shown by the number of abstracts presented at the annual meetings. Those contributions are not only the result of the work of brilliant researchers, but in many important cases, the cooperative effort of more members made possible by networking in ESPGHAN.

There is no doubt that the area where ESPGHAN as Society has been more linked to CD is the formulation of diagnostic criteria. Already in the second annual meeting of ESPGHAN (ESPGA at that time) a round table was organised to create a consensus especially concerning the permanency of gluten intolerance. Jarno Visakorpi remembers (2) that an inquiry made to prepare the conference showed that at that time only a minority of patients was treated with a gluten-free diet lifelong. The first diagnostic criteria for CD laid down by ESPGAN in Interlaken had the merit of including the concept of the permanent gluten intolerance as well as introducing the need to demonstrate an abnormal morphology of the small intestinal mucosa, its normalisation on gluten-free diet and the relapse following reintroduction of gluten, and of the 3 biopsies procedure (3). These strict criteria were soon applied by paediatricians throughout Europe: an enquiry conducted by ESPGHAN member David Shmerling in 51 centres showed that the great majority applied the criteria and treated all patients lifelong. An ESPGHAN working group on CD was founded under the presidency of Salvatore Auricchio; in its context the need for a revision of diagnostic criteria emerged in the late 1980s; after a workshop organised at the annual meeting in Budapest (1989), a subcommittee (Jacques Schmitz, John Walker-Smith, Stefano Guandalini, David Shmerling, Jarno Visakorpi) published in 1990 a revision of the criteria where the obligatory provocation was abandoned in typical cases and for the first time the value of determination of specific CD serum antibodies was emphasised (4). The rest is history of these days. A further revision has been published, after a long work initiated by a meeting in Tampere promoted in 2006 by Markku Maki. An inquiry led by Carmen Ribes (5) showed that the 1990 criteria were still largely applied throughout Europe, but also that was time for a change. The new criteria (6) published in 2012 by a committee chaired by Steffen Husby introduced significant changes in the very definition of the disease emphasising its systemic nature, with enteropathy being only one of its features, and the value of CD-associated autoantibody in some situations able to replace the demonstration of mucosal damage.

Diagnosis has been not the only area in CD where a joint effort by ESPGHAN members has brought significant progress. Epidemiology has been another area of strong cooperation. Important cooperative work was conducted by some ESPGHAN members (Jarno Visakorpi, Isabel Polanco, Salvatore Auricchio) at the end of 1980s to assess the prevalence of CD among first-degree relatives of CD patients. A few years before the antireticulin antibody, subsequently replaced by endomyosial and antitransglutaminase antibody, was shown to have a very high positive predictive value for the diagnosis of CD (7); the prevalence found in families where almost all members were biopsied approached 9% (8), but more importantly this was one of the first studies indicating how screening based on CD-associated autoantibodies allowed the identification of the vast majority of previously unrecognised cases.

In the same years the ESPGHAN working group on CD promoted a multicenter study of the epidemiology of the disease, whose results were discussed at the 24th annual meeting in London (June 1991) and in a special meeting organised in Capri by Salvatore Auricchio and Jarno Visakorpi. The study was the largest ever conducted involving 38 centres from 15 European Countries; there were contributions also from outside Europe, including North Africa and South America, and significant variation in the incidence emerged (9). Environmental factors, including type and amount of cereals, hypothesised to cause the different figures of prevalence in different countries. That was a critical time for epidemiology, as, thanks to the development of serological methods, the whole spectrum was displayed, from silent cases, to atypical cases (without gastrointestinal symptoms), to cases with minor enteropathy.

The detection of cases with positive autoantibody and mild enteropathy (or no enteropathy at all) represents today one of the main problems. A starting point of latency in CD, that is, the disease is existing but not manifest at the mucosal level, came from the Tampere group in 1990 (10). This publication, and many to come, question the same definition of CD and poses significant questions in terms of management. In a similar context are patients who received a diagnosis of CD and show no villous atrophy even after a long period of gluten-containing diet (11). Prospective randomised controlled studies are necessary to define the natural history, assess the risk they are exposed if on normal gluten-containing diet and to decide about the need of excluding gluten.

The central role played by HLA-restricted gliadin-specific T cells is nowadays fully recognised. Other important concepts emerged in the last decades: the activation of innate immunity and the autoimmune nature of the disease. Both came from within ESPGHAN. The recognition of the biological activity of the A gliadin peptide 31–43 (12) and its role in triggering mucosal innate immunity (13), both emerged from organ culture studies. Operating autoimmune mechanisms were first postulated in 1991, with ingested gluten as the environmental insult (14) and the hypothesis...
for autoimmune mechanisms were presented and discussed at the sixth International Symposium on Coeliac Disease held at Trinity College, Dublin, in 1992 (15).

An important area where major efforts are being concentrated is prevention. The increasing knowledge about genetic factors (HLA and non-HLA) involved in CD and hence the possible identification of at risk subjects, together with the information about environmental factors involved, may open the way to strategies for prevention. A first effort based on the possibility of inducing tolerance by feeding small amount of gluten has involved many ESPGHAN members, coordinated by Luisa Mearin (16). Another similar study (17) has been conducted in Italy involving other ESPGHAN members led by Carlo Catassi. Altogether, these data have been translated in ESPGHAN guidelines for infant nutrition (18). More importantly, these studies have paved the way for other prospective randomised intervention studies, reinforcing the hope that CD and its complications might be delayed, or even prevented, with interventions in the first year of life in genetically susceptible individuals.

Today CD is very much changed in comparison to the disease known when ESPGHAN moved its first steps; it is no more a disease of childhood and is not restricted to Europe. The attention by adult gastroenterologists is increasing worldwide and new challenges are faced. The progress in the comprehension of the molecular basis of CD has allowed the identification of possible targets for therapy (19). Enzyme supplement therapy using bacterial endopeptidases has been proposed to promote complete digestion of cereal proteins and thus destroy T-cell multipotent epitopes. The identification of specific epitopes may also provide a target for immunomodulation of antigenic peptides. Other promising areas include inhibition of the adaptive immune response activated by gliadin peptides, preventing gliadin presentation to T cells by blocking HLA binding sites or use of TG2 inhibitors. So far trials have involved mostly adult CD patients, but it is easy to predict that paediatric gastroenterologists will soon be involved and that ESPGHAN members will give their contribution thank to their consolidated ability to work together.

REFERENCES
Chapter 5.1.2. Infectious Diarrhoea

Alan Phillips, Simon Murch, and John Walker-Smith

In the 50 years since ESPGHAN’s inception the field of intestinal infectious diarrhoea has changed considerably. It is important to remember that ESPGHAN was a small society at the beginning and it is only in the last few years that the membership has expanded to 800 plus including trainees and allied health professionals (and an expanding emeritus category). There has been a huge expansion in the numbers of nonmembers attending the annual ESPGHAN meetings, dramatically changing the more informal atmosphere of earlier years to the formality of a major scientific congress. Around the 1980s and beyond ESPGHAN was largely driven by leading figures in centres of excellence, each with their own mix of areas of interest, which they independently investigated and funded having to satisfy their own Institutions’ demands of scientific activity and output. ESPGHAN’s strength at that time, in terms of infectious diarrhoea, was largely as a network of clinical expertise, a platform to present research for debate, rather than a source of funding or a stimulus of novel research. So it is not surprising that there was an uneven scientific interest in infective diarrhoea, which did not match the more widespread commitment to clinical areas of research such as coeliac disease. However, the Group led by John Walker-Smith at the Queen Elizabeth Hospital for Children in London had been involved in the field of infectious diarrhoea from an early stage. In recent years, the ESPGHAN Gastroenteritis Working group, involving especially Hania Szajewska and Alfredo Guarino, provided important work for establishing guidelines (see Chapter 5.4.1).

THE PRE-ESPGHAN PERIOD

Evidence of Viral Diarrhoea

In 1968 no viral causes of acute diarrhoea had been identified and presumed cases were called nonbacterial gastroenteritis. This was a result of using isolation and culture when viral culture was impossible. Coincidentally, the outbreak of acute diarrhoea from which the Norwalk Agent was detected, occurred in 1968, but the virus was not identified until 1972 when immune electron microscopy was applied to stored faecal samples (1). Shortly afterwards Bishop et al used thin section electron microscopy to study small intestinal biopsies taken from children with acute diarrhoea and identified viral particles (rotavirus) within enterocytes (2). It was also found that negative staining stool electron microscopy could be used on crude faecal extracts to identify viral particles (3) (Fig. 1). This paved the way for rapid viral diagnosis, and allowed several morphologically distinct viruses to be identified (rotavirus, adenovirus, astrovirus, small round structured viruses (Norwalk-like), small round viruses, and coronavirus). From a clinical point of view, having the ability to make rapid viral diagnoses gave an understanding of the prevalence of viral diarrhoea, especially rotavirus-related, permitted an analysis of whether there were particular diagnostic clinical associations and gave an important analytical tool in children with the postenteritis syndrome. Stool electron microscopy (EM) was taken over by immune based identification tests; subsequently, molecular biological analysis using polymerase chain reaction methods provided rapid and sensitive viral identification and has become the method of choice.

Contribution of Intestinal Biopsies

Although Bishop et al performed small intestinal biopsies in children with acute diarrhoea, in clinical practice intestinal biopsy was restricted to cases of chronic (>14 days) diarrhoea (2). The application of EM to an abnormal biopsy from a case of chronic diarrhoea in 1980 demonstrated a distinctive microvillous-effacing lesion at sites of bacterial adhesion (4). The bacteria were identified as enteropathogenic Escherichia coli (EPEC). The observation that host cell actin accumulated at sites of EPEC (and enterohemorrhagic E coli (EHEC)) infection both in vivo and in vitro, provided a host, cell-based virulence test, which handed to molecular biologists the key that unlocked the incredible bacterial processes underlying pathogenesis (5) (Fig. 2). Another major advance was the finding in the early 1980s that EHEC produced Shiga toxin explaining the association of haemorrhagic colitis and the haemolytic uraemic syndrome with infection (6). Advances were also made in the identification and understanding of a range of other bacterial toxins (7).

In terms of parasites, although Giardia lamblia is a frequent stool and intestinal biopsy finding, the identification of Cryptosporidium as a cause of acute and chronic infectious diarrhoea was perhaps a more important finding (8) (Fig. 3).

Geographical and Interdisciplinary Approach

It is clear that infectious diarrhoea is a particular problem in developing countries and is integral to the downward spiral of infection and malnutrition that blights populations and is responsible for high levels of morbidity and mortality. In Europe, a direct interest in these areas is particularly fostered by historical links with countries in the process of development, for example, the British Commonwealth, the French-speaking North African countries, and to population centres where immigration of people from these countries was prevalent. The Commonwealth Association of Paediatric Gastroenterology and Nutrition (CAPGAN) was founded to develop clinical and research links between developing and developed communities. Through FISPGHAN a similar interest was catalysed at the world congresses by ESPGHAN, and working group reports were published for the 2004 and 2008 World Congress meetings (9,10). It is clear that major advances are made when there is a high degree of interaction between clinicians and other disciplines with microbiological, basic scientific, and molecular biological expertise.

THE ESPGHAN PERIOD

Protracted Diarrhoea, Malnutrition, and Immune System

By the time of the founding of ESPGHAN, the relationship between repeated cycles of gastrointestinal infection and
**FIGURE 1.** Rotavirus. Left—negative staining EM (from stool sample) and Right—Transmission EM showing epithelial cell containing rotavirus particles (human infection).

**FIGURE 2.** Enteropathogenic *E. coli.* Left—scanning EM of in vitro organ culture infection. Right—in vivo infection of small intestine in child with chronic traveller’s diarrhoea returning to UK from India.

malnutrition diseases was just becoming appreciated (11). Although immune mechanisms were acknowledged, the importance of the lymphoid system was not then recognised. In the next 2 decades, the natures of T cells and B cells were clarified, and important peptide mediators of inflammation and the changes in malnutrition and chronic diarrhoea were discovered, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (12).

Collaboration between ESPGHAN and CAPGAN members in centres, including the Medical Research Council (MRC) Unit in The Gambia, contributed to changes in the nutritional management of infants with chronic diarrhoea (13), and identified that persistent increase in gut epithelial permeability predicted nutritional failure and death (14), associated with an unchecked Tlr1 immune response within the mucosa and failure of T regulatory responses (15). Consistent with this, it was confirmed that an elemental diet induced better weight gain than a traditional weaning diet (16). More recently, there has been recognition of the important role of the microbiome in malnutrition enteropathy (17). Thus, there has been a change of emphasis, away from a simple concept of undernutrition, towards recognition that mucosal immune responses and immune tolerance are critical players in determining outcome of infants with chronic diarrhoea in resource poor countries.

In the UK, both Sandy McNeish and John Walker-Smith encouraged younger scientists and electron microscopists (Alan Phillips and Stuart Knutton) to get involved in clinical concerns and this mentorship stimulated laboratory studies in viral, EPEC or Clostridium difficile diarrhoea which were presented at ESPGHAN meetings; it also helped clinician-pathological studies in viral, bacterial, parasitic, and traveller’s diarrhoea observations at Queen Elizabeth Hospital for Children, London (18–21). These observations were of relevance to developing and developed communities as the hospital served a deprived community in east London with significant numbers of immigrant children, especially from the Indian subcontinent and Bangladesh. Extensive work achieved understanding in E coli–related infectious diarrhoea. This arose in part from national and international collaboration between like-minded individuals with a balance of expertise and contacts. While not directly resulting from ESPGHAN initiatives, those involved benefited from an understanding of the clinical importance of the diseases caused by E coli, the access to clinical material (intestinal biopsy samples) from cases being investigated for unrelated conditions, and the ESPGHAN annual meeting platform to present research to intellectual scrutiny. The work itself used molecular biological, cell culture, in vitro human intestinal organ culture, biochemical, and morphological techniques to gain an understanding of the molecular basis of the interaction between enteropathogenic, enterohaemorrhagic, and enteroaggregative E coli with the intestine (22–27).

Light was also thrown onto the postenteritis syndrome, that is, chronic diarrhoea as an apparent sequel to acute infection (28). Evidence was presented at ESPGHAN meetings of cow’s milk sensitive enteropathy as a sequel to gastroenteritis, as well as persistent EPEC infection, and intermittent and/or superimposed viral infections causing enteropathies and prolonging diarrhoeal episodes (28). This work alerted ESPGHAN members that there were important causes of small intestinal enteropathy apart from coeliac disease.

ESPGHAN CONTRIBUTION IN GASTROENTERITIS MANAGEMENT

In reality, identifying the aetiology of the acute diarrhoeal episode did not, in the majority of cases, alter management. This was based on the degree of dehydration and centred on oral, or, in severely dehydrated cases, intravenous rehydration therapy. Compared to the more individual Institution based studies on aetiology and pathogenesis, ESPGHAN has taken a more active involvement in studies on the management of acute diarrhoeal disease.

**Oral Rehydration Therapy**

In 1978 The Lancet stated that a method of rehydrating patients with acute diarrhoea by mouth was “potentially the most important medical advance in this century” (29). This method was based upon the discovery that glucose stimulated sodium transport across a piece of rat ileum (30). This approach was called Oral Rehydration Therapy (ORT). “It was a remarkable example of theoretical scientific knowledge being applied directly to a clinical problem” (31). The effectiveness of this approach in practice was dramatically demonstrated in a chola epidemic in Bangladesh, with a dramatic fall in mortality (32,33).

In Europe, there was concern about the relatively high sodium levels of the original oral rehydration solution (ORS). This was at a time when hypernatraemic dehydration was an important problem for the children of Europe with gastroenteritis. Unlike children of the developing world who were malnourished, such children were often obese and fed with high solute milks. There was pressure upon paediatricians in developed countries such as those of Europe to set an example to their colleagues by using ORS but there were safety anxieties at a time when mortality from childhood gastroenteritis had fallen to low levels. ESPGHAN addressed these issues and the matter was discussed in detail at a workshop at the ESPGAN meeting in Copenhagen in 1988 (34).

**ESPGHAN Gastroenteritis Working Group**

There were 2 outcomes of this Copenhagen symposium in 1988. Firstly, an ESPGHAN working group was established as a collaboration between 13 ESPGHAN members from across Europe. This led to the publication of ESPGHAN recommendations for the composition of ORS for the children of Europe (35) promoting a solution containing 60 mmol/L sodium “to minimize the risk of hypernatraemia.” Secondly, intestinal perfusion models at St. Bartholomew’s Hospital in London permitted physiological studies of ORT (30). This led to modifications of ORS composition in order to maximise water and electrolyte absorption. Basically hypotonic solutions were recommended and they are now recommended worldwide by the WHO, effectively removing the risk of hypernatraemia.

Multicentre study with 18 collaborators across Europe established the value of early feeding in children with gastroenteritis. The ESPGHAN gastroenteritis working group continued and a medical position paper concerning recommendations for feeding in childhood gastroenteritis were published in JPGN in 1997 (36). A further collaborative ESPGHAN study investigated the value of adding lactobacillus GG to ORS (37) reporting some, but not dramatic, reduction of duration of diarrhoea. In a follow-up study, the group reported the practical success of the new recommendations for early feeding in gastroenteritis in a large Europe wide study (38). Other ESPGHAN studies in acute diarrhoea have included compliance with treatment guidelines (2001) (39), rotavirus vaccination (2008) (40), recommendations for management in Europe (2008, 2014) (41,42), and on the use of probiotics (2014) (43) (see Chapter 5.4.1).

The last 50 years has seen development from the identification of rotavirus as the most prevalent cause of acute gastroenteritis
in children proceed to the production of effective vaccine treatment. ESPGHAN has been active in guiding management of acute gastroenteritis and has members that have been involved in advances in aetiology, pathogenesis, and physiologically based treatment. As ESPGHAN increases in size and influence perhaps there is a place for stimulating research, either by highlighting areas of concern to attract the consideration of funding bodies, or by directly funding studies which would require significant financial backing and an increase in the philosophy of looking outside its own geographical borders.
Addendum: We join to this ESPGHAN history of infectious diarrhoea some pictures of many of those who contributed in the work at the Royal Free Hospital and in the world in Fig. 4A and B and Fig. 5A–C.

REFERENCES

Chapter 5.1.3. Forty Years of Helicobacter Pylori in ESPGHAN

Samy Cadranel, Giuseppina Oderda, and Sibylle Koletzko

In 1892, Bizzozero reported the presence of microorganisms in the stomach of dogs (1). Although some other investigators had described bacteria in the stomach of humans with gastric cancer the gastric milieu continued to be believed to be sterile. In 1983, the dogma on the sterility of the gastric cavity fell tumbling down due to the discovery by Robin Warren and Barry Marshall (2) (awarded the Nobel prize for medicine in 2005) of the Gram-negative, spiral-shaped microaerophilic microbe with unipolar flagellae they first named Campylobacter pyloridis, then C pylori and finally the new species, Helicobacter pylori. Soon after they succeeded in cultivating the strain, H pylori hit the stage in 1984 as a main factor causing gastric inflammation and peptic ulcer. The infection was soon reported in children with epigastric pain and peptic ulcer disease in the absence of other causes of ulceration and almost simultaneously published in prestigious European and American reviews (3,4).

After reports of a correlation between the prevalence of the infection and gastric cancer in various populations, WHO declared in 1994 H pylori, a microbe that infects half of the world’s population, a class I carcinogen. Therefore, it took some time to accept the idea of H pylori infecting children although, as early as 1974 antral nodularity (a reliable endoscopic sign of chronic H pylori gastritis in children) was endoscopically recognized. However, the abstract reporting this, submitted in 1979 to ESPGAN in London, was not accepted. Eventually the paper “H pylori associated gastritis in children” was presented at the ESPGAN 1986 meeting in Edinburgh. A correlation was also found between age and prevalence of infection although the majority acquires the infection before school age (5).

At the first specific European meeting on H pylori, organized in 1988 in Bordeaux by Francis Mégraud, a few paediatricians were present who subsequently regularly attended the following annual meetings of this new “European Helicobacter pylori study group” (EHPSG). The paediatric abstracts presented in specific workshops demonstrated the epidemiological importance of the primo-infection of H pylori acquired early in childhood. At the 1996 meeting of EHPSG in Copenhagen, the authors of this paper decided to develop the Paediatric Task Force.

The first task force meeting, supported by EHPSG council members Colm O’Morain and Francis Mégraud, was organized in 1997 by Samy Cadranel (S.C.) and Giuseppina Oderda (G.O.) in Estoril, Portugal. It was regularly followed by yearly meetings held prior to the EHPSG congress and by short meetings of the working group at the annual ESPGHAN meetings with reports to Council presented at the AGM by the steering committee (S.C., G.O., and soon also Sibylle Koletzko). In 2006, at the meeting in Kluczkiw Castle, Poland, the group voted to become an official ESPGHAN working group with Sibylle Koletzko as chair, Samy Cadranel and Giuseppina Oderda as co-chairs and Francis Mégraud as Honorary Chair.

The group gathers twice per year, at the annual ESPGHAN meeting and the 2 days prior the European H pylori study group congress. The 21st paediatric H pylori meeting was held in September 2017 in Bordeaux. During the past 20 years, several multicentre studies were implemented by the group on critical issues, including the accuracy of different noninvasive tests (6), the prevalence of antibiotic resistance (7) the frequency of H pylori infection as cause of peptic ulcer disease compared to other aetiologies (8,9), and the efficacy of different treatment regimens. Short but regular sessions were organized during our annual meetings in order to communicate our research topics and results to the members of ESPGHAN.

TREATMENT OF H PYLORI IN PEDIATRICS: A CHALLENGE

So Many Different Treatment Regimens

One of the first questions the group tried to answer was how H pylori was treated throughout Europe. A registry (10) was established on the ESPGHAN website and information on 597 children were entered by 23 European Centers, but only data of 518 treated children was complete enough to analyse. One amazing finding was that European paediatricians entering data in the register used 27 different regimens. Bismuth containing therapies resulted in higher eradication rate. Omeprazole containing triple therapies were the most used, although their efficacy was low. Therapies recommended for adults did not appear to be suitable for children. Overall eradication rates were unacceptably low with a mean of 65.6%, with higher rates in children with ulcer disease compared to those with gastritis only (79.7% vs 63.9%).

When given as first treatment bismuth-containing triple therapies were more efficacious than those without (77% vs 64%); however, numbers in subgroups were small. Since neither dose nor duration or adherence to therapy and most importantly results of susceptibility testing, were considered the results must be interpreted with caution. The data were confirmed by a systematic review and meta-analysis carried on the paediatric literature (11) revealing that data in the literature were scarce and the need for more and better designed trials. An important issue to be addressed before designing multicentre studies on treatment efficacy was to ascertain susceptibility to clarithromycin and metronidazole of H pylori strains harboured by children.

Emergence of Antibiotic Resistances

The next task was to assess the prevalence of antibiotic resistance. In a large prospectively multicentre study carried out from 1999 to 2002 our group collected data on antibiotic susceptibility of H pylori strains obtained from 1233 infected children living in 14 European countries, 1037 of them were treatment naïve (7).
Overall primary resistance rates in children were very high with 23% for metronidazole, 20% for clarithromycin, and 5% for double resistance. After failed therapy these figures increased to 35%, 42%, and 15%, respectively. Children living in Southern compared to Northern Europe had a more than 2 times higher risk of being infected with clarithromycin resistant strains (7).

Since second and third line antibiotics for H pylori infection used in adults are not recommended, and even contraindicated in children (eg, levofloxacin, tetracycline), the working group members evaluated the eradication rate in children with resistance to both antibiotics with a 14-day triple therapy of high-dose amoxicillin, metronidazole, and esomeprazole, which was successful in 60% not apply to children in many aspects. The consensus was published in 2000 and focused on the indications for investigating children for H pylori, and the role of noninvasive tests in clinical practice (17). Shortly thereafter the H pylori group of NASPGHAN (18) and in 2004 the Canadian working group published their paediatric guidelines also giving recommendations for therapy in H pylori–infected children (19). The first combined guidelines of ESPGHAN and NASPGHAN followed the strict methodology of evidence guidelines based with antral gastritis in children. These combined ESPGHAN and NASPGHAN guidelines were a huge step forward to guidance for physicians working on both sides of the Atlantic. Five years later the combined guidelines have been updated (16). The main changes consider the increasing rates of antibiotic resistance and the falling eradication rates. To reach the goal of a primary eradication rate of at least 90% it is recommended to perform antibiotic susceptibility testing and tailor treatment accordingly in children. Compared to previous guidelines it is now recommended to use higher drug doses and a treatment duration of 14 days (16).

**Strong Recommendation Against “Test and Treat Strategy”**

A clear recommendation is made against screening of children with abdominal pain with a non-invasive test (13) C-urea breath test, stool antigen test, or serology) and to treat in case of a positive result, the so-called “test and treat strategy”. In countries where H pylori infection is still quite common an H pylori positive gastritis without peptic ulceration may be found incidentally during upper endoscopy. While in adult patients treatment should be offered even in asymptomatic persons the benefit-risk ratio in children is different.

**Beneficial Effects of H Pylori?**

There is accumulating body of evidence from epidemiological studies in human and experimental animal studies that H pylori protects against childhood-onset asthma, probably through the gastric recruitment of regulatory T cells (21). H pylori infection is negatively associated with other immune mediated disorders including inflammatory bowel disease (22) and celiac disease (23). There is now major interest on the effect of the infection and its treatment on the gastric and intestinal microbiome. Current projects of the working group will include these aspects in the trials.

**GUIDELINES AND FUTURE DEVELOPMENTS**

**Working Groups and Transatlantic Consensus**

In 1998, at the paediatric H pylori meeting in Budapest, a decision was made for the first consensus on the management of H pylori infection in children, as it was recognized that adult guidelines may not apply to children in many aspects. The consensus was published in 2000 and focused on the indications for investigating children for H pylori, and the role of noninvasive tests in clinical practice (17). Shortly thereafter the H pylori group of NASPGHAN (18) and in 2004 the Canadian working group published their paediatric guidelines also giving recommendations for therapy in H pylori–infected children (19). The first combined guidelines of ESPGHAN and NASPGHAN followed the strict methodology of evidence guidelines based with a systematic review of the literature published from 2000 until 2009, by constructing evidence tables with grading per the Oxford system, and a Delphi process with anonymous voting of the members of the guideline group (20). The guidelines included recommendations for the following 4 areas: Who should be tested? What tests should be used? Who should be treated? What treatment regimens are most appropriate? These combined ESPGHAN and NASPGHAN guidelines were a huge step forward to guidance for physicians working on both sides of the Atlantic. Five years later the combined guidelines have been updated (16). The main changes consider the increasing rates of antibiotic resistance and the falling eradication rates. To reach the goal of a primary eradication rate of at least 90% it is recommended to perform antibiotic susceptibility testing and tailor treatment accordingly in children. Compared to previous guidelines it is now recommended to use higher drug doses and a treatment duration of 14 days (16).

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Over the last 50 years, major insights into the different aetiologies of severe diarrhoea of infancy have been gained, leading to the discovery of various distinct pathologies of the intestinal mucosa and to treatment plans with significantly improved outcome (see Chapter 5.2.2). One key advance in the understanding and the treatment of children suffering these disorders has been the development of supportive nutritional care, such as parenteral nutrition (see Chapter 5.2.3), as well as the use of new treatments such as immunosuppressive therapy and, even haematopoietic stem cell transplantation (HSCT). With improved survival, distinct clinical pictures have been identified in parallel with the development of new analytic tools, such as immunohistology of intestinal and colonic mucosal biopsies, immunological, and more recently, genetic investigations. In the year of ESPGHAN’s birth almost none of the diseases described in this paper were known, except in the field of inflammatory bowel diseases (IBD), mainly from adult experience. From the 1970s onwards, many ESPGHAN members described “new rare diseases” and contributed to the classification of paediatric immune-related congenital enteropathies (IRCE).

AUTOIMMUNE ENTEROPATHY AS ONE OF THE ANCESTORS

ESPGHAN has been involved in uncovering autoimmune enteropathies (AIE) from the very beginning; the first report of AIE in the literature goes back to 1978 (1). The term “autoimmune enteropathy” was introduced by Unsworth and Walker-Smith (2) in London, UK, for severe persistent diarrhoea in the absence of immune deficiency or signs of coeliac disease, but associated with autoimmune disorders and the presence of specific complement-fixing circulating antibodies directed against small intestinal and colonic epithelial cells. It was speculated that quantitative and qualitative variations of human leucocyte antigen product expression in the gut epithelium of children could reflect the severity of the autoimmune process underlying the clinical picture (3). Powell et al (4) observed 17 boys with various autoimmune disorders over 3 generations in the same family, suggesting an X-linked mode of transmission. However, some rare cases of girls presenting with AIE were reported. Based on further advances in the genetics of AIE, as well as the pathophysiology and clinical presentation, 3 distinct types of AIE were classified: immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)-syndrome (AIE type 1), IPEX-like, FOXP3-independent AIE (AIE type 2) and other forms of AIE (type 3) (5–7).

IPEX SYNDROME

IPEX syndrome is a severe systemic immune disorder with an extremely severe intestinal involvement in the majority of patients. It is caused by mutations in the FOXP3 gene (8) (chromosome Xp11.23–Xq13.3) coding for a DNA-binding protein of the forkhead family. FOXP3 is expressed predominantly in CD4+CD25+ regulatory T cells, where it may function as a transcriptional repressor and key modulator of regulatory T cell fate and function. Clinically, boys with IPEX syndrome manifest most commonly with severe protein-losing diarrhoea despite complete bowel rest, early onset of insulin-dependent diabetes mellitus, thyroid disorders, eczema, and high immunoglobulin E levels (5–7).

A collaborative effort (9) allowed for the first time to the identification of 2 different phenotypes of patients with IPEX syndrome; the originally described systemic form with haematological, endocrinological, and intestinal involvement, and a second form combining autoimmunity with severe allergic manifestations (severe food allergy and atopic eczema, hyper-IgE and eosinophilia). Molecular analyses revealed an almost complete defect of regulatory T cells functions in these patients (9,10). The first systematic analysis of regulatory T cells functions in 11 children with AIE was published in 2010 by the Paris-Necker group, giving additional insight into the complexity of regulatory T cell functions in patients with AIE (10). In this work, we identified FOXP3-dependent and independent forms of autoimmune enteropathy with or without defective regulatory T-cell functions (10). Recent collaborative research through the ESPGHAN Genius working group (see below), as well as other groups allowed to identify several molecular defects causing distinct forms of autoimmune enteropathy, such as mutations in MALT1 (11), IL2 Ralpha (12), STAT1 (13), CTLA4 (14), and others.

Given the increasing number of genes and the overlapping clinical pictures, it is helpful to separate 3 distinct clinical entities (see above) based on the clinical pictures (5–7). The diagnosis of AIE is based on the combination of clinical, immunological, histological, and eventually genetic data (5–7,15–17). The hallmark of AIE is severe often bloody diarrhoea with a marked protein-losing enteropathy in the presence of autoimmune signs (anti-enterocyte or anti-75 kDa antigen antibodies, which have a high specificity for AIE (18). On histological analysis, severe inflammation with lymphocytic infiltration and epithelial cell apoptosis is characteristic, but an almost completely destroyed intestinal mucosa is often observed in severe forms (16). Signs of autoimmunity can be observed in virtually all organ systems, most often in the endocrine, haematological, nephrological, and skin compartments. Testing of basal immune functions, as well as phenotyping of lymphocytes including staining for CD25 and FOXP3 is mandatory if AIE is suspected. Functional tests of regulatory T cells complete the diagnostic workup, but these are only available in few research laboratories, but well represented among ESPGHAN members (5–7). Genotyping of FOXP3 or other genes so far identified will confirm the initial diagnostic hypothesis. Treatment strategies for patients with AIE depend on the type and severity of the disease. Usually, all patients require stabilization with corticosteroid- and immunomodulator-based medication (5–7,19). Unfortunately, mortality remains high in patients with IPEX-syndrome, except if HSCT with an optimal donor is possible. The first HSCT in a boy with IPEX-syndrome was performed at Necker Enfants Malades Hospital in Paris in 2000 (20).
Distinct forms of IRCE are the so-called “very early onset inflammatory bowel diseases” (VEO-IBD). First described by Ian Sanderson, London, as intractable enterocolitis (21), over the last decade the concept of VEO-IBD truly emerged. The initial reports of Crohn disease (CD) or CD-like diseases starting in the first year of life (21,22) indicated a parallel to classical IBD with 2 major differences, most patients did not respond to classical IBD medication, such as the use of immunomodulators or more recently biologics and some patients developed during infancy or early childhood often lethal lymphomas (23). The discovery of CD-like patients related to mutations in one the IL10 receptor genes brought the breakthrough in the understanding of the pathophysiology of these children suffering from severe colitis and perianal fistulising disease, resistant to medical therapy, but healed by HSCT (24). A collaborative study involving some ESPGHAN members gathered evidence of mutations in genes encoding the IL10R subunit proteins in patients with early-onset enterocolitis, involving hyperinflammatory immune responses in the intestine (25,26). The GENetically determined ImmUne-mediated enteropathieS (GENIUS) working group of ESPGHAN collected infants with a proven defect of the IL10 axis for accurate phenotyping of disease presentation and evolution (26).

The recent discovery at Necker Enfants Malades, Paris, of a particular vulnerability to develop a T cell lymphoma of patients with defective IL10 sensing due to mutations in one of the 2 IL-10 receptors completed the initial report of the Londoner group (27). But not only the IL10 axis is of importance in the control of intestinal immune responses to maintain a balanced situation, mutations in XIAP (28,29), TTC7A (30), or genes causing chronic granulomatous disease are frequently seen in our patients with VEO-IBD (31).

INFLAMMATORY BOWEL DISEASES

ESP GHAN’s contribution in this field is enormous and not all aspects can be detailed. However, several important issues may be remained. One major issue is the use of enteral nutrition as first-line induction therapy in children with CD. In Europe, Sanderson et al first reported in children enteral tube feeding as first-line treatment of CD instead of steroids (32). It opened the door to a new and nutritional approach of CD, meanwhile largely confirmed by several meta-analysis (33,34).

Once more, the London group by Walker-Smith et al first reported the benefits of a special polymeric diet containing TGFbeta-2 as efficient in promoting mucosal healing (35). With time and more frequent use of exclusive enteral nutrition, the Paris group confirmed the efficacy of EEN in CD not only by tube feeding, but also when taken orally (36). This allowed to increase acceptance rates by teenagers of this therapy and thus positioning EEN as first-line induction therapy for luminal CD.

A second major initiative for studying IBD in ESPGHAN was the creation of a collaborative group of clinicians dedicated to IBD, the so-called Porto IBD group (Fig. 1) by Hans Büller and Hans Hildebrand in 2002. Several major projects came out of this productive group over the last 15 years, such as the EUROKIDS registry (37), the Porto diagnostic criteria of pediatric inflammatory bowel disease (PIBD) and its revision (38), the growth study, cancer and mortality study (39), the Paris classification (40) and more recently studies on the use of new biologics, such as vedolizumab (41). In collaboration with ECCO, ESPGHAN took the world-lead in creating the first paediatric-specific guidelines in how to treat paediatric CD (42) and ulcerative colitis (43,44), followed by surgical guidelines for CD and more recently guidelines on nutritional and endoscopic aspects in the care of children with IBD (to be published).

PERSPECTIVES

Research over the last 50 years allowed advancing markedly in the field of PIBD and immune-mediated intestinal diseases of infants and children. In 2018, we have distinct new diagnostic, as well as therapeutic approaches for our patients requiring often expert knowledge. To share and spread this clinical experience, collaborative groups, such as the ESPGHAN Porto Group for IBD, and the GENIUS working group of ESPGHAN for genetically determined immune-mediated intestinal disorders were created. The productivity over the last years proved already how important and helpful these collaborative exchanges within ESPGHAN are. Given the large panel of diseases and overlapping phenotypes, the challenge is to translate research approaches, such as a systematic diagnostic work-up with a gene panel for VEO-IBD combined with whole exome sequencing into clinical routine. The potential correlation (or not) of clinical phenotype and genotype, requires a secured database, such as the recently created by the GENIUS working group, allowing all ESPGHAN members to share these rare patients. This collaborative effort will help to improve diagnosis as well as therapy and ultimately outcome for our young patients suffering from immune-mediated GI disorders.
REFERENCES
Chapter 5.2.1. Short Bowel Syndrome: Half a Century of Progress

Olivier Goulet, Yigael Finkel, Sanja Kolacˇek, and John Puntis

The year 1968 is often considered to be one of the most turbulent in the 20th century. It began with the Tet Offensive in the midst of the second part of the Vietnam War, it was followed by the assassination of Dr Martin Luther King, Jr, and soon after by that of Robert F. Kennedy. Mass socialist movements grew not only in the United States but also in most of European countries. The most spectacular manifestation of this was the May 1968 protests in France, in which students linked up with wildcat strikes of up to 10 million workers, and for a few days the movement seemed capable of overthrowing the government. Another event of 1968 was in August, when the Soviet army entered Prague, the capital of Czechoslovakia. However, behind those events, important happy occurrences, such as the birth of ESPGHAN and the first publication, from Stanley Dudrick and Douglas Wilmore, reporting the successful management of short bowel syndrome in neonates using parenteral nutrition (PN) (1). It started a revolution in the management of short bowel syndrome-related intestinal failure (SBS-IF).

THE PIONEERS

In 1967 Rickham reported his experience in Liverpool, UK, where only 7 of 17 newborns with less than 75 cm or remaining small bowel survived long term (2); these data were later confirmed in follow-up in collaboration with the Swiss group (3). In Rickham’s unit at Alder Hey Hospital, PN was being used from 1962, comprised of Intralipid, 10% amino acid solution and 10% to 15% carbohydrate (glucose or fructose solution). Only a modest energy intake could be achieved, but in some cases it allowed time for gut adaptation to occur such that weaning to full enteral feeding became possible.

Rickham also described using a probiotic (lactobacillus) in short bowel patients, and experimental work he undertook in rats and piglets to investigate the phenomenon of small bowel adaptation. Subsequent work on gut adaptation by Hughes et al (4) showed that in dogs total PN/compete gut rest lead to mucosal hypoplasia, and that this could be prevented by giving daily injections of cholecystokinin and secretin, possibly through a trophic effect of pancreatico-biliary secretions.

Before the advent of PN, short bowel syndrome (SBS) carried a dismal prognosis. In the late 1960s, following Dudrick and Wilmore, yet another pioneer in the promotion and development of nutritional management of pediatric SBS patients in Europe was Claude Ricour, an active pediatrician and ESPGHAN member. As early as 1976 he published this letter in Journal of Pediatrics (5):

"The continuous infusion technique for management of short bowel syndrome (SBS) is very interesting. At the Hospital Necker-Enfants Malades in Paris, we have used it for six years. We have employed this nutritional program in 170 children; 36 of them had a subtotal resection of the small intestine and a complete recovery ensued in 28 patients. The preliminary results have been reported as a communication in the Sixth International Congress of Dietetic. However the methods used and the indications for ‘constant rate enteral nutrition,’ about 12 cases of SBS, have been described. It is a very important nutritional approach, combined or not with total parenteral nutrition. It is not a ‘new method’ of treatment of SBS, however, as Christie and Ament have stated” (6). Indeed, PN has become the key therapeutic tool for managing SBS patients. Its aim is to achieve normal growth and development during the period of time to full intestinal autonomy.

Another key ESPGHAN member, Michael Lentze, published in 1989 an important review on physiology of intestinal adaptation after intestinal resection (7). He concluded the paper as follows: "From a practical point of view, some of the substances involved such as enteroglucagon, prostaglandins and plerocercoid growth factor show some promise for future application in the management of the short-bowel syndrome. However, although adequate nutritional support and H2-receptor blocking agents can be administered, we still seem to be rather far away from being able to offer a more complete drug therapy to our patients suffering from short bowel syndrome."

WHAT IS SHORT BOWEL SYNDROME

SBS is the leading cause of pediatric intestinal failure (IF). SBS-IF is characterized by a compromised bowel absorptive capacity due to severely reduced mucosal surface resulting in diarrhoea, water-electrolytes imbalance, and protein-energy malnutrition. SBS usually follows extensive surgical resection leaving the bowel length below a critical value necessary for adequate nutritional supply (8).

Not surprisingly, the conditions giving rise to SBS have not really changed, although the relative importance in relation to each other has altered. Common causes still include small bowel atresia, complex gastrochisis, mid gut volvulus, neonatal necrotising enterocolitis (NEC), and long segment Hirschprung disease. The precise anatomy of the small intestine causing IF is an important predictor of the final outcome of SBS (Fig. 1).

While the proportion of very preterm infants surviving has gone up the incidence of NEC has not diminished (9), generating more cases with massive gut resection resulting in SBS. A striking increase in the incidence of gastrochisis has been noted in a range of countries (10), with a small proportion of cases being complicated by intestinal atresia, or antenatal/perinatal bowel infarction. Data from the UK show a fourfold rise from 1993 to 2012 in numbers of long-term intestinal failure patients, with an increase in the proportion with SBS rising from 27% to 50% (11).

WHAT CHANGED IN THE MANAGEMENT?

During the 1980s, many children dependent on PN for long periods of time experienced high rates of sepsis, cholestatic liver disease, bone disease, and mortality. The high rate of mortal complications raised serious doubts about the safety of PN which ultimately led to intestinal transplantation being considered as the final solution for the SBS-IF. With the advent of tacrolimus the
following decade saw the onset of the European perspective in intestinal transplantation (see Chapter 5.2.4).

Nevertheless, following the pioneer period, an increasing number of infants and children survived after extensive intestinal resection (12). Case report and cohort follow-up studies from USA and Europe allowed identification of factors influencing the outcome: the underlying diagnosis, the type of segments preserved a long-term stoma versus a primary anastomosis, the presence of the ileo-caecal valve and the age of the patient at the time of surgery (13–19). Goulet from the team of Claude Ricour in Paris (13) reported outcomes in 87 patients with major gut resection; they were divided into group 1 with less than 40 cm remaining bowel, and group 2 with 40 to 80 cm. Underlying disorders included 36 atresia, 22 volvulus, 10 gastrochisis, 11 NEC, and 8 with other conditions. Survival was 92% in group 2 and 67% in group 1; overall more than 90% survived. Outcome was better after 1980 following the introduction of a home PN service.

Nutritional support teams (NST) developed in response to the increasing sophistication of medical interventions, in order to share knowledge and skills, provide management advice and act as an expert resource across different departments (20). The care of children with SBS was aimed at maintaining growth and development while promoting adaptational changes in the gut that would facilitate eventual weaning from PN, as well as avoiding recognised complications such as catheter-related blood stream infection and intestinal failure–associated liver disease. NST commonly brought together nurse, dietician, gastroenterologist, surgeon, and pharmacist with clinical chemist, speech and language therapist, and interventional radiologist also closely involved. The “nutrition nurse specialist” was crucial, and often the starting point of the team, being a novel appointment employed solely to foster effective nutritional support. This role was shown to be cost effective through having an important impact on complications such as catheter-related blood stream infection (21). Nutrition nurse specialists subsequently played a key role in the development of home PN services, training carers, coordinating with community services, and supporting families at home. In some centres, pharmacists took on PN prescribing functions, and the development of computer-assisted PN prescribing facilitated the provision of individualised feeding regimens (22). An evaluation of children referred for consideration of intestinal transplantation (mostly with SBS) suggested that those who had been cared for in a medical unit without NST were less well nourished, had more CVC related complications and experienced greater early mortality than those cared for by a multidisciplinary team (23). Quality standards in some countries such as the UK now dictate that specialist gastroenterology services have to include an NST.

CONTROVERSIES IN SHORT BOWEL SYNDROME FEEDING MANAGEMENT

The management of SBS aims to promote the adaptation of the remnant intestine, which is a physiological process. The role of PN is to maintain optimal nutritional status during the time required for the intestinal adaptation to achieve intestinal autonomy. The GI tract should be used for feeding as much and as early as possible since it is the most physiological and safest route to provide nutrition. However, PN should not be stopped until adequate intake and growth can be achieved with oral feeding (OF) and/or enteral tube feeding (ETF). The optimal strategy for enteral feeding, OF versus ETF and bolus versus continuous, remains a matter of debate (24). A European group of expert agreed in promoting as much OF as possible allowing the maintenance of sucking and swallowing functions along with the interest and enjoyment associated with eating thus helping to prevent eating disorders (24). Moreover, OF promotes the release of epidermal growth factor (EGF) from salivary glands and increases gastrointestinal secretion of trophic factors (25). As emphasized by the Rotterdam group, breast-feeding should be encouraged (26). Human milk (HM) contains a number of factors supporting the developing neonate’s immune system including nucleotides, EGF, immunoglobulin A, and leucocytes (27). Very few studies involved the choice of an “ideal” formula for SBS patients. In Europe, only Ksiazyk et al provided data showing the tolerance and efficiency of polymeric diets (28). However they are
not usually used. Extensively hydrolysed formulas are usually preferred with the advantage of containing short peptides easily absorbed as well as medium-chain triglycerides (MCT) (24). Amino acid–based formulas (AABF) are generally used in the treatment of food allergies or in case of milk protein hydrolysat intolerance. True food allergies have been rarely documented in children with SBS (29). In spite of 2 retrospective studies reporting that the use of an AABF was associated with earlier weaning off PN and also a reduced rate of allergies (30,31), the very small sample sizes and the lack of control groups do not support the recommendation of using AABF in SBS patients. The small number of SBS patients as well as their heterogeneity precludes the design of randomized controlled trials investigating both, the type of the diet and the mode of its administration. Therefore, the current clinical practice is based more on expert opinion and experience based on large cohorts, than on evidence-based medicine. The European view has been published by ESPGHAN members, d’Antiga and Goulet (32), and the ESPGHAN Working Group on Intestinal Failure (33).

INTESTINAL MICROBIOTA: THE BLACK BOX
The Yin and Yang of the Colon
The role of the colon, as well as the intestinal microbiota, are crucial for the prognosis of the SBS by reducing loss of energy and by producing trophic factors (34). In animal models, supplementation of an elemental diet with pectin, which is fermented to short-chain fatty acids in the colon, improved adaptation of the small intestine and the colon in SBS (35). PN with short-chain fatty acids reduced mucosal atrophy and intestinal immune dysfunction following massive small bowel resection (36). Interesting results have been obtained by Finkel et al by infusing pectin-supplemented elemental diet (37). However, clinical manifestations such as abdominal distension, bloating and nausea—due to fermentation in the colon—may impair daily life and should be monitored. They are the consequences of the intestinal malabsorption leading to huge load of undigested CHO reaching the colon. This condition may be worsened by hyperphagia or aggressive tube-feeding with the risk of developing l-lactic acidosis, a rare complication of the colonic hypermetabolism (38).

Small Intestinal Bacterial Overgrowth and Cholestasis
Cholestatic liver disease (CLD) has been shown to be more frequent in the SBS patients than in any other IF conditions (39). It is generally accepted that CTF offers the advantages of optimal digestion and absorption rate (26). However, continuous infusion changes the intestinal motility pattern by missing fasting period (40). Significant dysmotility—impairing intestinal bacterial clearance—leads to small intestinal bacterial overgrowth (SIBO) with consequent enterotoxin release or Gram-negative sepsis. SIBO and cholestasis are common, especially in patients without ileo-caecal valve and in those with abnormal motility (eg, intestinal atresia, gastrochisis, NEC). Aggressive continuous ETF is often attempted with the aim of weaning the child off PN, thought to be the cause of liver injury. These patients present with dilated loops of bowel containing residual nonabsorbed nutrients. This strategy results in increasing SIBO that can cause mucosal inflammation and increased permeability leading to sensitisation and allergy as well as bacterial translocation, sepsis, and cholestasis (32) (Fig. 2). Interestingly, a group of Finish paediatric surgeons demonstrated, recently, the link between small bowel dilation, mucosal damage, bowel-derived bloodstream infections, and hepatic injury (41). In addition, overaggressive ETF may also result in abdominal discomfort, intestinal distension, and loss of self-regulation of intake leading to eating disorders. IFALD occurrence is a strong limiting factor in continuing PN. Fish oil–based lipid emulsions have been shown to reverse cholestasis (42–44), and the studies on their efficacy have been recently reviewed by the ESPGHAN Committee on Nutrition providing recommendations for their use in chronic IF patients (45). Both their availability and SBS-IF management improvements might explain why, in Europe, the rate of end stage IFALD leading to death or liver-intestine transplantation is much lower than reported by the US Intestinal Failure consortium (46).

Dysbiosis as a New Paradigm
The evolution of knowledge on the gut microbiota leads to changes in paradigms and terminology. SIBO should not be neglected or confused with what it is now referred to as ‘‘intestinal dysbiosis.’’ Available data are limited, but the study by Joly et al has opened this field by showing ‘‘imbalance’’ in the gut microbiota of adults with SBS, therefore suggesting ‘‘intestinal dysbiosis’’ (47). Two recent European studies have been conducted in children with SBS (48,49). The faecal microbiome of children with SBS was different from that of controls with a significant abundance of gamma-proteobacteria and bacilli (48). Overall, these studies seem to report a decreased bacterial diversity associated with a reduction or dominance of some bacterial species. These characteristics appear to be correlated with the level of PN dependence and the use of gastrointestinal decontamination.

Ulcerations in the small intestine in the vicinity of ileocolonic anastomosis are rare and relatively unknown complication of SBS, especially in children, as reported by 2 groups from Paris (50,51). These ulcerations appear as externalized or occult gastrointestinal hemorrhages (hypochromic microcytic anemia). The pathophysiology is not known but it could be caused by dysbiosis and, perhaps by a specific bacterium. The role of NOD2/CARD15 mutations has been suggested (51).

HOW TO ENHANCE BOWEL ADAPTATION AND INTESTINAL AUTONOMY
Do Surgeons Have the Answer?
Surgical approaches aimed at maximizing gastrointestinal digestive and absorptive function are crucial to the management of SBS. These include stoma closure and restoration of bowel continuity together with resection of strictures and closure of fistula. There are situations where surgical interventions aimed at reducing stasis in very dilated bowel, possibly decreasing SIBO (with its negative effects on digestion, absorption, and the liver) in the process and increasing contact time between luminal nutrients and mucosa might improve overall absorption. The most common procedures are Longitudinal Intestinal Lengthening and Tapering (LILT) developed by Adrian Bianchi in Manchester, UK (52) and Serial Transverse Enteroplasty (STEP) mostly used in North America (53). The precise indications and the potential benefits of these procedures remain a matter of debate (54,55). LILT involves longitudinal splitting of the small bowel remnant along its mesenteric and anti-mesenteric border, ending up with 2 tubes of bowel of identical length each with their own blood supply, which are then joined together (52). STEP is a newer and less complex technique that involves serial transverse application of a stapler, from opposite directions to create a zig-zag channel (53); unlike LILT, no anastomosis is needed, and the mesenteric blood supply is not put at risk. If the bowel re-dilates, a further STEP procedure can be undertaken. Unfortunately there are no surgical techniques that can
reliably increase small bowel surface area, and by so doing rapidly achieve more than the background process of gut adaptation.

Plasma citrulline is a marker of small bowel enterocyte mass (56,57). It increases significantly within the first weeks following the STEP procedure (58), suggesting that, by reducing SIBO, it restores small intestinal mucosa integrity and improves villous size. Surgical bowel-lengthening should be considered in any chronically PN-dependent patient when there is substantial bowel dilatation and symptoms of SIBO, regardless of the remaining bowel length.

**Hormonal Therapy**

The role of recombinant human growth hormone (rhGH) alone or in combination with glutamine has been investigated by ESPGHAN members in PN-dependent children with SBS (59,60). Despite some decrease in PN requirements during treatment these trials showed little benefit on body composition and mucosal absorption in the long term. Glucagon-like peptide 2 (GLP-2) is produced by the L-cells of the terminal ileum in response to luminal nutrients and has a trophic effect on the intestine, promoting absorption and adaptation (61). Clinical trials suggest it has the potential to decrease PN dependency in patients with SBS when given as a daily subcutaneous injection. A 12-week, open-label study, involving the Great Ormond Street Hospital in London, enrolled SBS PN-dependent patients aged 1–17 years (62). It has been concluded that Teduglutide (GLP-2 analogue) was well tolerated at 0.025 or 0.05 mg/kg per day and was associated with trends toward reductions in PN requirements and advancements in enteral feeding. However, study limitations included its short-term, open-label design, small sample size and heterogeneity of both patients and management because of the multicentre study.
CURRENT PERSPECTIVES

Tremendous progresses have been achieved during the last half a century, changing the face of SBS-IF. Significant contributions have been provided by both sides of the Atlantic Ocean, even if clinical practices often differ (8,24,26,32,65,66). SBS-IF moved from a high mortality condition to a model of intestinal physiology and PN efficiency promoting new concepts and paradigms for the daily clinical practice, lending special importance on preserving oral skills and improving the quality of life. Nevertheless, some patients still remain at risk of developing irreversible IFALD due to extremely short bowel or type 1 SBS, mostly caused by very long segment Hirschsprung disease. In spite of availability and safety of home-PN improving their quality of life, those patients are candidates for hormonal treatment that is already available, intestinal transplantation that showed limits or tissue engineering that might be one hope for the future.

As management strategies of these patients are aimed at preventing the need for small bowel transplantation by avoiding the life-threatening complications of PN, effective interventions to reduce the incidence of NEC and congenital bowel defects will be needed to reduce the numbers of patients with SBS. Progress may come from further understanding of molecular and genetic influences on congenital gastrointestinal anomalies, recently reviewed (67). Gene regulatory factor X6 (RFX6) is possibly linked with enteral adaptation in SBS-IF patients still remain at risk of developing irreversible IFALD due to extremely short bowel or type 1 SBS, mostly caused by very long segment Hirschsprung disease. In spite of availability and safety of home-PN improving their quality of life, those patients are candidates for hormonal treatment that is already available, intestinal transplantation that showed limits or tissue engineering that might be one hope for the future.

It might be interesting to use other trophic factors such as EGF, insulin-like growth factor-1 (IGF-1) or GLP-1 in SBS-IF.

REFERENCES


Chapter 5.2.2. From the Syndrome of Intractable Diarrhea of Infancy to Molecular Analysis and Cell Biology: 50 Years of Evolution

Olivier Goulet and Alan Phillips

In the year of ESPGHAN’s birth, Avery et al. described a “syndrome of intractable diarrhea of infancy” defined as a diarrhea occurring in a newborn younger than 3 months of age and lasting more than 2 weeks with 3 or more negative stool cultures for bacterial pathogens (1). Most cases were managed in hospital using intravenous fluids while the diarrhea was persistent and “intractable.” The mortality rate from infection or malnutrition was high and no specific diagnosis was performed in most patients who survived or died (2). Paediatricians and new specialists, who are nowadays known as “paediatric gastroenterologists,” developed digestive and nutritional management, including continuous enteral feeding using protein hydrolysates, already available at that time. Parenteral nutrition (PN) became available in the early 1970s and dramatically changed the outcome of this syndrome (3,4). Such severe protracted diarrhea resulted from associated factors, including increased intestinal permeability, food antigen sensitisation, bacterial overgrowth, infection and malnutrition, thereby leading to a vicious circle. Distinguished ESPGHAN members, Guarino et al (5) and Catassi et al (6) proposed the term “severe diarrhea requiring PN.” Two major subtypes can be differentiated within this group. The first includes patients with “protracted diarrhea of infancy” (PDI), which results despite its initial severity. PDI can result from a specific immune deficiency or a sensitisation to a common food protein (eg, cow’s milk or gluten), it can be secondary to a severe infection of the digestive tract (postenteritis syndrome). The second group is characterised by “intractable diarrhea of infancy” (IDI), based on the clinical observation of abundant diarrhea (>100 mL/kg and day) starting within the first days or weeks of life, persistent despite bowel rest along with an abnormal intestinal mucosa. Diarrhea rapidly becomes life threatening requires long-term PN and persists for years despite prolonged bowel resting and various therapeutic trials.

PROGRESSES IN ESPGHAN CLASSIFICATION OF CONGENITAL DIARRHOEAL DISORDERS

Clinically, diagnosis of IDI may be easy according to the date of symptom onset, clinical presentation and associated disorders. Many cases are associated with affected siblings and consanguinity among families. Histopathological analysis is required for performing or orienting the diagnosis. An attempt to classify IDI according to villous atrophy was proposed by the Paris group, on the basis of immunohistological criteria emphasising the role of activated T cells in the intestinal mucosa (7). An ESPGHAN multicentre survey led by O. Goulet, collected cases of IDI and villous atrophy with precisely defined light microscopic characteristics, thereby allowing several types of IDI to be categorised (8). Two clearly different groups of IDI have been separated. The first one included autoimmune enteropathies first described by Unsworth and Walker-Smith from London, UK (9) and immune-mediated enteropathies. The second group includes early onset of severe intractable diarrhea with various degree of villous atrophy with low or without mononuclear cell infiltration of the lamina propria, but specific histological abnormalities involving the epithelium. These diseases are related to defects in enterocytes differentiation and polarisation (Table 1). More recently, with Roberto Berni Canini, we proposed a classification of congenital diarrhoeal disorders (CDDs) in 4 groups of CDDs according to the main pathogenetic mechanism (10): defects in absorption and transport of nutrients and electrolytes; defects in enterocyte differentiation and polarisation; defects in enteroendocrine cell differentiation; and defects in intestinal immune-related homeostasis. Many ESPGHAN members contributed to highlight the setting of CDDs including defects in absorption and transport of nutrients and electrolytes (Table 2). In this paper, we will focus on defects in enterocyte differentiation and polarisation.

THE LEADING DEFECT IN ENTEROCYTE DIFFERENTIATION

In 1978 Davidson et al from Australia reported 5 infants with severe, persistent diarrhea beginning in the newborn period (11). Light microscopy revealed crypt hypoplastic villous atrophy while electron microscopic examination showing severe brush-border abnormalities and increased liposome-like bodies and intracytoplasmic cysts made up of brush border (Fig. 1). Further children were reported with these characteristic cytoplasmic inclusions of the brush-border membrane and were well described by Alan Phillips abnormalities by using electron microscopy (12). This “new” disease was called microvillus inclusion disease (MVID) or microvillous atrophy. A. Phillips (London, UK) and J. Schmitz (Paris, France) reported an ESPGHAN survey of 23 cases (13). The group of Necker Paris, reported a single centre survey of 24 patients (14) in which some children have successfully received an intestinal allograft (15).

Many hypotheses have been designed for explaining the very specific histological pictures observed: a defect in the membrane trafficking of immature and/or differentiating enterocytes, or a disorder of the enterocytes’ cytoskeleton, which produces an abnormal assembly of microvilli. Studies have suggested that the direct and indirect constitutive pathways are intact in this disorder and speculated that the abnormal staining pattern reflects accumulation of glycopcalyx-related material (16). Finally, European collaboration involving ESPGHAN members allowed to identify the MYO5B mutation responsible for MVID (17). Several genotypes have been identified by the Robert Debré Paris groups (18). Girard et al (19) from Paris-Necker reported that MVID patients are at risk of developing a PFIC-like liver disease. Whole-exome sequencing of DNA from MVID patients, with milder clinical phenotypes permitting partial or complete weaning from total parenteral nutrition, showed homozygous truncating mutations in syntaxin 3 (STX3) an apical receptor involved in membrane fusion of apical...
vesicles in enterocyte (20). Loss of STX3 function causes variant MVID Interestingly, another ESPGHAN member by using a new-generation sequencing approach, identified MYO5B mutations in patients with progressive familial intrahepatic cholestasis-like phenotype with normal serum gamma-glutamyl transferase activity without intestinal disease (21).

Cell biology is nowadays an approach for understanding both the pathophysiology of MVID and the development and organisation of intestinal epithelial cells and mucosa (22,23). According to the initial outcome before the 1980s, PN now allows most infants and children to survive. However, chronic water-electrolytes imbalance and PN-related complications do limit the long-term survival. Thus, intestinal transplantation has become the only definitive treatment of this rare intestinal disease (24).

ANOTHER STRANGE EPITHELIAL PICTURE

In 1994 Reifen et al in Toronto, Canada (25) and in 1995 Goulet et al in Paris, France (26), reported cases of neonatal severe diarrhoea with abnormal epithelial pictures, which were clearly different from MVID (Fig. 2). Studies performed in these patients by the Necker-Paris group, allowed the identification of IED as a constitutive epithelial disorder involving both the small intestine and colon (26,27). Congenital intestinal epithelial dysplasia (CIED) is frequent in patients of Arabic origin and in Middle East or North Africa as well as Malte Island (28). A main characteristic of this disease is its clinical and histological heterogenicity and its association with malformation or other epithelial diseases such as keratitis and choanal atresia for the most frequent (29,30).

### TABLE 1. Defects in enterocyte differentiation and polarization

<table>
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<tr>
<th>Disease</th>
<th>Gene</th>
<th>OMIM number</th>
<th>Position</th>
<th>Protein</th>
<th>Inheritance and incidence</th>
</tr>
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<tbody>
<tr>
<td>Microvillous inclusion disease</td>
<td>MYO5B</td>
<td>606540</td>
<td>18q21.1</td>
<td>Myosin B</td>
<td>AR; rare; highest frequency among Navajo</td>
</tr>
<tr>
<td>Congenital tufting enteropathy*</td>
<td>EPCAM</td>
<td>185535</td>
<td>2p21</td>
<td>Protein for cell-cell interaction</td>
<td>AR; 1:50–100,000; higher among Arabs</td>
</tr>
<tr>
<td>Trichobhepatoenteric syndrome (Syndromic diarrhoea)</td>
<td>TTC37</td>
<td>614589</td>
<td>5q15</td>
<td>Component of the SKI complex</td>
<td>AR; &lt;1/1,000,000</td>
</tr>
<tr>
<td></td>
<td>SKIV2L</td>
<td>600478</td>
<td>6p21.33</td>
<td>Component of the SKI complex</td>
<td>AR; &lt;1/1,000,000</td>
</tr>
</tbody>
</table>
*Congenital tufting enteropathy associated to EPCAM mutation is characterised by only intestinal involvement, while mutation in SPINT2 lead to a syndromic form with extra-intestinal abnormalities.

### TABLE 2. Defects in absorption and transport of nutrients and electrolytes

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>OMIM number</th>
<th>Position</th>
<th>Protein</th>
<th>Inheritance and incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital chloride diarrhoea</td>
<td>SLC26A3</td>
<td>126650</td>
<td>7q31.1</td>
<td>Cl-/base exchanger</td>
<td>AR, sporadic; common in some ethnic groups</td>
</tr>
<tr>
<td>Congenital sodium diarrhoea</td>
<td>SLC9A;</td>
<td>614868;</td>
<td>5p15.33;</td>
<td>Na⁺-H⁺ exchanger</td>
<td>AR, &lt;1:1,000,000</td>
</tr>
<tr>
<td></td>
<td>GUCCY2C</td>
<td>270420</td>
<td>12p12.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital lactase deficiency</td>
<td>LCT</td>
<td>603202</td>
<td>2q21.3</td>
<td>Lactase-phlorizin hydrolase</td>
<td>AR; 1:60,000 in Finland; lower in other ethnic groups</td>
</tr>
<tr>
<td>Sucrase-isomaltase deficiency</td>
<td>SI</td>
<td>609845</td>
<td>3q26.1</td>
<td>Isomaltase-sucrase</td>
<td>AR; 1:500; higher in Greenland, Alaska and Canada</td>
</tr>
<tr>
<td>Maltese-glucoamylase deficiency</td>
<td>MGAM</td>
<td>154360</td>
<td>7q34</td>
<td>Maltase-glucoamylase</td>
<td>Only few cases described</td>
</tr>
<tr>
<td>Glucose-galactose malabsorption</td>
<td>SLC5A1</td>
<td>182380</td>
<td>22q13.1</td>
<td>Na⁺/glucose cotransporter</td>
<td>AR, a few hundred cases described</td>
</tr>
<tr>
<td>Fructose malabsorption</td>
<td>SLC2A5</td>
<td>138230</td>
<td>1p36.23</td>
<td>Fructose transporter</td>
<td>More than 40%</td>
</tr>
<tr>
<td>Fanconi-Bickel syndrome</td>
<td>SLC2A2</td>
<td>138160</td>
<td>3q26.2</td>
<td>Basolateral glucose transporter</td>
<td>AR, rare</td>
</tr>
<tr>
<td>Acrodermatitis enteropathica</td>
<td>SLC39A4</td>
<td>607059</td>
<td>8q24.3</td>
<td>Zn²⁺ transporter</td>
<td>AR; 1:500,000</td>
</tr>
<tr>
<td>Lysinuric protein intolerance</td>
<td>SLC7A7</td>
<td>603593</td>
<td>14q11.2</td>
<td>Cationic amino acid transporter</td>
<td>AR; approximately 1:60,000 in Finland and Japan; rare in other ethnic groups</td>
</tr>
<tr>
<td>Primary bile acid diarrhoea</td>
<td>SLC10A2</td>
<td>601295</td>
<td>13q33.1</td>
<td>Ileal Na⁺/bile salt transporter</td>
<td>AR</td>
</tr>
<tr>
<td>Enteroendocrine deficiency</td>
<td>TMPRSS15</td>
<td>606355</td>
<td>11q13.3</td>
<td>Bile acids negative feedback</td>
<td>Only few cases described</td>
</tr>
<tr>
<td>Abetalipoproteinemia</td>
<td>MTTP</td>
<td>157147</td>
<td>4q23</td>
<td>Microsomal triglyceride transfer protein</td>
<td>AR, about 100 cases described; higher frequency among Ashkenazi</td>
</tr>
<tr>
<td>Hypobetalipoproteinemia</td>
<td>Apo B</td>
<td>107730</td>
<td>2p24.1</td>
<td>Apolipoprotein B 100/48</td>
<td>Autosomal co-dominant</td>
</tr>
<tr>
<td>Familial diarrhoea syndrome</td>
<td>GUCCY2C</td>
<td>601330</td>
<td>12p13.1-p12.3</td>
<td>Receptor for heat-stable enterotoxins</td>
<td>Described in 32 members of a Norwegian family</td>
</tr>
<tr>
<td>Diarrhoea associated DGAT1 mutation</td>
<td>DGAT1</td>
<td>604900</td>
<td>8q24.3</td>
<td>Diacylglycerol acyltransferases</td>
<td>One family has been reported</td>
</tr>
</tbody>
</table>

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*S78 www.jpgn.org*
EPCAM gene mutation has been shown by Sivagnanam et al from San Diego, California (31). EPCAM belongs to cell adhesion receptors, which in addition to structural functions, play a role in signalling, migration, proliferation and cellular differentiation (31). By mediating homotypic interactions between intraepithelial lymphocytes and intestinal epithelial cells, EPCAM contributes to form an immunological barrier against mucosal infections, and vice versa in case of absence may contribute to the inflammatory reaction observed in the CIED as reported by Simon Murch (32). A second group of CIED individuals is characterised by mutations in SPINT2 (33). SPINT2, like EPCAM, is a transmembrane protein also called hepatocyte growth factor activator inhibitor type 2 (34). This potent serine protease inhibitor is involved in epithelial regeneration, as well as in the NF-kB and TGF-β signalling pathways. The Paris-Necker group showed that SPINT2 patients present with a syndromic form associated with superficial punctate keratitis and choanal atresia in half of the cases, as well as other sporadic abnormalities, suggesting a syndromic form of CIED (34). Taken together, these findings establish SPINT2 as a second gene associated with CIED. The different but overlapping enterocyte abnormalities suggest that the 2 CIED-associated genes belong to distinct pathways both regulating cell adhesion the most recent and cytoskeleton dynamics leading to CIED phenotype (34). Recently, inspired by the characterisation of cellular defects in EpCAM-related CIED, Julie Salomon and Delphine Delacour (Institut Jacques Monod, Paris, France) reported that these unusual cell organisation and intestinal tissue defects are driven by the loss of actomyosin network homeostasis and contractile activity clustering at tricellular contacts, reversed by myosin-II inhibitor treatment (35). This might open the door to targeted new therapies, since EpCAM modulation protects against epithelial dysplasia and stabilises human tissue architecture.

**WHEN LIVER AND INTESTINE MEET**

The so-called “phenotypic diarrhoea” or “syndromatic diarrhoea” was described by the Paris-Necker group as diarrhoea starting within the first 6 months of life without histological specific abnormalities but with several associated features, including small for gestational age (SGA), facial dysmorphism and a distinct abnormality of hair with tricorrhexis nodose (36). The reported patients had defective antibody responses despite normal serum immunoglobulin levels and defective antigen-specific skin tests despite positive proliferative responses in vitro. The reported prognosis was poor, most patients died between 2 and 5 years of age, most with early onset of liver disease (37). From a cohort of patients with early onset unknown liver disease associated with diarrhoea and abnormal hairs, the Birmingham group identified a mutation of the gene TTC37 (38). From
Clinical approach of early onset severe diarrhoea

**Onset day 1-30**

<table>
<thead>
<tr>
<th>Family history</th>
<th>Reduced at bowel rest</th>
<th>Family history</th>
<th>Disappears at bowel rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydramnios / prematurity</td>
<td>Chloride diarrhea SLC26A3</td>
<td>Hydramnios / prematurity</td>
<td>Glucose-galactose Malabsorption (SLC5A1)</td>
</tr>
<tr>
<td>Wetty diarrhoea Biological presentation</td>
<td>Sodium diarrhea SPINT2, GLUCY2C</td>
<td>Mitochondrial disease</td>
<td>Primary lactase deficiency (LCT)</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>Consanguinity SGA birth</td>
<td>Neurogenin 3 deficiency</td>
<td>Lymphangiectasia</td>
</tr>
<tr>
<td>Abundant watery diarrhea</td>
<td>Facial dysmorphism</td>
<td>Bile salts malabsorption SLC10-A2</td>
<td>Entero kinase deficiency (TMRPSS15)</td>
</tr>
<tr>
<td>Defects in enterocyte differentiation and polarization</td>
<td>Hair abnormalities</td>
<td>HSPG deficiency</td>
<td>Other Defects in absorption and transport</td>
</tr>
<tr>
<td>Microvillous atrophy MYO5B, STX3, UNC 45A</td>
<td>Liver disease</td>
<td>Early IPEX and AIE*/VEOIBD *</td>
<td>CMPA and IPEX as well as sucrase deficiency are rarely of early neonatal onset</td>
</tr>
<tr>
<td>Epithelial dysplasia EpCam / SPINT2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other « new » diseases/mutations to be founded</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**From O. Goulet**

**FIGURE 3.** Proposed algorythm for the clinical approach of early onset severe diarrhoea.

Phenotypic or Syndromatic diarrhoea to the so-called tricho-hepato-enteric syndrome (THES). The gene TTC37 encodes a hypothetical protein known as Thespin, which Fabre et al from Marseille (France) showed the existence in many tissues (vascular endothelium, lymph, pituitary stalk, lung and intestine), but is not, contrary to what the clinic might suggest, expressed in the live (39). TTC37 is reported as being the ortholog of yeast SKI3, which encodes a key component of the SKI complex, a multiprotein complex required for exosome-mediated RNA surveillance (40). Subsequently, mutations in SKIV2L in a group of 6 individuals affected by typical SD/THES syndrome, but negative for TTC37 mutations, have been described by Fabre et al (41). The mutation types suggest that the disease mechanism is loss of function SKIV2L a cytoplasmic-exosome cofactor involved in various mRNA decay pathways and required for normal cell growth (42). The mechanism by which mRNA-surveillance defects lead to various clinical symptoms, such as severe diarrhoea, hair abnormalities, or immunodeficiency, needs further investigations (43).

In conclusion, CDDs represent a group of challenging clinical conditions for paediatricians because of the severity of the presentation and the broad range of possible differential diagnoses. CDDs arise from alterations in the transport of nutrients and electrolytes across the intestinal mucosa, from enterocyte and enteroendocrine cell differentiation and/or polarisation defects, and from the modulation of the intestinal immune response. The number of well-characterised disorders attributed to CDDs has gradually increased over the past several years, and many new genes have been identified, opening new diagnostic and therapeutic perspectives. The research that enabled these advances in knowledge to be made occurred for most, in European centres of paediatric gastroenterology. The partnership between clinicians and scientists has been of key importance in these developments. The recent ESPGHAN paper leaded by Roberto Berni Canini and Olivier Goulet, entitled “Congenital Diarrheal Disorders: an evolving web of inherited enteropathies,” summarised the current knowledge in that evolving disease setting (10). For the clinician facing to early onset intractable diarrhoea of infancy, gene panel analysis, as it has been developed in some European centres such as Necker-Imagine (Paris, France) by the group of Nadine Cerf-Bensussan or the European Laboratory for the Investigation of Food Induced Diseases, University of Naples, Federico II, Naples, Italy, diagnosis has become easier especially in case of atypical presentation. Molecular analysis has changed the diagnostic scenario in CDDs, and led to a reduction in invasive and expensive procedures. Moreover, this approach may make possible the diagnosis of especially rare digestive disease as reported by other ESPGHAN members, such as heparan-sulfate (44) or neurogenin3 deficiency (45).

With the onset of adequate nutritional support, the so-called “intractable diarrhoea of infancy” has moved from a mysterious syndrome with a high mortality and morbidity to specific diseases, genetic in origin. However, behind this apparent easiness, management raises many important questions, including ethical issues and therapeutic choices. Infants with IDI remain dependent on PN for months, years and, for most, forever because of the permanent intestinal malabsorption and a high rate of digestive losses. Because
of complications of long-term PN and/or poor quality of life, alternative treatments, such as intestinal transplantation, have been considered (24).

REFERENCES

Chapter 5.2.3. Parenteral Nutrition and Home Parenteral Nutrition Changed the Face of Paediatric Gastroenterology

Antonella Diamanti, John Puntis, Sanja Kolacek, Susan Hill, and Olivier Goulet

The history of parenteral therapy extends back to at least the 17th century, following William Harvey’s publication in 1628 of his treatise ("De Motu Cordis") describing the circulation of the blood (1). William Courten, at the University of Montpellier in France, in 1678 injected warm olive oil into dogs, which died within a few minutes from fat embolism. A few years later Christopher Wren and Robert Boyle experimented with infusing wine, ale and opium into a dog using a goose quill as a venous cannula. The Scottish physician Thomas Latta used an infusion of hypotonic saline to treat victims of the 1831/32 cholera pandemic, and later in the 19th century there were trials of subcutaneous injection of nutrients to malnourished patients. By the 1940s, hydrolysed proteins and glucose were being given to adult surgical patients, and in Europe in 1944 the first protein hydrolysate was marketed, developed by Arvid Wretlind in Sweden. Such products were later superseded by solutions of crystalline amino acids, first used in Germany in 1964. Wretlind went on to develop a more balanced amino acid solution (Vamine), as well as an effective and “non-toxic” soybean oil based lipid emulsion (Intralipid) introduced in 1961, permitting a dual energy supply during parenteral nutrition (PN). For all these innovations he is remembered as the “father of complete parenteral nutrition” (1).

In the USA in 1968 (incidentally coinciding with the foundation of ESPGHAN), Wilmore and Dudrick reported a landmark case of long term PN in a child with short bowel syndrome (SBS) (2). Introduction of PN into wider clinical practice soon followed, with it becoming a standard intervention in the care of premature newborn as well as proving life-saving support for children with intestinal failure (IF). From the early 1970s, complete PN feeding regimens for children were described by Grotte et al in Sweden, Borreson and Knutrud in Norway, Jurgens et al in Germany (3), Harries in the UK (4) and Ricour in France (5). Continuous advances have been made in the provision of effective and safe nutritional support, with a transformed outcome for children with chronic IF (CIF). Many of these can now be discharged on home-parenteral nutrition (HPN) as a viable alternative to both long term hospitalisation and intestinal transplantation. Together with our colleagues across the world, ESPGHAN members and their teams have made a very significant contribution to this process. This short history paper focuses mostly on long-term use of PN and home-PN related to chronic intestinal failure (CIF).

ESPGHAN AND THE ADVANCEMENT OF PARENTERAL NUTRITION

While ESPGHAN strongly endorsed the use of enteral tube feeding whenever possible, this form of nutritional support was clearly unsuitable for managing patients with severe and/or protracted IF. PN not only contributed to saving the lives of many newborns, infants, and children, but also helped the concept of IF to be developed, and aided the identification of many of its underlying causes. This was especially the case for so called “intractable diarrhoea of early onset” (see Chapter 5.2.2), and transformed the outcome in short bowel syndrome (see Chapter 5.2.1). As a complex new therapy requiring multiprofessional and interdisciplinary management in addition to careful monitoring, PN can be regarded as one of the most important stimuli for the development of paediatric gastroenterology as a clinical specialty. Moreover, by sustaining life PN made it possible to undertake metabolic studies, in both stable and unstable conditions, using indirect calorimetry, stable isotope infusions and body composition measurements, generating improved knowledge of the physiology of PN. Much of this clinical research was carried out in North America (mainly in Canada by the group associated with Paul Pencharz), and in Europe with the group of Claude Ricour (6–15).

Over time PN has become safer through experience and learning, multidisciplinary nutritional team working, research, and development of novel feeding products. Amino acid solutions have been adapted for particular age groups, lipid emulsions have evolved to become more physiological, and additive products have been refined. ESPGHAN members have contributed to this progress by performing randomised double-blind clinical trials (RCTs) supporting new generations of intravenous lipid emulsion (ILE) (16–19). Deficiency states from taurine and selenium have been recognised (retinal abnormalities; skeletal and cardiac myopathy), and the hazards of oversupply of chromium (renal damage), manganese (neurotoxicity, Parkinson’s like state) and aluminium (bone disease, neurotoxicity, liver disease) identified – all leading to changes in clinical practice. Knowledge, protocols and suggestions for research priorities have been shared, most notably in the ESPGHAN/ESPE joint guideline on PN published in 2005 at the initiative of Berthold Koletzko, Raanan Shamir and Olivier Goulet (20) and further revised and updated to be published in 2018.

In his 1971 “personal practice” paper reviewing the state of PN, John Harries (4) listed some of the important complications including sepsis, metabolic acidosis, phlebitis/venous thrombosis, catheter displacement, hypoglycaemia, and heart failure. To this list can be added intestinal failure associated liver disease (IFALD), the term proposed for encompassing the effects of both PN and IF (21). After decades of advances, some of these complications continue to present challenges.

FROM INTESTINAL FAILURE TO “NUTRITIONAL FAILURE”

Catheter-related Bloodstream Infections (CRBSIs) and Venous Thrombosis

The central venous catheter (CVC) is an essential device for delivering long-term PN. CRBSIs are the most frequent complications during PN whatever its indication and duration. These complications have been studied in large cohorts, and have contributed
Intestinal Failure Associated Liver Disease

Cholestasis was an early recognised and common complication of PN, particularly in preterm infants. It was initially thought to be due to a toxic effect of PN components on the liver, giving rise to terms such as “PN related cholestasis,” and “PN associated liver disease.” Subsequently, lack of enteral nutrition, immaturity of liver function, small intestinal bacterial overgrowth (SIBO) (see Chapter 5.2.1) and CRBSIs have been identified as major risk factors for what is now recognised as a multifactorial disorder. This topic has recently been comprehensively reviewed by an ESPGHAN working group and individual authors (31–34). A study from London, involving 87 infants requiring PN for at least 28 days, reported IFALD in 29 infants (33%) (32). In a Paris study of 302 children receiving long term home PN from 1980–1999, 23% developed IFALD. Lambe et al. from the Paris-Necker group, reported beneficial results of using taurodoxilin locks in a home-PN cohort achieving an incidence of 0.8/1000 PN days (29).

CRBSIs promote venous thrombosis that can be seen in up to 40% of patients with a CVC in situ and is sometimes symptomatic (eg, superior vena cava obstruction; pulmonary embolus). Loss of venous access through thrombosis in individual patients over the years became an indication for intestinal transplantation (ITx), and as discussed by d’Antiga and Goulet can be considered one of the elements of so-called “nutritional failure” (30). Limiting CVC insertion to experienced operators, planned replacement during daytime hours and the involvement of interventional radiologists as part of the nutritional support team are likely to be important in protecting veins, as is minimising the risk of CRBSI. Novel approaches such as a stereotactic passage of a guidewire and stenting can facilitate reinsertion of a CVC in a patient with venous thrombosis.

Metabolic Bone Disease

PN related metabolic bone disease (MBD) in children can result in permanent bone damage or reduced bone mineralisation and increased fracture risk (40). Several causes of BMD have been highlighted by ESPGHAN member pioneers in PN and include aluminium exposure from PN, imbalanced parenteral calcium and phosphorous intake, variable parathyroid hormone concentrations, and vitamin D toxicity (41,42).

With the development of dual-energy x-ray absorptiometry (DXA), assessment of bone mineral density (BMD) can be easily achieved while a high-risk population may be defined. A cross sectional study from the Great Ormond Street Hospital in London, reported that approximately 50% of children were short with height SDSs less than −2 at baseline, and one-third of children had low BMD. Children with enteropathy or intestinal mucosal inflammation are at greatest risk of growth failure (43). Two more recent studies from France showed similar results (44,45). The issue of BMD remains important as shown by the ESPGHAN Guidelines debate recommending optimal calcium and phosphorous intake for long term PN (PN Guidelines to be published in Clinical Nutrition 2018).

Finally, paediatric PN achieved tremendous progress from its onset 50 years ago. Several ESPGHAN members have been pioneers in the field and ESPGHAN provided the first Guidelines in 2005 (to be updated in 2018). Their aim is to “guide” the ESPGHAN guidelines for all members in the field in which randomized controlled trials (RCTs) are available at least for the short- and mid-term use. Although it is considered that obtaining long term safety data based on RCTs will remain almost impossible, this should not impede the use of the last generation that provide the advantages of containing less potentially detrimental (excess n-6 fatty acids) or toxic components (phytosterols) and more beneficial components (such as antioxidant agents (alpha-tocopherol) or n-3 fatty acids including EPA and DHA (39).
decreased risk of CRBSI and improved psychosocial development and quality of life (49,50). A prerequisite in most European countries for home PN to be established has been the growth of home care companies to undertake compounding of feeds, and their home delivery together with supplies of consumables and equipment. Companies also provide an element of nursing support, including continuation of training for carers following hospital discharge when necessary. The overall clinical condition of the child needs to be stable, but with careful planning and ongoing telephone support from expert nurses and dieticians in the nutrition support team, even those with additional requirements such as enteral tube feeding or high stoma losses can often be cared for out of hospital. Long-term follow-up studies from Paris-Necker (33) showed that outcome was good, with survival at 2, 5, 10, and 15 years of 97%, 89%, 81%, and 72%, respectively. Children with intractable diarrhoea had the highest mortality (25%) and the highest incidence of IFALD (48%). More recent results from the same group show continuous improvements in survival and incidence of CRBSIs and IFALD (34). Other groups in Europe, from Croatia (23), Sweden (51), Poland (52), Czech Republic (53), UK (54), Italy (55–57), or France (58), reported encouraging results. Moreover, Loris Pironi from Bologna designed an ESPEN and ESPGHAN collaboration providing an important European survey on Home-PN in Europe (59).

While neonatal SBS accounts for the majority, the number of patients receiving HPN continues to rise, in part through an increase in the prevalence of certain conditions such as congenital enteropathies, chronic intestinal pseudo-obstruction syndrome or extreme and/or complex SBS. Even children with less than 10 cm small bowel (ultra-SBS) can do very well on long-term HPN (54), avoiding life-threatening complications and enjoying a good quality of life despite the severe handicap from SBS. The aim of nutritional management is the weaning from PN and HPN, but when this cannot be achieved the future presents significant challenges. HPN is very beneficial for the children but can be difficult for the parents and siblings to accept especially in the absence of an alternative strategy other than intestinal transplantation (60). Social and familial environment should always be carefully assessed and monitored to ensure not only safety but familial harmony and function. Today, ‘transition’ has become an important issue because of an increasing number of adolescents needing to be referred to adult intestinal rehabilitation centres. Very few data are available on the outcome after ‘transition’. Interestingly, a recent paper from France reported successful pregnancy in young women on long-term home PN for CIF (61).

**CONCLUSIONS AND PERSPECTIVES**

Commenting on intravenous therapy for cholera patients in 1831, a Dr Lewins promised that “this ‘astonishing method of medication’ will lead to wonderful improvements in the practice of medicine” (62). The history of PN over the last 50 years proves him to have been prescient. However, problems as well as controversies still manifest when attempting to establish recommendations and guidelines. There are difficulties in reaching a consensus in defining duration of PN as short-, mid- or long-term PN together with very different groups of children from newborns and premature babies to pre-adolescents and adolescents. Controversies emerged recently regarding the appropriateness of using PN in critically ill children as illustrated by the so-called ‘PEPaNIC Trial’ (63) and commented by ESPGHAN members (64,65).

Fortunately, continual advances have been made in the provision of effective and safe nutritional support, with a transformed outcome for children with IF. PN is a well-recognized life-saving therapy, while long-term home-PN has become a viable alternative to both long-term hospitalisation and intestinal transplantation. Together with our colleagues across the world, ESPGHAN members and their teams have made a very significant

**FIGURE 1.** View of extremely malnourished children in the early 1970’s. Parenteral nutrition made them surviving and recovering from severe protein-energy malnutrition. (Photos by courtesy of Claude Ricour).
Management of children requiring HPN should be undertaken only in specific centres by multidisciplinary teams, including physicians (neonatologists, gastroenterologists and surgeons), pharmacists, nurses, dieticians, social workers and psychologists. The Network for Intestinal Transplantation in Europe (NITE) provided a recent overview of the organisation and current practice of specialised paediatric IF teams across Europe (66) and compared these results to the ESPGHAN/ESPEN guideline (20). Most practices have a low-level evidence base, being mostly conducted on the basis of expert opinion. Harmonisation and optimisation of clinical guidelines for managing long-term PN in IF patients is a goal that we should aim to achieve in the future (Fig. 2).

REFERENCES


FIGURE 2. From medical prescription to home delivery. It illustrates how the multi-professional approach makes Home-PN possible.


Chapter 5.2.4. Intestinal Transplantation: On a Long and Uneven Road From the Past to the Future

Florence Lacaille, Girish Gupte, and Olivier Goulet

The first ever reported organ transplantation was reported around 250 AD by 2 Greek physicians, Cosmas and Damiano, who implanted a leg from a dead to a living man, with immunosuppression based on Holy Water (1). The experience then faded away, until the second half of the 20th century. Following the success of kidney then liver transplantation, and after extensive experimental work, 1 of the first intestinal transplantations (ITx) in the world was performed in 1987 on a baby with short bowel syndrome (SBS), using cyclosporine, in the institution of several eminent members of ESPGHAN, Necker-Enfants Malades in Paris (Fig. 1) (2–4). The first attempt with cyclosporine as the immunosuppressive agent failed until tacrolimus has been available in Europe, restarting ITx in Paris in 1993. This institution not only pioneered the development ITx, but had the foresight to develop integrated care of children with intestinal failure (IF) as promoted by Olivier Goulet (5), thus establishing the pathway for intestinal rehabilitation (IR) centres (6–8). In 2015, the international Intestinal Transplant Registry reported on 3067 patients, including 1697 children: 1621 only (822 children) of them were still alive, even fewer off parenteral nutrition (9). The 10-year graft survival was 40% to 60%, with a consistent improvement in the survival of children transplanted within the last 10 years. The relatively small number, as compared to other solid organ transplantation, highlights the difficulties of this rare and demanding procedure, whose long-term results are far from satisfactory. We must acknowledge the crucial role of Thomas Starzl and his Pittsburgh team in promoting ITx (Fig. 2). Building up experience is difficult, when only a few centres in the world have transplanted more than 100 patients in 20 years. The 3 large European paediatric centres are, Necker-Enfants Malades in Paris (Fig. 3) (10), Birmingham Children’s Hospital (Fig. 4) (11), and La Paz in Madrid (12). The world champion of long-term survivor following intestinal transplantation is a French child transplanted in March 1989 with cyclosporine-based immunosuppression (13). However, ITx numbers increased in the 1990s after the introduction of tacrolimus. The first Intestinal Transplant Registry report, published in demonstrated the leadership of US transplant group that remains until now (14).

WHAT ARE THE SPECIFICITIES OF INTESTINAL TRANSPLANTATION?

The intestine harbours 80% of the body’s immune cells and is certainly not sterile, conditions that make its transplantation challenging. In addition, it is a bacteria-hosting organ, suffering from ischaemia-reperfusion, and denervation (Fig. 5). Many improvements have been achieved in the last 25 years in the selection of patients, surgical technique, immunosuppression, anti-infection therapy and follow-up, with a marked increase in short-term survival (15). At the early phase, acute rejection has been thought to be cellular (16). Today it is well established that humoral rejection may be predominant. The diagnosis and management of humoral rejection benefited from the donor specific antibody (DSA) knowledge and technology as well as the availability of new generations of monoclonal antibodies (17). The risk of rejection is higher in the first months, but late acute rejection and chronic rejection remain important causes of late graft (9). Medium- and long-term follow-up showed a significant rate of late graft loss as well as severe complications, either from the medications or the psychological burden of a chronic condition often present from birth (9).

Parallel to the slow increase in numbers of ITx, the management of children with IF improved, due to the establishment of specialized centres in many European countries, called “Intestinal Rehabilitation Centres” (IRC) associated for most with homeparenteral nutrition programmes (HPN) (18). The scientific societies, in first place ESPGHAN, were instrumental in getting physicians together and creating networks for such a rare condition as IF (19). A network, called NITE for “Network for Intestinal Transplantation in Europe,” was created under the umbrella of ESPGHAN, to strengthen the cooperation for clinical work and research, both in IF and transplantation.

INDICATIONS FOR INTESTINAL TRANSPLANTATION: A DEBATED QUESTION

Intestinal transplantation is indicated in children with irreversible IF, highly dependent on PN (receiving over 100% of their resting energy expenditure requirements through PN) with associated life-threatening complications. It was confirmed by the working group on IF and ITx, including clinical nutrition in the 2° World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition (Paris 2004) (20). The medium-term mortality of children on HPN is nowadays nearly zero (21), and uncontrollable complications of long term PN only are an indication for ITx (22). A proportion of patients eventually develop life-threatening complications such as severe septic episodes, fluid and electrolytes imbalance, loss of venous access for PN, and end-stage liver disease. The term “nutritional failure” was proposed by d’Antiga and Goulet as the incapacity to continue PN on the long-term because of such life-threatening complications (22). IF is a rare condition that should be managed in experienced centres or in close collaboration with such centres offering an interdisciplinary management to facilitate an early referral rather than a referral at the terminal stage of a life-threatening complication (23). The waiting times for ITx are usually long, and the child should remain on PN in pre- and post-intestinal transplant period until nutritional rehabilitation can be established. The Birmingham group reported improvements in long-term survival of children referred for ITx they attributed to earlier referral and innovative surgical strategies (24).

The irreversibility of IF is obvious if the child has a very short gut, microvillous inclusion disease, long segment Hirschsprung disease, severe form of chronic intestinal pseudo-obstruction syndrome. Successful transplantations have been reported by the Paris-Necker group in infants and children suffering microvillous
inclusion disease (25), long segment Hirschsprung disease (26). ITx may be an option in the most severe form of chronic intestinal pseudo-obstruction syndrome (27). The Birmingham ITx unit reported encouraging results in chronic intestinal pseudo-obstruction syndrome patients (28). In dubious situations, HPN should be optimised so as to allow for a successful ITx in the future. With the improvement of HPN management, the availability of non-transplant surgery (29) and the perspective of using GLP-2 analogues (30), SBS should become a rare indication (see Chapter 5.2.1).

One rare indication for ITx may be when a child with irreversible IF is long-term resident in the hospital for social or medical reasons. This does raise ethical issues requiring to be discussed in the IRC by the multi-professional (psychologists, social workers, physiotherapists) and inter-disciplinary (paediatric gastroenterologist and nutritionist, paediatric surgeons) group (31).

Psychological intolerance to HPN is a difficult situation, where the patient «who feels like a dog on the leash», does not realize that the leash will not disappear after ITx but only become transparent, but can develop non-compliance and new complications related to ITx (32).

THE MANY FACES OF INTESTINAL TRANSPLANTATION

Due to stereometry, the graft usually comes from a size-matched child, which explains the long waiting time. The Birmingham group promoted techniques of tissue expansion to facilitate liver and small bowel transplant in young children with contracted abdominal cavities (33) or staged abdominal closure techniques (34). The small bowel can be transplanted alone, together with the right colon when the disease also involves the colon (congenital enteropathies, motility disorders), together with the liver in case of IFALD, or together with the whole intestinal tract (from stomach to colon, and the liver) in motility disorders or severe portal hypertension. The Paris group was the first to report successful right colon transplantation (35). During the last decade, the Birmingham group promoted the indication for isolated liver Tx in SBS children with end-stage IFALD and a bowel length estimated sufficient for PN weaning (36,37). Taha et al reported a group of children with SBS and IFALD who have the potential for adaptation in the residual bowel underwent isolated LTx (38). The prognosis remains poor after this procedure, with 8 survivors out of 14 children undergoing ITx (38). This indication can be avoided in the first place by...
preventing IFALD in infants. With changes in clinical management of SBS and the onset of fish oil based lipid emulsions, IFALD incidence has decreased and this option can be progressively abandoned.

Improved outcome has been reported in animal models when intestinal allograft is transplanted with the liver (39–41). The advantages in human were reported by several centres and the intestinal transplant Registry but remain debated (8,42,43). A stoma is created on the terminal ileum, in order to follow-up the function of the transplanted organ (making stool) and to perform biopsies. The stoma is usually closed several weeks or months after transplant surgery in the absence of surgical complications following the transplant procedure (44).

The immunosuppressive therapy is based on usual drugs, but at higher doses than for the liver or the kidney. Every centre has its own immunosuppression protocol, showing that none of the protocols are superior than the others. Inclusion of the liver in the graft is probably protective on the long-term, and immunosuppression should not be too minimized for isolated intestinal transplants.

**IS THE TRANSPLANTED INTESTINE FUNCTIONAL?**

Depending on ITx related complications and on the tolerance of enteral feeding, PN can be discontinued after a few weeks (45). Protocols for diet are as diverse as for immunosuppression, both highlighting the many uncertainties of ITx (46). A normal diet is possible in long-term, especially when there are no associated feeding disorders. Adapting the caloric intake to the intestinal

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**FIGURE 3.** The complexity of the transplanted intestine.

**FIGURE 4.** Transplantation group at Birmingham Children’s Hospital. From the left: Girish Gupte, Deidre Kelly and Sue Beath.
function, with supplemental enteral feeding as needed, allows a normal growth in most patients (47). There are very few reports in the literature about the function of the transplanted intestine. Stool balance analysis, routinely used by the Paris group, is a very precious tool for assessing, both in a short and long term, intestinal absorption capacity after ITx (45,47).

In the short to medium and long-term follow-up, the patients remain exquisitely sensitive to acute diarrhoea and dehydration, which is poorly tolerated by the transplanted bowel. Diarrhoea may be a confusing symptom as it can be the first manifestation of acute rejection or of viral gastroenteritis, the treatment of which is diametrically opposite. Digestive symptoms should always ring a bell for a possible rejection, and prompt further investigations. Early clinical suspicion and early diagnosis along with rapid treatment is a key to reversion of a late acute rejection. Close follow-up of growth is a key issue. Stunting without any obvious endocrine cause should alert the clinician to a possibility of chronic graft rejection. There are no clear well established international consensus criteria for diagnosis of chronic rejection and more research is needed to understand about the treatment and timing of reversibility of chronic rejection.

As an example, among the 103 patients, transplanted in Necker from 1994 under tacrolimus, 20 have nowadays a functional small bowel graft for more than 10 years (15 more than 15 years), 3 among them with a second ITx procedure; one more, “the world champion” was transplanted in 1989 (48).

**HOME-PN VERSUS INTESTINAL TRANSPLANTATION: IS IT A DILEMMA?**

There is probably a different threshold for ITx on both sides of the Atlantic Ocean. The European approach inclines to support long-term home PN, which is cost-effective and provides an acceptable quality of life (see Chapter 5.2.3). Pironi et al have performed a 3-year prospective study including both adults and children on long-term PN for IF (49). The results showed that only patients with nutritional failure due to IFALD or major catheter complications had an increased risk of death on home PN, thus supporting its use as the primary treatment for IF. Therefore, it was suggested that ITx should be used only as a life-saving procedure. Although experienced North-American transplantation centres have suggested that the role of ITx should be expanded to a pre-emptive/rehabilitative procedure applicable to all patients with irreversible IF, the recent findings have shown that home PN is the treatment of choice for IF in adults as well as in children (49). An early referral to a multi-disciplinary IR programs is essential to optimise the long-term management of IF (23,24).

Advances in the knowledge of factors implicated with PN and IF complications and improvements in the medical and surgical management of SBS result in better outcomes. Isolated liver Tx for SBS patients who have the potential of bowel adaptation should be no longer required. Interestingly, the most recent International Intestinal Transplantation Registry reported in New York in June 2017, showed evidence of a worldwide trend of reduction in the number of paediatric ITx since 2007. This might be explained by several factors:

1. the provision of guidelines and training
2. the development of IR centres with increasing IF expertise
3. the enlarged use of nontransplant surgery
4. the better prevention of IFALD, with fish oil based lipid emulsions playing a role
5. the improved prevention of catheter related sepsis by using taurolidine or ethanol locks.

**FUTURE AND RESEARCH**

After 25 years, intestinal transplantation (ITx) remains a challenging procedure, where optimism and realism should travel together. Collaborative working within various intestinal transplant centres is needed especially as the patients with long-term functioning grafts expose us to new challenges. The results of ITx can improve if there is understanding of the complex interplay between the immune system and gut microbiota. Future areas of research should concentrate on the intestinal microbiome after ITx and its relationship with immunological and infectious events, the changes of innate and adaptive immunity in the host...
and organ. The network, called NITE for ‘‘Network for Intestinal Transplantation in Europe’’ can be a useful platform within Europe to promote clinical exchanges and collaborative research (19). Major efforts are needed to improve the outcome of ITx that will likely remain part of the armamentarium required to prolong the survival of children with life-threatening IF complications (50). When outcome of ITx and long-term PN are compared, it is clear that PN outcome is better than after ITx (51). In the future, we do hope that improvements of ITx will make us able to propose ITx over long-term PN, in patients with chronic IF for a better quality of life and for transporting life (52).

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Chapter 5.3.1. ESPGHAN History of Gastrointestinal Paediatric Endoscopy

Samy Cadranel, Jean-François Mougenot, and Mike Thomson

Attempts to inspect the internal cavities of the human body in vivo are probably as ancient as medicine itself. A challenge was to find a safe source of light that would not generate heat that could damage tissues. Following the adaptation of fiberoptics for medical instruments, endoscopy of the GI tract became a popular tool in gastroenterology units, to such an extent that adaptation of fiberoptics to gastrointestinal endoscopy has been considered the major advance in gastroenterology in the last 70 years (1). Diagnostic investigations of digestive diseases in children were formerly based on contrast radiology, although a few children would occasionally be treated in such units, mainly for retrieval of foreign bodies. The possibility to directly observe the GI tract and take guided biopsies represents a major progress in paediatric gastroenterology. It contributes not only to the solution of some diagnostic mysteries but also to the treatment of diseases that before were reserved to invasive surgery.

FROM CONVENTIONAL FIBERSCOPES TO PAEDIATRIC ENDOSCOPES

In the early 1970s only first-generation conventional fiberscopes were available and, due to their large diameter, only a few older children could be investigated using them. During the 1972 annual meeting of ESPGA in Hamburg we paid a visit to the European branch of Olympus and convinced their engineers to adapt a slim “industrial” fiberscope into a medical instrument suitable for children. This prototype allowed safe GI endoscopies in children and can be considered the first step of the development of paediatric GI endoscopy (2). At the very first ESPGHAN workshop, held in Bern in 1981, we were able to gather the few paediatric endoscopists who presented their findings and technical expertise. It was an opportunity to discuss with instrument makers our requirements for the manufacture of slim instruments adapted to our diverse needs (Figures 1–4).

Thanks to the reduction in instrument diameter, further technical improvements and progress in sedation and anaesthetics, examinations of the GI tract in children have become easier and safer. Publications highlighted the importance of pediatric endoscopy, its diagnostic and therapeutic value and contribution to our knowledge of many GI diseases in infants and children (3–10). Less than 10 years after its introduction in paediatric gastroenterology, endoscopy was the subject of several books in Spanish, German, and English (11–14).

Jean François Mougenot, one of the very first paediatric endoscopists who actively contributed to the advancement of these instruments, has been invited to write about the progressive innovations and the passage from fiberendoscopy to videendoscopy. Through ESPGHAN the 3 authors of this historical chapter have been training a great number of fellows over a period of almost 50 years; Mike Thomson, the youngest colleague of this trio has accepted to write about the very important topic of training in endoscopy.

FROM CONVENTIONAL FIBERSCOPES TO VIDEOENDOSCOPY

Today the fiberoptic endoscope has largely been replaced by the electronic video endoscope, first introduced in the 1980s. The objective lens at the tip of the video endoscope forms an image of the object in view on the distal face of the electronic image sensor. The image is captured by a charge-coupled device (CCD), or by a complementarity metal-oxide semiconductor sensor (CMOS), transmitted electronically, and displayed on a video monitor. There is substantial additional cost associated with the video endoscope and its required accessories. However, in contrast to older instruments in which the endoscopist viewed the image through a proximal eyepiece, the image display on a monitor is more comfortable for the endoscopist and allows shared simultaneous viewing by trainees and assistants.

In pediatric practice an important consideration is the choice of an appropriate endoscope suitable for the patient’s age or size. Companies including Fujinon, Olympus, and Pentax now produce a comprehensive range of endoscopes. However, light sources, processors, video endoscopes, and some accessories are not interchangeable. Smaller endoscopes (4.9–6.0 mm) are preferred for neonates and infants. These smaller instruments have disadvantages in relation to image resolution, biopsy size, and durability. Moreover, only instruments with sufficiently large operating channels are suited for therapeutic endoscopy.

Pediatric single-channel colonoscopes have been developed with the following characteristics: length: 133 to 150 cm; diameter: 9.5 to 11.5 mm (insertion tube diameter); accessory channel: 3.2 mm. They have a narrow tip deflection radius and short bending section, adapted for paediatric use. Since there is no colonoscope designed specifically for infants, tiny gastroduodenoscopes must be used despite their asymmetrical distal bending and excessive stiffness. In patients older than 7 years, colonoscopes with an accessory channel of 3.7 or 3.8 mm are preferable.

NEW TECHNOLOGY FOR ENDOSCOPIC DIAGNOSIS

In adult patients, dyeless virtual chromoendoscopy is a valuable technique, assisting in the characterization of lesions, such as polyps, and predicting the histological findings. Contrast enhancement is based on the phenomenon that the penetration of light into the mucosa varies according to the wavelengths: 400 to 500 nm are ideal for analysing surface structures whereas, because of the absorption properties of haemoglobin, longer wavelengths of about 550 nm are more effective for visualization of blood vessels (15). In Narrow Band Imaging (NBI) developed by Olympus a rotating optical interference filter is interposed after the white light source to restrict the incident light into 2 narrow bands of different wavelengths. The blue at 415 nm image channel analyses the fine
surface architecture of the mucosa and the superficial capillary network. The green at 540 nm image channel analyses the deeper collecting vessels. After colour adjustment by the processor that further enhances the contrast by reassessing the colour channels, the superficial and deep details are superimposed in a single final mixed NBI image. Although the image is significantly darker than with normal white light, enhanced visualization of fine morphology of the mucosal layer and especially of the capillary pattern is provided by combining the NBI system with a magnifying endoscope (16).

Flexible spectral Imaging Color Enhancement (FICE), manufactured by Fujinon, is a technology based on digital image processing that performs spectral estimation processing of a real-time endoscopic image to produce spectral images, selects images of given wavelengths, and assigns these to the Red Green Blue monitor input channels. With real-time electronic wavelength manipulation, an infinite number of combinations can be used to create reconstructed images. Ten channels with different predefined absorption wavelengths are available. FICE allows instantaneous switching between conventional white light and FICE-images, and between any of the 10 preset FICE-images in order to select the most suitable wavelength for any particular examination. In children virtual chromoendoscopy is used in the follow-up of patients with polyposis syndrome or identification of dysplasia lesions. The advent of numerical endoscopy has enhanced the diagnostic analysis possibilities (confocal endoscopy, endoscopic ultrasonography, wireless video capsule endoscopy (17) but also the treatment of GI tract lesions to a much wider development than what was expected from fiberendoscopy.

ENDOSCOPY TRAINING AND RECENT ADVANCES IN PAEDIATRICS

It has become increasingly apparent in recent years that the landscape of paediatric endoscopy training varies widely, not only between differing health systems and countries, which in principle may aspire to identical standards of training excellence, but even between apparently comparable endoscopy units who are ostensibly seen to be ‘training’ units for our next generation of trainees in this procedural specialty, unique in pediatric medicine. ESPGHAN and the JPGN have been pivotal in nurturing such views and in promoting such a philosophy. This has accelerated in recent years. As more senior endoscopy trainers, and as such representative of a generation who have had variable training ourselves, we have an acute responsibility to get it right for the next generation of pediatric endoscopists.

How do we achieve the following unimpeachable imperatives of paediatric endoscopy training? Namely: uniformity of excellence of training; uniformity of excellence of trainers; uniformity of the best possible training environment; exposure early in training to the correct principles and models of practice going forward; that these goals are achieved in a safe and paediatric-specific environment. We suggest that a number of models have
their merits but that, in principle, the following are basic building blocks of such training structures and are now tried and trusted within the pediatric endoscopy sphere:

1. Trained trainers who are competent not only in paediatric endoscopy themselves but, crucially, effective in imparting this knowledge and skill base to their trainees in a constructive manner;
2. Internet-based lesion recognition tools with examination sections, and web-based learning opportunities;
3. Hands-on small number participating courses at the inception of training including virtual model training, animal models for therapeutic work, and physical artificial models for diagnostic, with graduation to actual patients when appropriate;
4. National and International responsible bodies tasked with the awarding of competency-based endoscopy-specific qualifications in paediatric endoscopy at varying levels of competency;
5. Competency-based assessments which are both formative, at the beginning of training, and summative, prior to the award of competency recognition;
6. Contemporaneous log book electronic records of experience in training;
7. Regular Training Unit accreditation and assessment of ability and appropriateness of training environment.

This approach may facilitate the ideal: that we may join as a world community of like-minded individuals in order to attempt to establish ground rules for how excellence in paediatric endoscopy training may be achieved (18–21).

Paediatric endoscopy has had a golden era over the last 20 years, and advances in diagnostic and therapeutic applications have been nothing short of transformational for our capabilities, and in consequence with positive effects on children’s lives. Extending the capability anatomically to include a pan-enteric reach with the advent of wireless capsule video-endoscopy is now standard in many units and the sister technology of enteroscopy without need for surgical assistance has added a therapeutic arm to this approach. It could not have entered the imagination of pediatric endoscopists in the 1970s or 1980s that such therapies as ileal polypectomy, argon plasma ablation of blue rubber blebs or percutaneous endoscopic jejunostomies would be available within a few decades. So many laparotomies have been prevented by minimally invasive endoscopic approaches recently—or sometimes with the joint approach of laparoscopy and endoscopy combination. Examples of this include: endoscopic anti-reflux procedures; endoscopic pyloromyotomy; tran gastric endoscopic pancreatic cyst drainage; percutaneous endoscopic jejunostomy; duodenal stenosis endoscopic division; Hemospray and other endoscopically delivered treatments for acute GI bleeding; mid small bowel polypectomy; and mid small bowel variceal banding. These are a small example mix and represent the tip of the iceberg in terms of potential. The responsibility of those being trained at present is to stand on the shoulders of their trainers, the previous generation of pediatric endoscopists and build on their progress, with a view to extending our ability along similar lines over the next 20 to 30 years. The only limit is imagination—technology will catch up. An example of imagination running ahead of technology is seen in Natural Orifice Trans-Endoscopic Surgery (NOTES) which may be the future. It has yet to show significant advantage over more established minimally invasive techniques such as those involving laparoscopy but it is very close to this. Surgical triangulation, sepsis and a viable endoscopic “tool-box” remain challenges in this area and it will be fascinating to observe the next paradigm shift from laparoscopic to NOTES and its velocity, compared to the previous generational change which occurred when laparotomy and “open” surgery gave way to laparoscopy. Pediatric endoscopy should remain at the front of the minds of those taking this forward in the next 10 to 20 years.

REFERENCES

Common upper and lower gastrointestinal (GI) motility disorders, such as gastro-oesophageal reflux disease and functional constipation, but also relatively rare motility disorders, such as achalasia, Hirschsprung disease, and chronic intestinal pseudo-obstruction, have always been the core business of paediatric gastroenterologists worldwide. Enormous strides have been made in the understanding of these motility disorders using novel tools to investigate and treat them. This chapter briefly touches on what has happened in the last 50 years.

Because of the increasing interest in (paediatric) motility disorders, particularly since the turn of the century, experts from all over the world met, and continue to meet, to discuss the latest findings in the area of GI motility. These invaluable interactions occur within a number of collaborative initiatives such as regular Pediatric GI Motility Meetings supported by ESPGHAN (the first in Capri 2001) as well as under the auspices of the dedicated ESPGHAN Motility Special Interest Group.

THE RHYTHM OF THE GUT

A hundred years ago the rhythm of the gut was seen as simple and straightforward. It was a tube, which moved the intraluminal contents by a peristaltic movement induced by distension. Studies over the last century have shown that it is much more complex than this and that the bowel contents are transferred from one specialised region of the gut to another by the co-ordinated contraction of the smooth muscle coats. The pattern of motility is related to and integrated with the function of particular regions of the gastrointestinal tract.

Development of our understanding of basic smooth muscle physiology, of enteric neurons forming an enteric nervous system with higher levels of control, has revealed the beauty and sophistication of the rhythm of the gut. The musculature of the gut is the motor-effector system, which is controlled by the enteric nervous system and the central nervous system. Control of the musculature involves an integrated hierarchy of neural centres and pacemaker cells the Interstitial Cells of Cajal. Starting at the level of the gut there is the enteric nervous system, which has local neural circuits for the integration of contraction. These local neural circuits can be modulated by higher levels of integration. The second level of integration occurs in the prevertebral sympathetic ganglia where peripheral reflex pathways are influenced by preganglionic sympathetic fibres from the spinal cord. In the central nervous system, there is sympathetic and parasympathetic outflow to the gut determined by reflexes with sensory fibres that travel with the autonomic nerves. Higher brain centres supply descending signals, which integrate with the sympathetic and parasympathetic outflow of the gut. For effective contraction to take place intermediaries are required between enteric neurotransmission and the smooth muscle cells. Interstitial Cells of Cajal serve as these intermediaries and may also facilitate the propagation of electrical events along and around the gastrointestinal tract, and in doing so act as slow-wave pacemaker generators for the muscle coats of the bowel. Smooth muscle cells, however, are inherently excitable and this is due to the property of rhythmic variation of transmembrane potentials, which occurs even during complete motor quiescence. The cycle of depolarisation and repolarisation is the result of rhythmic changes in the activity of membrane ion pumps.

The enteric nervous system coordinates activity of this primary motor-effector to produce meaningful patterns of contraction throughout the whole organ. The structure and function and neurochemistry of the enteric neurons are very similar to those of the central nervous system and the neurons contained in ganglia are interconnected to function in a similar fashion with mechanisms for integration and processing of information.

The motor neuron pool of the enteric nervous system consists of excitatory and inhibitory neurons. Excitatory motor neurons release neurotransmitters (acetylcholine and substance P) that evoke muscle contraction and mucosal secretion. Inhibitory motor neurons release neurotransmitters that suppress contractile activity of the musculature. Important examples are vasoactive intestinal peptide and nitric oxide. The inhibitory motor neurons are of particular significance in the relationship of the excitable nature of smooth muscle cells to the Interstitial Cells of Cajal.

The activity state of these neurons determines when the omnipresent slow-waves will initiate contraction as well as the distance and direction of propagation once the contraction has begun. The circular muscle can only respond to the electrical slow-wave when the inhibitory motor neurons in that segment of the intestine are switched off. Thus, loss of the intrinsic inhibitory neurons will result in tonic contraction of that segment of intestinal circular muscle.

While the signals to the enteric nervous system may come from the lumen of the bowel, its activity may also be altered by humoral secretion of polypeptide hormones from entero-endocrine cells and by the activity of the mucosal associated lymphoid tissue. There is now a large body of evidence, which shows that the motor and secretory responses in the gut to specific antigens are as a consequence of direct communication between the immune system and the enteric nervous system. This communication results in adaptive behaviour of the bowel in response to stimuli within the lumen. In addition to this local neuro-immune interaction there is also evidence that mast cells are involved in the defence mechanism apart from local antigen sensing and signalling to the enteric nervous system. The brain to mast cell connection is a mechanism that can link psycho-emotional events to the enteric neuro-musculature.

The journey in understanding the basic physiology of smooth muscle, enteric neurons and their higher levels of control, and the enteric nervous system has been required to understand the whole and increasing scope of neuro-gastroenterology. Much of this journey was undertaken with simple tools such as this recording of the first small intestinal migrating motor complex in an infant using home-made pressure catheters and a pen and ink recording.
device (Fig. 1). Disturbance of these various elements is almost certainly responsible for the gastrointestinal symptoms seen in a wide variety of disease states, which affect the central nervous system, the immune system, and the gut itself.

**OESOPHAGEAL MOTILITY DISORDERS**

The first papers on oesophageal motility disorders in children date back to the late 1940s and were mainly focused on “infantile cardiospasm” or achalasia. From that moment onwards numerous studies started to investigate the pathogenesis of these disorders in the paediatric age. The understanding of the mechanisms underlying the onset of oesophageal motility disturbances has always been one of the main fields of interest for ESPGHAN. In fact, over the past 50 years several ESPGHAN members have dedicated their efforts to the identification of the conditions associated with altered oesophageal function.

From the outset, a key player in motility disorders has undoubtedly been gastro-oesophageal reflux (GOR). Already in 1986, Cucchiara et al demonstrated the presence of oesophageal motor abnormalities in children with GOR (1). Thereafter numerous other studies confirmed this association, and the close correlation between GOR and oesophageal motility. ESPGHAN attention to GOR has always been very high, leading in 2009 to the first combined ESPGHAN and NASPGHAN guidelines on GOR management (2). These guidelines represent a milestone in ESPGHAN’s history, given that, from that point on, many other combined guidelines were produced.

However, GOR is not the only condition associated with oesophageal dysmotility. For example, in 2009 Nurko et al identified the presence of ineffective peristalsis in children with eosinophilic oesophagitis, a condition now recognised as one of the causes of oesophageal motor dysfunction (3). Since Cucchiara et al’s description in 1986 of the return of peristalsis in a child with oesophageal achalasia, significant developments have been made in the measurement of pressures in the oesophagus (4). High-resolution manometry, pioneered in historical studies by Annamaria Staiano working with Ray Clouse, has replaced conventional manometry and, as in adults, paediatricians now use the Chicago classification to describe the different forms of upper motility disorders such as achalasia (5,6).

Moreover, oesophageal motility disorders also represent one of the main comorbidities in patients with neurological disabilities. In 1991 Staiano et al found that the oesophageal motility abnormalities identified in children with neurological impairment persisted after the treatment of GOR, suggesting that motility disorders in this subgroup of patients are directly associated with neurological damage, rather than being a consequence of GOR (7).

**ENTERIC NEUROPATHIES**

Submerged within the vast oceans of coeliac disease and inflammatory bowel disease that have bathed the society over the last decades is a group of uncommon largely enigmatic conditions termed “enteric neuropathies.” The literature is perhaps reflective of this. In the 20 years before ESPGHAN was formed there were 400 publications on Hirschsprung disease, 500 in the 20 years after, but more than 3500 in the 30 years since. The picture for chronic intestinal pseudo-obstruction in children, however, is very different—virtually undescribed before 1968 and only 500 publications since. Yet ESPGHAN has been at the very heart of “neurogastroenterology and motility” the science dedicated to the study of such disorders, and a branch of paediatric gastroenterology that is seeing a surge of interest that will, undoubtedly, form a big focus for the society in the future.

**GASTROPARESIS**

Gastroparesis in children remains very poorly described or indeed understood with the majority of cases still considered idiopathic. In an elegant series of articles Peter Milla, together with the surgical pioneer Lewis Spitz and physiologist Paul Andrews, provided strong rationale for the careful consideration of fundoplication, especially in neurologically impaired children, given its effects on gastric emptying and post-operative complications (8). Cucchiara et al showed the potential use of medication in

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**FIGURE 1.** Example of recording intestinal migrating motor complex in an infant using home-made pressure catheters and a pen and ink recording device.
In toilet trained children, the following additional criteria may be used: Intestinal pseudo-obstruction have been described (15,16). For the worst colleagues a number of genes involved in Hirschsprung and intes-
tgenesis of Hirschsprung disease gleaned through his interactions with ENS developmental biologists and a keen self-interest (13,14). Together with the work of Alberto Aurrichio, A Ballabio and with ENS much of the scientific understanding of the aetiopatho-
gastroparesis and that, akin to adults, diabetic children also dis-
disturbances in gastric motility function, which appeared to correlate with glycaemic control (9). Milla’s group showed primary 
infant rumination syndrome Must include all of the following: 
1. Two or more periods of unremitting paroxysmal vomiting with or without retching, lasting hours to days within a 6-month period 
2. Episodes are stereotypical in each patient 
3. Episodes are separated by weeks to months with return to baseline health between episodes of vomiting

Functional constipation Must include 1 month of at least 2 of the following in infants up to 
4 years of age: 
1. Two or fewer defecations per week 
2. History of excessive stool retention 
3. History of painful or hard bowel movements 
4. History of large diameter stools 
5. Presence of a large fecal mass in the rectum
In toilet trained children, the following additional criteria may be used: 
6. At least 1 episode/week of incontinence after the acquisition of toileting skills 
7. History of large diameter stools which may obstruct the toilet

Cyclic vomiting syndrome Must include all of the following for at least 2 months: 
1. Repetitive contractions of the abdominal muscles, diaphragm, and tongue 
2. Effortless regurgitation of gastric contents, which are either expelled from the mouth or rechewed and reswallowed 
3. Three or more of the following: a) Onset between 3 and 8 months; b) Does not respond to management for GERD and regurgitation; c) Unaccompanied by signs of distress; d) Does not occur during sleep and when the infant is interacting with individuals in the environment

Infant dyschezia

Hirschsprung disease and Chronic Intestinal Pseudo-obstruction

Hirschsprung disease, the most commonly recognised enteric neuropathy, has historically been the preserve of surgeons rather than gastroenterologists. The last decades has seen much more of a joint effort between both these specialists together with basic scientists to progress both our understanding and management of this condition. This collaboration is evident in early publications from Peter Milla with Lewis Spitz (12). Milla also brought into ESPGHAN much of the scientific understanding of the aetiopathogenesis of Hirschsprung disease gleaned through his interactions with ENS developmental biologists and a keen self-interest (13,14). Together with the work of Alberto Aurrichio, A Ballabio and colleagues a number of genes involved in Hirschsprung and intestinal pseudo-obstruction have been described (15,16). For the worst diseases such as total intestinal aganglionosis the work of ESPGHAN intestinal transplant pioneers such as Olivier Goulet has been critical (17). These poor outcomes, however, have driven ESPGHAN to remain contemporary and futuristic with bold steps into regenerative medicine. Nikhil Thapar and colleagues have seen considerable success with the potential of harvesting neural stem cells from patients themselves and developing novel stem cell replacements as curative for enteric neuropathies such as Hirschsprung disease (18,19).

Chronic intestinal pseudo-obstruction (CIPO), perhaps presents an even more challenging and devastating group of disorders of the gastrointestinal tract and ESPGHAN experts have been at the core (20). It is only the advent of parenteral nutrition around the birth of ESPGHAN in 1968 that children could now be kept alive (21). Surgical management of patients suffering CIPO remain very debated and challenging as reviewed by Goulet et al (22). One of the biggest challenges was the diagnosis. In the 1970s a significant proportion of intestinal physiology studies were still be carried out in experimental animals such as dogs. It was Peter Milla and colleagues working in London in the early 1980s that made the first recordings on small intestinal activity in children using prototype catheters with triple lumens and 3 measuring ports placed in the stomach and proximal duodenum, using somatostatin and cholecystokinin administered to patients during the studies in an
attempt to replicate body physiology (23,24). In the 1990s Salvatore Cucchiara together with Aurrichio and colleagues described manometric characteristics of children with intestinal pseudo-obstruction (25). Their work together with those of others in ESPGHAN and its sister society NASPGHAN have contributed to establishing antroduodenal manometry as a robust tool for diagnosing CIPO. Additionally, Peter Milla together with Virpi Smith also brought to the field of intestinal pseudo-obstruction their deep knowledge of histopathology of enteric neuropathies and myopathies (26,27).

Most recently they were part of the London Classification initiative led by Charles Knowles that aims to make uniform and expert the application of histopathology to adult and paediatric motility disorders (28). An ESPGHAN expert group led by Nikhil Thapar together with neurogastroenterology and motility giants from ESPGHAN (Annamaria Staiano, Marc Benninga, Yvan Vandenplas and Osvaldo Borrelli) as well as from NASPGHAN (Carlo Di Lorenzo and Christophe Faure) now oversees the forward initiatives that aim to tackle much need work in Intestinal pseudo-obstruction (now

TABLE 2. Rome IV criteria for the diagnosis of functional gastrointestinal disorders of the child/adolescent

<table>
<thead>
<tr>
<th>Functional nausea and vomiting disorders</th>
<th>Rumination syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cyclic vomiting syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>Must include all of the following:</td>
<td></td>
</tr>
<tr>
<td>1. Two or more periods of intense, unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-month period</td>
<td></td>
</tr>
<tr>
<td>2. Episodes are stereotypical in each patient</td>
<td></td>
</tr>
<tr>
<td>3. Episodes are separated by weeks to months with return to baseline health between episodes</td>
<td></td>
</tr>
<tr>
<td>4. After appropriate evaluation, the symptoms cannot be attributed to another medical condition</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Functional nausea</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Must include all of the following*:</td>
<td></td>
</tr>
<tr>
<td>1. Bothersome nausea as the predominant symptom, occurring at least twice per week, and generally not related to meals</td>
<td></td>
</tr>
<tr>
<td>2. Not consistently associated with vomiting</td>
<td></td>
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<tr>
<td>3. After appropriate evaluation, the nausea cannot be fully explained by another medical condition</td>
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<table>
<thead>
<tr>
<th>Functional vomiting</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Must include all of the following (Criteria fulfilled for at least 2 months prior to diagnosis):</td>
<td></td>
</tr>
<tr>
<td>1. On average, one or more episodes of vomiting per week</td>
<td></td>
</tr>
<tr>
<td>2. Absence of self-induced vomiting or criteria for an eating disorder or rumination</td>
<td></td>
</tr>
<tr>
<td>3. After appropriate evaluation, the vomiting cannot be fully explained by another medical condition</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Functional abdominal pain disorders</th>
<th>Abdominal migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional dyspepsia¹</td>
<td></td>
</tr>
<tr>
<td>Must include 1 or more of the following bothersome symptoms at least 4 times a month for at least 2 months prior to diagnosis:</td>
<td></td>
</tr>
<tr>
<td>1. Postprandial fullness</td>
<td></td>
</tr>
<tr>
<td>2. Early satiation</td>
<td></td>
</tr>
<tr>
<td>3. Epigastric pain or burning not associated with defecation</td>
<td></td>
</tr>
<tr>
<td>4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition</td>
<td></td>
</tr>
</tbody>
</table>

| Irritable bowel syndrome                |                     |
| Must include all of the following*:    |                     |
| 1. Abdominal pain at least 4 days per month associated with one or more of the following: a) Related to defecation ; b) A change in frequency of stool ; c) A change in form (appearance) of stool |
| 2. In children with abdominal pain and constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not IBS) |
| 3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition |

| Functional abdominal pain—not otherwise specified |                     |
| Must be fulfilled at least 4 times per month and include all of the following*: |                     |
| 1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g., eating, menses) |
| 2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine |
| 3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition |

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After appropriate evaluation, the symptoms cannot be fully explained by another medical condition. The updated Rome IV Criteria coin an “Paediatric Intestinal Pseudo-obstruction” or “PIPO”) and related disorders.

**FUNCTIONAL DEFECATION DISORDERS**

In the past 2 decades, in a joint effort, ESPGHAN and NASPGHAN members played an important role in defining functional gastrointestinal disorders in children of all age groups, including infant dyschezia, functional diarrhoea, functional constipation, and functional nonretentive faecal incontinence (29,30). ESPGHAN Members, such as Peter Milla, Anna Maria Staiano, Jan Tamini and Marc Benninga, played prominent roles in updating the Rome Criteria (29,30). The updated Rome IV Criteria are summarised in Tables 1 and 2.

Functional diarrhoea (FD) or non-specific chronic diarrhoea is considered the most frequent cause of chronic diarrhoea without failure to thrive in toddlers. Although the pathophysiology of FD is not well understood, Peter Milla in 1983 had already suggested that food may fail to interrupt the migrating motor complex (31). Hans Hoekstra and Frank Kneepkens, suggested that in fruit juices, the increased presence of nonabsorbable sugars is an important pathological factor in FD (32). Despite the high worldwide prevalence and large interest in functional constipation the pathophysiology is still not fully understood. Pioneers in functional testing in children with functional constipation, Meunier and Loening-Baucke, showed that hyposensitivity of the rectum is a relevant factor in the aetiology of chronic constipation (33,34). Benninga and Di Lorenzo however showed that rather than impaired sensitivity, increased rectal compliance is of major importance in these children (35,36). Furthermore, abnormal defecation dynamics have been described as a major factor involved in the development and persistence of childhood constipation. It was again Loening-Baucke and later Benninga, more than 30 years ago, that showed that more than half of the children with functional constipation, indeed contract rather than relax their sphincter complex during a defecation attempt (37,38). Inconsistent data have been published about the efficacy of biofeedback/ pelvic physiotherapy in these children (38,39). In recent years several groups, using either conventional or HRM colonic manometry, have shown abnormalities in colonic motility patterns in children with slow transit constipation (40–43). The group of Great Ormond street recently showed that HR colonic manometry even accurately predicts colonic neuromuscular pathological phenotype in paediatric slow transit constipation (44).

The treatment of children with functional constipation is a challenge and in many children long-lasting. In 2014, a combined ESPGHAN and NASPGHAN guideline on functional constipation extensively described the different treatment options (45).

In 1994, Benninga et al, described a group of children, mainly boys, presenting with faecal incontinence without any other symptom of constipation; functional nonretentive faecal incontinence (FNRFI) (46). As in constipation, the underlying mechanism of FNRFI is still largely unknown. Colonic transit studies using radio-opaque markers clearly showed normal transit through all colonic segments (47). Whereas anorectal manometry and rectal barostat studies also failed to identify abnormalities in children with FNRFI (36). Current treatment options are disappointing with success rates after 2 years of intensive follow up of only 29% (48). Loperamide has shown to be an alternative treatment in these children (49). In summary, there has been a considerable historical and ongoing contribution to the field of functional defecation disorders in children from ESPGHAN.

**REFERENCES**


Chapter 5.3.3. The Story of Gastro-oesophageal Reflux That Became a Disease

Gigi Veereman, Yvan Vandenplas, and Peter Milla

Infants have been spitting up since Adam and Eve, but it took the critical look of Yvan Vandenplas and colleagues in distant countries to describe, register and analyse all burps and spits some 30 years ago (1–4). Curiosity and technical developments enabled researchers to register esophageal acidity and intestinal motility and helped to establish a large body of knowledge on the development of gastrointestinal motility and gastro-oesophageal reflux. The focus has been on discriminating between physiological and pathological states, pathophysiology, associated conditions and underlying conditions such as inflammation. The purpose of this paper is to walk through the major developments in intestinal motility and gastro-oesophageal reflux (disease) GOR(D), with a focus on work published by ESPGHAN members, but not to provide a comprehensive scientific overview. Therefore we apologize for any omissions of important work by other colleagues and for lack of scientific rigour.

First of all . . . the basics—A FEELING FOR GUT RHYTHM

A hundred years ago the rhythm of the gut seemed straightforward. It was a simple tube which moved the intraluminal contents by a peristaltic movement induced by distension. Studies over the last century have shown that it is much more complex than this and that the bowel contents are moved from 1 specialised region of the gut to another by the co-ordinated contraction of the smooth muscle coats. The pattern of motility is related to and integrated with the function of particular regions of the gastrointestinal tract. Thus, the oesophagus is a propulsive conduit for the ingestion of food, the stomach initiates digestion, transit through the small intestine is related to the digestion and absorption of nutrients and the colon an organ of conservation of water, electrolytes and calories. This is the rhythm of the gut in early 20th century terms.

Development of an understanding of basic smooth muscle physiology, of enteric neurons forming an enteric nervous system with higher levels of control, has revealed the beauty and sophistication of the rhythm of the gut as it really is. The musculature of the gut is the motor-effector system which is controlled by the enteric nervous system and the central nervous system. Control of the musculature involves an integrated hierarchy of neural centres and pacemaker cells that interstitial cells of Cajal. Starting at the level of the gut there is the enteric nervous system which has local neural circuits for the integration of contraction. These local neural circuits can be modulated by higher levels of integration. The second level of integration occurs in the prevertebral sympathetic ganglia where peripheral reflex pathways are influenced by preganglionic sympathetic fibres from the spinal cord. In the central nervous system, there is sympathetic and parasympathetic outflow to the gut determined by reflexes with sensory fibres that travel with the autonomic nerves. Higher brain centres supply descending signals which integrate with the sympathetic and parasympathetic outflow of the gut. For effective contraction to take place intermediaries are required between enteric neurotransmission and the smooth muscle cells. Interstitial cells of Cajal serve as these intermediaries and may also facilitate the propagation of electrical events along and around the gastrointestinal tract, and in doing so act as slow-wave pacemaker generators for the muscle coats of the bowel. Smooth muscle cells, however, are inherently excitable and this is due to the property of rhythmic variation of transmembrane potentials which occurs even during complete motor quiescence. The cycle of depolarisation and repolarisation is the result of rhythmic changes in the activity of membrane ion pumps. The movement of potassium, particularly, across the plasma membrane of the smooth muscle cell results in depolarisation of the cell membrane and the voltage change opens voltage sensitive calcium channels in the sarcoplasmic reticulum which then allows calcium to gain access to the contractile proteins of the smooth muscle cell which results in contraction.

The enteric nervous system co-ordinates activity of this primary motor-effector to produce meaningful patterns of contraction throughout the whole organ. The enteric nervous system is a local mini-brain within which is stored a library of programmes for different patterns of gut contraction and each programme can be called up from the programme library either by commands from the brain or by local sensory detection of events in the lumen of the bowel. The structure and function and neurochemistry of the enteric neurons are very similar to those of the central nervous system and the neurons contained in ganglia are interconnected to function in a similar fashion with mechanisms for integration and processing of information.

The motor neuron pool of the enteric nervous system consists of excitatory and inhibitory neurons. Excitatory motor neurons release neurotransmitters (acetyl choline and substance P) that evoke muscle contraction and mucosal secretion. Inhibitory motor neurons release neurotransmitters that suppress contractile activity of the musculature. Important examples are vasoactive intestinal peptide and nitric oxide. The inhibitory motor neurons are of particular significance in the relationship of the excitable nature of smooth muscle cells to the interstitial cells of Cajal.

The activity state of these neurons determines when the omnipresent slow-waves will initiate contraction as well as the distance and direction of propagation once the contraction has begun. The circular muscle can only respond to the electrical slow-wave when the inhibitory motor neurons in that segment of the intestine are switched off. Thus, loss of the intrinsic inhibitory neurons will result in tonic contraction of that segment of intestinal circular muscle.

Whilst the signals to the enteric nervous system may come from the lumen of the bowel its activity may also be altered by humoral secretion of polypeptide hormones from enteroendocrine cells and by the activity of the mucosal associated lymphoid tissue. There is now a large body of evidence, which shows that the motor and secretory responses in the gut to specific antigens are as a consequence of direct communication between the immune system and the enteric nervous system. This communication results in...
adaptive behaviour of the bowel in response to stimuli within the lumen. In addition to this local neuroimmune interaction there is also evidence that mast cells are involved in the defence mechanism apart from local antigen sensing and signalling to the enteric nervous system. Ultrastructural and light microscopic studies suggest that enteric mast cells are always in association with nerves in the mucosa of the bowel and that these nerves may be both projections from the central nervous system and intrinsic primary afferent neurons. The brain to mast cell connection is a mechanism that can link psychoemotional events to the enteric neuromusculature.

Our understanding the basic physiology of smooth muscle, enteric neurons and their higher levels of control, and the enteric nervous system, has been required to understand the whole and increasing scope of neurogastroenterology. Disturbance of these elements is almost certainly responsible for the gastrointestinal symptoms seen in a wide variety of disease states which affect both the central nervous system, the immune system and the gut itself. A long and tortuous journey from a simple tube responding to distension to a complex sophisticated system with greater computing power to control it than many modern computers.

And then facing the spitting ... GASTRO OESOPHAGEAL REFLUX DISEASE UNMASKED

When the beautiful downstream motion of food is inversed, it is called ‘reflux’. Reflux of gastric contents into the oesophagus of neonates and spitting up of ingested food has long been naively accepted as normal ... but no longer so when it was understood that acid regurgitation may cause pain and oesophageal inflammation (Fig. 1).

Measuring the acid ... pH-METRY ... AND IMPEDANCE

In the early 1980s the first pH-metry devices were commercialised. The first device registered during 17 hours 1 pH per minute in memory, exactly storing 1020 items of data in memory and printing them on a curve. That was it. But it was revolutionary at that time. For the first time it became possible to detect reflux outside a postprandial period. Technical possibilities changed continuously during the 1980s (Fig. 2A–D). Therefore, ESPGHAN-consensus papers were published proposing some standardization to avoid too much discrepancy in published results because of differences in methodology. During the same years, the combat against sudden infant death syndrome (SIDS) became a priority and Belgium had chosen to invest in risk-screening with polysomnography. The (still unanswered) question whether reflux may cause apnoea or respiratory irregularities dates from that period. Because of the wide screening program for SIDS-risk, pH-metry was performed in healthy infants as part of the polysomnography. But the dilemma was: what is a normal infant? Is it an infant that does not regurgitate (probably too selective), or is it an infant that is not treated for reflux-disease (probably including infants that should be treated). No-one ever evaluated if pH 4.0 was an appropriate cut-off in infants and children. It was simply taken over from the adults, in whom it was shown that pH 4.0 was the best cut-off in patients with noncardiac thoracic pain caused by acid reflux.

Cisapride was launched in the same period. Because pH-metry was gaining popularity during the same period, many clinical trials were started, suggesting that pH-metry was needed to diagnose reflux, and that cisapride was needed in every regurgitating infant. But then cisapride disappeared because of safety issues. Next, impedance was developed, to measure nonacid reflux as well acid reflux. However, measuring nonacid reflux lacks clinical impact since there is no medical treatment for nonacid reflux.

A group of ESPGHAN members interested by the indications, methodology and interpretation of pH-metry published multiple consensus papers. Other papers focused on treatment. These publications can be considered position papers or guidelines avant la lettre. In 2005 (6), the NASPGHAN published recommendations for the diagnosis and management of reflux. In 2009, a combined ESPGHAN and NASPGHAN guideline on GER was published, which has been cited by 92 Pubmed articles (7). An updated version has been published in 2018 (8).

Fighting the acid ... not the cause—PATHOPHYSIOLOGY AND TREATMENT

FIGURE 1. pH probes glass and antimony.
The desire to unveil the pathophysiology of GORD went viral and it is “down under” that the inappropriate LES relaxations were revealed and incriminated. Now we are back to the basics: motility. Although this knowledge could have led to pharmacological intervention, there is still no satisfactory etiological treatment to help physicians tackle the frequent manifestations of GORD. We are left with treating the consequences of GORD with proton pump inhibitors after installing conservative measures such as thickening the feeds and positional treatment. As a consequence, the market proposes a broad selection of thickened formulas and paediatricians are never left without another option. Babies were positioned on the left side or prone to diminish GOR but the battle was won by the SIDS risk group establishing that supine is the safest position. The GORD rescue team then proposed supine but elevated (Fig. 3), which as a side effect may have prevented any occurrence of vertigo later in life (no studies available). Paediatricians are still awaiting the safe compound that will move things in the right direction.

Acknowledgments: Mrs Kris Vandemaele was dedicated in developing the motility lab at UZBrussels and protected the collection of pH monitoring devices and probes over the years. We are indebted to her for the pictures that bring up memories from industrious years.

REFERENCES

**Chapter 5.4.1. Acute Diarrhoea**

*Alfredo Guarino, Hanna Szajewska, Jehan-François Desjeux, and Yvan Vandenplas*

Acute gastroenteritis has always been a topic of major interest within ESPGHAN and parallels the development of the Society. In the 1960s acute gastroenteritis was a major cause of infantile death throughout the world, including Europe, much more than what is now. However, the reader may be surprised to learn that even now in Europe not less than 500 children die every year because of acute gastroenteritis (1).

**THE EARLY YEARS: BASIC RESEARCH**

When ESPGHAN was founded most agents of gastroenteritis were unknown. Rotavirus was first to be described in 1973, by Ruth Bishop, and most other viruses were discovered afterwards (2). In the early years of ESPGHAN several members were actively involved in basic research, which was then regarded as the top-level science compared to clinical research (many people are still convinced of that). Three groups were highly active and provided substantial novel information on the mechanisms of diarrhoea. Alan Phillips was working as a PhD student with John Walker-Smith and then with Peter Mills (later on, they became JPN Editor 1995 to 2000 and the President of ESPGHAN, respectively 2001 to 2004) and he was an outstanding expert of enterocyte morphology, using electron microscopy and immunofluorescence. Alan Phillips (before becoming ESPGHAN Treasurer) published several papers including some with—at that time—spectacular images of the enterocyte-enteropathogenic *Escherichia coli* interaction (3).

The other major research group was guided by Stefano Guandalini (Fig. 1), who later became the President of ESPGHAN (1998–2001). Guandalini, who had been trained in Italy and then in the United States by Michael Field, was an expert of in vitro studies in intestinal ion transport. In turn, he trained several young scientists, including Alfredo Guarino (JPN Editor-in-Chief, 2005 to 2009), Alessio Fasano (current Chair of Pediatrics at Harvard Medical School), and Carlo Di Lorenzo (NASPGHAN President, 2014 to 2016), before going back to USA where is presently leading the Celiac Center in Chicago. Another outstanding ESPGHAN investigator was Jean-François Desjeux, who was actively involved in top-level research on diarrhoeal mechanisms and rehydration (see BOX).

The Ussing chamber system allowed the discovery of bacterial and viral toxins as well as antidiarrheal drugs active on intestinal transport (4–6) (Fig. 2A and B). It was an in vitro model to investigate the transepithelial fluxes of charged electrolytes (chloride, sodium, potassium, and bicarbonate). The Ussing chamber model was based on Ohms law, and allowed to monitor the passage of each electrolyte across the intestinal epithelial layer. This system played a crucial role in the understanding of glucose-sodium co-transport as well as the development of Oral Rehydration Solution (ORS).

**BOX**

*From Biophysics to Public Health; the Discovery of Oral Rehydration Therapy (by Jehan-François Desjeux)*

Oral Rehydration Therapy (ORT) is a major medical achievement of the second part of the last century. It is not the discovery of 1 person; rather it involved many people from a wide diversity of expertise. Here, I will try to simply present how that discovery was closely linked with my professional life, as paediatric gastroenterologist. In 1967, during my military duties, I was sent to Tunis, as resident in Paediatrics. My main activity was to take care of children with severe dehydration and malnutrition. Unfortunately, many children died whatever my frantic activity. I rushed to the medical library, but could not find good answers dealing with the care of those children. At that time diarrhoea was treated with antibiotics, severe malnutrition with high protein diet and dehydration with complex IV therapy. This is how I decided to try to solve that issue. It rapidly became obvious to me that I needed to understand the mechanism of diarrhoea (7). In 1970, I joined the department of Biophysics at Yale University. Based on irreversible thermodynamic concepts, the mechanism of water movement across the epithelium was linked to sodium and an experimental model of diarrhoea (cholera) was validated on rabbit. Thus, I learned that cholera toxin caused water and electrolyte secretion and glucose could stimulate water and electrolyte absorption. When I came back as resident in paediatrics in Paris, I was called by the World Health Organization (WHO) to be a Scientific Adviser for the just starting Control of Diarrhoeal Disease Programme. This is where I met with Dilip Mahalanabis, just hired as Secretary of the group of 7 people. He is the paediatrician who discovered in 1973 the beneficial effect of oral rehydration solution in severely dehydrated children escaping the war of Bangladesh (8). He told me: “Within two or three weeks, we realized that it was working and that it seemed to be all right in the hands of untrained people… We were just happy that it worked there and that we could help these people.” The aim of the programme was to implement ORT in children at the global scale. At that time, in the late seventies, more than 5 million children were dying of diarrhoea every year, many with severe malnutrition. Although the scientific basis was solid and the first clinical trials encouraging, there were many questions to be solved before implementing a global programme. I was now on 2 seats: a scientific one to further understand the mechanisms of diarrhoea using a biophysical approach, essentially based on concepts developed by Hans Ussing in 1951 (9). We started by showing that the child intestine reacted to infectious agents and glucose like the rabbit’s. The other seat was clinical. We needed firm results of standardized clinical trials in different regions of the globe to make effective recommendations. We thus trained clinicians all over the world and wrote WHO recommendations (10). ORT is now used globally. The global mortality is probably less than 1 million per year. In addition, in Dhaka, Bangladesh, we could recently show that with a combination of IV and oral rehydration, no children with severe dehydration and malnutrition died (11). Nowadays, to further improve and sustain ORT expertise also needs to involve...
sociology, economics, and its marketing together with paediatric gastroenterology.

Translation of Basic Science to Children: The Era of Clinical Trials

The composition of ORS was an issue since it had been developed for adults with cholera. A group of investigators worked to adapt the solute content to the conditions and etiologic agents of children of Europe (12). A low sodium low osmolality solution was developed and a subsequent paper reported a reduced need of intravenous rehydration, lower stool volume and less vomiting in children (largely in developing countries) compared to those receiving standard WHO ORS (13). Administration of ESPGHAN ORS was implemented with spectacular results. Subsequently it became clear that active intervention could reduce symptoms duration and intensity when used in adjunct to oral rehydration (which remains the key step in the management of diarrhoea).

Starting in the early 1990s, several groups within ESPGHAN started to conduct clinical trials in the attempt to investigate the effects of various therapies to reduce the duration and severity of acute gastroenteritis. Erika Isolauri, Alfredo Guarino, Hania Sza- jewska, Yvan Vandenplas, and others, produced data that brought to the concept that in acute gastroenteritis the best option was ‘‘to do little, but do well.’’ The main role of basic research was progressively replaced by well-conducted clinical research including trials.

Some papers focused on smectite (14) and racecadotril (15) and other drugs, but most focused on probiotics (16–18) (Table 1). Many of those papers were published in JPGN and provided the main source for meta-analyses and guidelines that brought ESPGHAN to the EBM era.

From Clinical Studies to Guidelines and Implementation Science

The first ‘‘modern’’ ESPGHAN guidelines on acute gastroenteritis were developed by a combined working group of ESPGHAN and the European Society of Pediatric Infectious Diseases (ESPID) that discussed trials and meta-analyses in meetings held in various European airports (at that time this was a stress-free and feasible option). The drafts were circulated and discussed by emails with a progressive tailoring of the text until the final paper was obtained. This helped to minimize the costs. For the guidelines on management of gastroenteritis, thousands of papers were screened

TABLE 1. Active interventions – in adjunct to oral rehydration- for reducing duration and intensity of acute gastroenteritis according to ESPGHAN guidelines

<table>
<thead>
<tr>
<th>Strains</th>
<th>Study</th>
<th>Evidence</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Lactobacillus GG</td>
<td>15 RCTs</td>
<td>Strong</td>
<td>In adjunct to ORS</td>
</tr>
<tr>
<td>S.boulardii</td>
<td>13 RCTs</td>
<td>Strong</td>
<td>In adjunct to ORS</td>
</tr>
<tr>
<td>L.reuteri</td>
<td>2 RCTs</td>
<td>Weak</td>
<td>In adjunct to ORS</td>
</tr>
<tr>
<td>Smectite</td>
<td>11 RCTs</td>
<td>Weak</td>
<td>In adjunct to ORS</td>
</tr>
<tr>
<td>Racecadotril</td>
<td>9 RCTs</td>
<td>Weak</td>
<td>In adjunct to ORS</td>
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by title, many abstracts were carefully read and the entire text with results of hundreds of data were carefully reviewed in order to develop evidence based recommendations. To support the accuracy and rigor of the recommendations, the guidelines included the tables of evidence that showed the real data on which the guidelines had been constructed. In this manner, the reader and interested parties may check the data included in the analysis, evaluate eventual missing paper or reasons for exclusion. The guidelines underwent a severe peer-review process and approval by ESPGHAN council before publication. They were published in open access in 2008 (19).

The guidelines on management of acute gastroenteritis were the first guidelines to be freely accessible in JPGN. This contributed to the spreading of such documents toward the medical and scientific community. The application of the guidelines was monitored and was fairly accurate and widespread. The guidelines on management of gastroenteritis of children of Europe were published in a revised update edition (1), which largely confirmed the previous recommendations. Afterwards many other similar documents were produced by several institutions and agencies with very similar recommendations.

The subsequent step brought research from a clinical approach to implementation science. The TEEN-AGE (Tutorial Electronic European Network on Acute Gastroenteritis), an ESPGHAN project led by Alfredo Guarino, was awarded a grant upon competitive application by the United European Gastroenterology Federation (UEG). The project was based on the concept of spreading ESPGHAN guidelines through e-learning and evaluate their effect. This specific strategy was explored in a population of physicians from 11 European Countries, who completed an e-learning specific course encompassing 6 modules available on ESPGHAN website. The course resulted in increased application of recommendations, and also in a reduction of the ‘average time needed to manage a case’ by each physician (measured before and after the course). Being gastroenteritis such a common problem, this approach is likely to provide a substantial improvement in the management of diarrhoea (20).

A further initiative consisted in the development of an app for mobile phones on the management of acute gastroenteritis (21). This was part of a larger project for the management of common gastrointestinal problems in children. The app is possibly suitable for improving the management of gastroenteritis also developing countries. This leads us back to the role of ESPGHAN in the management of gastroenteritis outside Europe, closely linked to FISPGHAN.

A Global View From ESPGHAN to FISPGHAN

ESPGHAN has always played a major role in the management of acute diarrhoea at the global level with an impact on policies and practices well outside the continental borders. A major breakthrough was achieved with the series of the World Congresses of Pediatric Gastroenterology, Hepatology and Nutrition. This was a major development from the joint meeting between ESPGHAN and NASPGHAN in 1986 in New York. Subsequently, a giant enterprise was undertaken in order to promote common initiatives by the 4 continental societies in Europe (ESPGHAN), North America (NASPGHAN), Latin America (LASPGHAN) and the Asian Pan Pacific (APPSPGHAN) to merge in the Federation of the Continental Society of Pediatric Gastroenterology Hepatology and Nutrition (FISPGHAN). The Commonwealth Association (CAPGAN) joined FISPGHAN as an affiliate Society and more recently the Pan Arab Society of Pediatric Gastroenterology Hepatology and Nutrition (PASPGHAN) also joined FISPGHAN (Fig. 3).

FIGURE 3. A “family picture” taken at the 2012 World Congress in Taiwan.
FISPGHAN mission was to promote a global strategy of cooperation for health care, research and education among paediatric gastroenterologists mainly through the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition (WCPGHAN). This is held every 4 years and is now in its second round 20 years after the first edition (Table 2).

Because FISPGHAN has a worldwide perspective, a major interest is directed toward geopolitical areas in need of help and implementation, that is, the so-called developing countries.

An organizing model to achieve FISPGHAN mission are the so-called FISPGHAN Working Groups that have a double purpose. First, to provide indications of what needs to be done to promote research, medical interventions and educational activities in order to improve the health of the digestive system of children of the world. The other aim is to promote cooperation among scientists and physicians from all over the world. The other aim is to promote cooperation among scientists and physicians from all over the world.

The priorities in research, medical interventions and education indicated in Working group report in 2012 are reported below as an example of FISPGHAN vision (Table 3) and include the implementation of Rotavirus immunization the spreading of oral rehydration within the proposed “medical interventions” and education of physicians, social workers and using social media (23).

The Working Groups that worked from 2012 to 2016, actively carried on a collaborative activity which resulted in practical achievements as follows: Starting from a joint ESPID/ESPGHAN medical position papers recommending the worldwide implementation of Rotavirus immunization (24) a survey was published on Rotavirus immunization, which includes the barriers that at local level hamper the effective spreading of immunization (25). A collaborative paper was published comparing the guidelines for management of gastroenteritis in the world, showing that the indications are largely similar (26). As a result, the group is carrying on an initiative to produce the “Universal guidelines” for the management of gastroenteritis (26).

FISPGHAN goals should be considered in a timeframe of a quarter of a century and they have been at least partially achieved. Not all the working groups that operated in the various editions developed an active collaboration and, in some cases, their report were limited to a well written document consisting in a more or less comprehensive state of the art review. However, in many cases, an active cooperation developed that brought to important collaborations, examples of which are the translation of the ESPGHAN guidelines on gastroenteritis in China and in Russia. The World Congress is not only a large paediatric gastroenterology, haepatology, and nutrition scientific meeting, it also provides an opportunity for sharing ideas between physicians and scientists of rich and less rich countries.

Overall, ESPGHAN has deeply affected the fight against acute gastroenteritis in several ways and had a major role in the successful development of effective strategies to prevent and counteract this disease at the world level. Several members of the society in those 50 years of history provided major contributes and many are still actively working facing the new challenges such as Clostridium difficile and other conditions such as trying to find effective strategies to counteract diarrhoea where it is most dangerous. Today, the focus is directed at malnourished children in Africa. “ESPGHAN goes Africa” is a recent initiative that aims at bringing solid support to counteract gastroenteritis as well as

### TABLE 2. The series of World Congresses of Pediatric Gastroenterology and the Presidents of FISPGHAN

<table>
<thead>
<tr>
<th>Location</th>
<th>Presidents</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012 – Taipei, Taiwan – Chair, Yen-Hsuan Ni</td>
<td>Kathy Schwarz (2012–2016)</td>
</tr>
<tr>
<td>2016– Montreal, Canada – Chair</td>
<td>Bert Koletzko (2016–2020)</td>
</tr>
</tbody>
</table>

### TABLE 3. The priorities indicated in the acute diarrhea Working group report in 2012

<table>
<thead>
<tr>
<th>Priorities</th>
<th>Medical Interventions</th>
<th>Education</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rotavirus immunization (target coverage &gt;80%)</td>
<td>Hygiene procedures focused on 3 issues:</td>
<td>Understand the perturbations of the intestinal microbiome and the metabolome during episodes of acute gastroenteritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hand washing with soap/access to safe water/toilet construction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family education and promotion of ORS provided during well-being visits</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Implementation of breast feeding</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Promote early use of optimal composition ORS</td>
<td>Dissemination and implementation of guidelines for management of acute gastroenteritis. Education of women improves child health</td>
<td>Investigate environmental and host factors, such as immune function, that may affect outcomes in children with acute gastroenteritis</td>
</tr>
<tr>
<td>3</td>
<td>Reduce inappropriate medical interventions</td>
<td>e-Learning programs for a worldwide education on acute gastroenteritis with an emphasis on education of girls and women</td>
<td>Apply systems biology methodology integrating host, microbial, immunologic, genetic, and epigenetic factors to identify novel metabolic pathways, which will lead to the discovery of new therapeutic interventions and more effective ORS</td>
</tr>
</tbody>
</table>

www.jpgn.org
building effective cooperation between people living in the various parts of the world.

REFERENCES

Chapter 5.4.2. ESPGHAN Made the Gastrointestinal Microbiota Grow

Yvan Vandenplas, Hania Szajewska, and Alfredo Guarino

Rapid progress in the field of probiotics and prebiotics is linked to the interest in the microbiota (1). Humans have 10 times more microbial cells than human cells, with the highest concentration of microorganisms located within the gut, specifically in the colon. Many of these microbes maintain health, while others are potential pathogens and can cause illness. Consequently, microbiota and its modifications have become the focus of active research of many scientists, including members of ESPGHAN.

SHORT HISTORY

An interest in probiotics started in the 1950s, with papers published on their use in combination with antibiotics in the treatment of whooping cough and tuberculosis. In 1965, the first paper to claim that probiotics have an effect on the growth of other microorganisms was published in Science (2). In 1984 Wadström showed for the first time that probiotics can prevent acute gastroenteritis (3). Still, in the 1980s, the probiotic literature focused mostly on the indications and applications of probiotics in veterinary medicine. In 1990, Reid et al. returned the focus of attention to the use of probiotics in humans while in 1992, Hekmat and McMahon published on different vehicles for administering probiotics (1,5). The authors showed that the bacteria can be grown to high numbers in an ice cream mix and remain viable during frozen storage (5). In 1991 Isolauri et al. reported that Lactobacillus GG in the form of fermented milk or freeze-dried powder is effective in shortening the course of acute diarrhea (6). The first 2 papers on the use of probiotics in preterm infants date from 1993, showing that Lactobacillus GG was well tolerated and did colonize the intestines of premature infants (7,8). However, there was no evidence that such colonization had any positive clinical benefit. In addition to probiotics, prebiotics are also an area of interest. The first paper on the presence of oligosaccharides in breast milk was published in 1957 (7). While Gibson and Roberfroid, regarded as pioneers in the field, published their paper almost 40 years later (10).

FIRST PEDIATRIC PROBIOTIC PAPERS

The paper regarded as the take-off point for the explosion of paediatric literature on probiotics is the Lancet paper by Saavedra et al published in 1994. In this randomized controlled trial, the authors showed that 8 (31%) of the 26 patients who received the control formula compared with only 2 (7%) of the 29 who received the formula supplemented with B bifidum & Str thermophilus developed diarrhea during the course of the study (P = 0.035) (11).

FIRST PEDIATRIC PREBIOTIC PAPER

It took until the early 2000s before the first paper on the use of prebiotics in infant formula was published, indicating that supplementation of a term infant’s formula with a mixture of galacto- and fructooligosaccharides had a dose-dependent stimulating effect on the growth of Bifidobacteria and Lactobacilli in the intestine (12).

THE JOURNAL OF PEDIATRIC GASTROENTEROLOGY AND NUTRITION (JPGN)

JPGN published its first “probiotic” papers in the mid-to-late 1990s (13,14). A 1997 JPGN paper documented the results of a randomized controlled trial in which the administration of lyophilized Lactobacillus GG reduced the duration of diarrhea and the rate of rotavirus-positive stools in a population of 100 children with acute gastroenteritis (14). Since then, an increasing number of papers have presented evidence in favour of using microbes to fight microbes.

FIRST PROBIOTIC TRIAL UNDER THE UMBRELLA OF ESPGHAN

One of the first probiotic randomized controlled trials, published under the umbrella of ESPGHAN, was a multicentre randomized controlled trial evaluating the effectiveness of Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea (15). By now, this ESPGHAN paper, written by Guandalini et al and published in JPGN in 2000, has been cited more than 700 times!

FIRST ESPGHAN META-ANALYSIS ON PROBIOTICS

A meta-analytical approach was introduced within ESPGHAN by the JPGN publication in 2001 of the first meta-analysis of the effectiveness of probiotics in the treatment and prevention of acute infectious diarrhea in infants and children (16). By now, it has been cited more than 500 times.

ESPGHAN OPINION LEADERS ON PROBIOTICS/ PREBIOTICS

It became increasingly obvious that probiotics and prebiotics were going to play an important role in paediatric nutrition and health care, for both prevention and treatment. In a paper published in 2002, ESPGHAN opinion leaders stated: “In today’s attempt to improve infant and follow-up formulas, probiotics or prebiotics supplementation represents a fascinating concept and the presently available scientific knowledge justifies from now on the consumption of some of these products by infants. However, despite recent important advances, the data available actually remain, in many cases, preliminary. Ongoing and upcoming research will certainly bring, in the near future, new and convincing data to answer the main questions. In any case, there is a need for a rigorous scientific evaluation of all products marketed to insure their safety and efficacy. For this reason, intervention studies are absolutely necessary to evaluate the immediate and long-term benefits and the

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absence of harmful consequences of any new formula. This evaluation must be part of a program of public health policy and not only performed by industry” (17).

COMMITTEE ON NUTRITION

ESPGHAN has the merit of being a Society that regards scientific evidence as a priority. In 2011, the ESPGHAN Committee on Nutrition published a paper in JPGN stating that “scientific data suggest that the administration of currently evaluated probiotic-and/or prebiotic-supplemented formula to healthy infants does not raise safety concerns with regard to growth and adverse effects. The safety and clinical effects of one product should not be extrapolated to other products. At present, there is insufficient data to recommend the routine use of probiotic-and/or prebiotic-supplemented formulae. The Committee considers that the supplementation of formula with probiotics and/or prebiotics is an important field of research. There is a need in this field for well-designed and carefully conducted randomized controlled trials, with relevant inclusion/exclusion criteria and adequate sample sizes. These studies should use validated clinical outcome measures to assess the effects of probiotic and/or prebiotic supplementation of formulae. Such trials should also seek the optimal doses and intake durations, as well as provide more information about the long-term safety of probiotics and/or prebiotics. Because most of the trials were company funded, independent trials, preferentially financed jointly by national/governmental/European Union bodies and other international organizations, would be desirable” (18). The latter statement is a cause of major concern for many nutritional studies conducted in infants and children: it is quite difficult, although not impossible, to obtain governmental money for this kind of study.

In 2011 the Consensus Group on Outcome Measures Made in Paediatric Enteral Nutrition Clinical Trials (COMMENT) initiative was launched, involving the ESPGHAN Committee on Nutrition, with the aim of developing common outcome measures for nutritional interventions in clinical trials. Five working groups were formed with the mandate to provide indications on definitions and key outcomes for evaluating functional nutrients in trials on growth, acute diarrhea, atopic dermatitis and cows’ milk protein allergy, respiratory infections and ‘gut comfort’ (19). The COMMENT initiative is expected to provide guidance in the design of trials on functional nutrients, thereby overcoming differences in definitions and key outcome measures to make the results of different trials suitable for comparative evaluation and meta-analysis. Key outcomes for acute gastroenteritis and for respiratory infections have already been published (20), and others are in preparation within the COMMENT initiative.

ESPGHAN WORKING GROUP FOR PROBIOTICS AND PREBIOTICS

The Working Group, established in 2000, has been consistently active in promoting collaborative work and in discussing data and future directions. The main impact of the group has been in the development of algorithms and guidelines. The group developed guidelines for the management of acute gastroenteritis (22) and the prevention of antibiotic-associated diarrhea (23). A manuscript on the quality of probiotic food supplements has been published and indicated that there is an urgent need for a more stringent quality control process (24). Several other papers on the indications of probiotics are in preparation. The group would like to do active clinical research; however, it struggles to find funding, as the group does not want to conduct clinical trials “for” industry, and industry is not interested in financing trials that are not of direct interest to them. At this stage, various governments and the European Union seem to have other priorities.

PROBIOTICS AND ESPGHAN GUIDELINES

Initially, the approach used to include the full representation of the original data on which the recommendations are based was innovative. However, subsequently, this rigorous approach was adopted for the development of ESPGHAN guidelines. First, for those related to the management of acute gastroenteritis (led by Alfredo Guarino) (25,26) and then for those on the use of probiotics to manage antibiotic associated diarrhoea (23). Currently, all ESPGHAN guidelines undergo a rigorous peer review process and are published in JPGN in an open access mode. Many of these guidelines are the result of a series of consecutive meetings held at international airports to minimize costs.

ACTIVITIES ENDSORED BY ESPGHAN

The development of ideas and trends on how to exploit the clinical applications of probiotics and prebiotics has been at least, in part, driven by the discussions developed within a series of Rome meetings on “Probiotics, Prebiotics and New Foods” which has brought together the most active members of ESPGHAN every 2 years since 1997 (26). More recently, a novel forum was developed called “Probiotics and Prebiotics in Paediatrics” (or PPP). The Rome meetings provide expert overviews of data in order to facilitate inclusion of probiotics in algorithms and clinical guidelines and also in the design of new directions for in vitro and in vivo research. The PPP is more oriented toward the presentation and discussion of clinical data, again with ESPGHAN playing a major role.

THE CURRENT SCENARIO

It is now clear that on the one side “there is some efficacy of probiotics in selected childhood diseases”. On the other hand, there is a major interest of commercial companies in developing, marketing, and promoting this novel class of products that is positioned between a drug and food supplement. As a matter of fact, customers do like the concept of probiotics, because of the “natural” approach as opposed to the more aggressive and hostile perceptions linked with chemical medications. Moreover, probiotics are devoid of adverse effects, have a relative low cost and good palatability, and create the perspective of being “tailored to the problem,” that is, offer a gentle approach to actively fighting a disturbing, although not severe, clinical condition.

Progressively, probiotics are becoming part of the standard management of several conditions, either for prevention such as in the case of antibiotic-associated diarrhea (23) or as an additional intervention or main treatment as in the case of intestinal and extra-intestinal inflammatory conditions. Probiotics also have become an important part of the management of conditions such assteatohepatitis (27). The role of probiotics in the prevention of narcotising enterocolitis in preterm infants is still being debated (28).

FUTURE DIRECTIONS

The option of targeting the intestinal microbiome is in its early stages of development and is profoundly affected by methodological issues. However, active research is ongoing with the aim of investigating the long-term effects of nutritional interventions that include use of probiotics and prebiotics in newborns, both term and preterm, and infants. The reason to target this age group is obvious, as if there exists a “window of opportunity” to skew the immune system in a health-promoting direction, it is situated in early life. The effects of such interventions in children are somehow easier to investigate than those in adults, because of the “naive” nature of the child to previous interventions as well as the limited exposure to confounding variables including lifestyle features that
are common in adults. Interventions in infants and young children may offer unique opportunities to exploit immunological windows and decrease the risk of chronic inflammatory/allergic diseases.

CONCLUDING REMARKS

Overall, it can be said with some pride (supported by evidence) that the work by pediatricians within ESPGHAN has been productive and successful in ensuring an effective use of probiotics and prebiotics for clinical purposes. The rigor and scientific solidity have led to major progress in the inclusion of these strategies in clinical protocols to the advantage of children. Yet, after more than 25 years of work, the feeling is that we are still in the initial stage of application of these strategies. Future developments are already focusing on areas in which we have been fighting microbes for decades such as cancer and premature birth. However, recent data suggest that adding microbes (the good ones!) in the initial stage of application of these strategies may offer unique opportunities to exploit immunological windows.

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Chapter 6. ESPGHAN’s Contributions to Paediatric Hepatology

*Martin Burdelski, **Etienne Sokal, §Pilar Nannini, §§Anil Dhawan, Giorgina Mieli-Vergani, *Diego Vergani, #Nedim Hadzic, **Giussepe Maggiore, ††Pietro Vajro, §§Giovanna Alfano, ‡‡Roderick Houwen, and *****Deirdre Kelly

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Chapter 6.0—History of Paediatric Hepatology in ESPGHAN; Manuscript: 302 words; Abstract: 179; Figures: 4; Tables: 2.
Chapter 6.1—Pediatric Chronic Hepatitis B and C: 30 Years of ESPGHAN Clinical Research and Recommendations; Manuscript: 1861 words; Abstract: 143 words; References: 36
Chapter 6.2—Immune Function-related Liver Disease and ESPGHAN’s Contribution to the Advancement of Science in the Last Three Decades; Manuscript: 4635; References: 60; Figures: 1.
Chapter 6.3—Studies on Hepatic Metabolic Disorders Driven by ESPGHAN Members: The Case of Alpha1-Antitrypsin Deficiency, Cystic Fibrosis, and Urea Cycle Defects; Manuscript: 3075 words; References: 65.
Chapter 6.4—Diagnostic Progress in Cholestatics; Manuscript: 1884 words; References: 20; Figures: 2.
Chapter 6.5—Pediatric Liver Transplantation; Manuscript: 2048 words; References: 15; Figures: 5.
Chapter 6.6—The Role of ESPGHAN in Developing Effective Immunosuppression Following Paediatric Liver Transplantation; Manuscript: 724 words; References: 12.

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Chapter 6.0. History of Paediatric Hepatology in ESPGHAN

Martin Burdelski

ABSTRACT

Hepatology played an important role in ESPGAN from the beginning. In 1989, the Hepatology Committee was started. In the early 1990s H for hepatology was included in ESPGHAN. Hepatology Summer schools were held from 1995 and later monothematic conferences met the needs of many young ESPGHAN members. The role of ESPGHAN members in the progress of diagnostic and therapeutic measures in hepatitis B and C will be elucidated (Chapter 6.1) as well as the role of other ESPGHAN members in the understanding of immunological hepatic disorders of childhood (Chapter 6.2). During childhood, many metabolic hepatic disorders threaten the life and health of children making orchestrated measures in diagnostic and therapeutic efforts necessary (Chapter 6.3). The pathophysiology of cholestasis was cleared by the detection of bile salt transporters, which were identified by ESPGHAN members in the Netherlands, France, United Kingdom and Germany (Chapter 6.4). Finally liver transplantation for acute fulminant and chronic end stage liver disease was established as a meanwhile standard treatment option (Chapter 6.5). Immunosupression in liver transplantation was improved and standardized through the cooperation of many ESPGHAN member driven studies (Chapter 6.6).

Right from the beginning of ESPGAN hepatology played an important role in this Society. ESPGAN members such as Alec Mowat, Birgitta Strandvik, Daniel Alagille, later Giorgina Mieli-Vergani, Deirdre Kelly, Carla Colombo, Etienne Sokal, and Martin Burdelski contributed significant presentations and papers to ESPGAN meetings and to the official journal of the Society, the Journal of Pediatric Gastroenterology and Nutrition. In 1989 the Hepatology Committee of ESPGAN was founded and started to attract young members of the Society and those who wanted to attend regular sessions at the biannual meetings of ESPGAN.

To attract even more young scientists to develop an interest in paediatric hepatology Hepatological Summer Schools were initiated, the first being that in the Lueneburg heather in Wilsede, Germany. A list of all hepatological summer schools held so far is shown in Tables 1 and 2.

In the 1990s, the importance of hepatology in ESPGAN had grown to such an extent, that Hepatology was added to the title of this Society, which was then renamed ESPGHAN. Having in mind that there was only a minority of studies performed on behalf of ESPGHAN, most of the studies reported here concerning paediatric hepatology were done by members of the society and were presented in the meetings (Figs. 2–4).

TABLE 1. List of all hepatological summer schools held as of year end of 2017

<table>
<thead>
<tr>
<th>Date</th>
<th>Place</th>
<th>Organizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>Wilsede, Germany</td>
<td>D. Kelly, M. Burdelski</td>
</tr>
<tr>
<td>1999</td>
<td>Ischia, Italy</td>
<td>A. Vegnente</td>
</tr>
<tr>
<td>2001</td>
<td>Kokke-le Zout, Belgium</td>
<td>E. Sokal</td>
</tr>
<tr>
<td>2003</td>
<td>Azores, Portugal</td>
<td>I. Goncalves</td>
</tr>
<tr>
<td>2006</td>
<td>Balatonfured, Hungary</td>
<td>A. Nemeth, L. Szonyi</td>
</tr>
<tr>
<td>2008</td>
<td>Venice, Italy</td>
<td>L. d’Antiga</td>
</tr>
<tr>
<td>2010</td>
<td>Cracow, Poland</td>
<td>P. Socha</td>
</tr>
<tr>
<td>2014</td>
<td>Salerno, Italy</td>
<td>P. Vajro</td>
</tr>
</tbody>
</table>

TABLE 2. Time, location, and organizer of monothematic ESPGHAN conferences

<table>
<thead>
<tr>
<th>Cell Genes and Molecules Monothematic Conference</th>
<th>2009</th>
<th>United Kingdom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Transplant Monothematic Conference</td>
<td>2013</td>
<td>Hanover, Germany</td>
</tr>
<tr>
<td>First Liver Transplant School</td>
<td>2015</td>
<td>Rovin, Croatia</td>
</tr>
</tbody>
</table>
In the following pages, the most important issues in paediatric hepatology and their relation to ESPGHAN will be discussed. These are

Chapter 6.1. Viral hepatitis in paediatrics by Etienne Sokal and Pilar Nannini.
Chapter 6.2. Immunological disorders in paediatric hepatology by Anil Dhawan, Giorgina Mieli-Vergani, Diego Vergani, Nedim Hadzic, and Giuessepe Maggiore.
Chapter 6.3. Hepatic metabolic disorders by Pietro Vajro, Giulia Paolella, and Giovanna Alfano.
Chapter 6.4. Development of understanding of cholestasis by Roderick Houwen.
Chapter 6.5. Liver transplantation in children by Martin Burdelski.
Chapter 6.6. Development of immunosuppression in liver transplantation by Deirdre Kelly.
Chapter 6.1. Pediatric Chronic Hepatitis B and C: 30 Years of ESPGHAN Clinical Research and Recommendations

Etienne M. Sokal and Pilar Nannini

ABSTRACT

The expression of hepatitis B and C virus infections in children differs from that in adults and requires specific paediatric expertise. The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) has been a pioneer in this field, having stressed the need for straightforward recommendations since the mid-1980s. Following much observation, surveillance, and research, a panel of ESPGHAN experts was able to develop such recommendations on hepatitis B infection in children in 2009, which was then followed in June 2013 by proper guidelines. In the field of Chronic Hepatitis C, in 2011 ESPGHAN experts published also the Guidance for Clinical Trials for Children and Adolescents, and approved in 2012 the NASPFGAN guidelines for treatment. The ESPGHAN Society is to be commended for its pioneering work in furthering our understanding of chronic hepatitis B and C disease presentations in infants, children, and adolescents.

Key Words: Chronic Hepatitis B, Chronic Hepatitis C, children, recommendations

(EJP 2018;66: S119–S121)

HEPATITIS B

Epidemiology and Natural History

Hepatitis B virus (HBV)—related chronic hepatitis (CHB), defined as positive HBsAg for ≥ 6 months, is typically asymptomatic in childhood. Nevertheless, 25% of all HBV chronic carriers worldwide exhibit a life-long risk of developing hepatocellular carcinoma (HCC), with an incidence of cirrhosis of 2% to 3% per year (1). HBV is transmitted through exposure to infectious blood, semen, vaginal secretions, and saliva (2). The infection prevalence has been declining worldwide since 1991, when the World Health Organization (WHO) called for all countries to incorporate HBV vaccinations in national immunization programs (3,4). Additionally, strict blood-donor and pregnant women screenings have been instrumental in decreasing the prevalence. Ten HBV genotypes (A–J) have been reported, with genotype A predominant in Europe, while genotypes B, C, D, and F are more common in high/intermediate HBV prevalence countries (5–7). In Western countries the vertical transmission is prevalent (8). Vertical-infected infants become immunotolerant to the virus and develop a lasting asymptomatic infection, characterized by high viral replication yet no liver injury. Nevertheless, these infants exhibit a 90% risk of developing CHB, and 25% will die from chronic liver disease during adulthood.

Treatment

Since the mid-1980s, the ESPGHAN society has been pushing for straightforward recommendations to clarify who needs to be treated and when to start the treatment. Management proposals were published by an expert group in 2009 (9), with proper guidelines published in 2013 by a panel of ESPGHAN experts (10) who developed a treatment algorithm to assist practitioners in their decision-making process. Antiviral treatment should be considered for children with high ALT levels for at least 6 months, an indirect marker of ongoing liver injury, in order to avoid treating patients undergoing spontaneous HBeAg seronconversion. Since the upper limit of normal (ULN) for ALT in children has not been established, ESPGHAN guidelines recommend those patients to be considered for antivirals if ALT levels exceed 1.5 times the laboratory ULN. In the presence of high ALT levels, the assessment of serum HBV DNA is required, with high HBV DNA values warranting antivirals, whereas low levels require further investigations to exclude other causes for liver injury. Other factors must be considered prior to initiating therapy: liver histology, family HCC history, coexisting liver diseases, and prior treatments (10). Antivirals are indicated in children undergoing liver transplantation, while prophylactic administration is recommended for HBsAg-positive patients due to receive immunosuppressive or cytotoxic therapy (11,12). The Food and Drug Administration (FDA) has approved 6 medications for treating CHB in children: interferon-alfa (IFNα), lamivudine, adeovir, entecavir, adefovir, tenofovir, with all these drugs tested in children in multicenter ESPGHAN-NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) trials.

IFNα, the first drug approved for CHB in children, is associated with a virological response (VR: undetectable HBV DNA and HBeAg clearance) in 26% of IFNα-treated children after 24 weeks versus 11% of untreated controls (12). This response rate increases to 35% when only patients with elevated ALT levels are considered. HBsAg clearance is noted in 10% of treated children versus 1.2% of controls. Response probability is shown to be associated with low baseline HBV DNA, younger age (<5 years old), and female gender (13). In early years, IFNα was presumed to accelerate HBeAg seroconversion, and it was confirmed by 3 studies, though with similar long-term HBeAg clearance rates between treated and untreated patients (14–16). Despite having no long-term consequences, IFNα therapy is shown to cause transient impairment of growth. Today IFNα administration is recommended in HBeAg-positive children aged ≥ 2 years, with abnormal ALT and low-intermediate HBV DNA levels. Several
trials were implemented by ESPGHAN–NASPGHAN members in order to assess nucleotide/nucleoside analogues in CHB children with multiple European and US centres involved. Lamivudine was the first nucleoside analogue to be FDA-approved for CHB treatment in children aged ≥3 years. VR is achieved in 23% of patients, in 34% if considering patients with elevated ALT levels (17,18). Lamivudine’s essential limitation is the risk of developing lamivudine-resistant mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) viral locus. Combination of lamivudine and IFNs in immunotolerant patients is shown to achieve 17% rate of complete viral control (HBsAg loss) (19). Adefovir dipivoxil, a purine analogue, was FDA-approved in 2010 for treating CHB children aged ≥12 years. VR is achieved in 23% of patients aged 12 to 17 years. Compared to lamivudine, adefovir offers a major advantage of proving effective against all hepatitis B viruses, including lamivudine-resistant strains, and in the long run adefovir resistance rates are lower (20). Moreover, adefovir appears to be effective in HBsAg-negative hepatitis. Entecavir, a carbocyclic analogue of 2-deoxyguanosine, is active on both lamivudine-resistant and adefovir-resistant strains. It is approved by FDA for children ≥2 years old, and it is effective in inhibiting viral replication, but only patients with HBsAg seroconversion are likely able to discontinue treatment without relapse, thus this may require several years of treatment. VR is reported in 24% of patients after 48 weeks (21), significantly associated with lower DNA (<8 log10), transaminase levels >2 × ULN, and genotype A/C. Based on these data, ESPGHAN now recommends to carefully select candidates eligible for treatment. Tenofovir, a nucleotide analogue similar in structure to adefovir but less nephrotoxic, is among the first-line treatments for adult CHB, along with PegIFN and entecavir. Like entecavir, tenofovir has proven to be effective against lamivudine-resistant mutations. Tenofovir was investigated in children aged 12 to 18 years old, with 89% of them achieving VR. However, after 72 weeks of therapy, HBsAg-Ab seroconversion rate was not higher in the treated patients as compared to placebo (22). Telbivudine, a L-nucleoside analogue, was approved by FDA in 2006 for children ≥16 years. In comparison with adefovir and entecavir, resistance rates for telbivudine have proved to be higher, increasing with the duration of treatment.

Novel antiviral approaches that target various steps and components of the HBV lifecycle are being investigated, with the hope of a complete viral eradication. These approaches include HBV entry inhibitors, such as Myrcludex B, a lipo-myristolated peptide mimicking the pre-S1 domain that competes with HBV particles to bind to the sodium taurocholate co-transporting polypeptide (NTCP). Studies on the drug’s safety carried out on healthy adults bind to the sodium taurocholate co-transporting polypeptide (NTCP). Combination of lamivudine and IFNs in immunotolerant patients is shown to achieve 17% rate of complete viral control (HBsAg loss) (19). Adefovir dipivoxil, a purine analogue, was FDA-approved in 2010 for treating CHB children aged ≥12 years. VR is achieved in 23% of patients aged 12 to 17 years. Compared to lamivudine, adefovir offers a major advantage of proving effective against all hepatitis B viruses, including lamivudine-resistant strains, and in the long run adefovir resistance rates are lower (20). Moreover, adefovir appears to be effective in HBsAg-negative hepatitis. Entecavir, a carbocyclic analogue of 2-deoxyguanosine, is active on both lamivudine-resistant and adefovir-resistant strains. It is approved by FDA for children ≥2 years old, and it is effective in inhibiting viral replication, but only patients with HBsAg seroconversion are likely able to discontinue treatment without relapse, thus this may require several years of treatment. VR is reported in 24% of patients after 48 weeks (21), significantly associated with lower DNA (<8 log10), transaminase levels >2 × ULN, and genotype A/C. Based on these data, ESPGHAN now recommends to carefully select candidates eligible for treatment. Tenofovir, a nucleotide analogue similar in structure to adefovir but less nephrotoxic, is among the first-line treatments for adult CHB, along with PegIFN and entecavir. Like entecavir, tenofovir has proven to be effective against lamivudine-resistant mutations. Tenofovir was investigated in children aged 12 to 18 years old, with 89% of them achieving VR. However, after 72 weeks of therapy, HBsAg-Ab seroconversion rate was not higher in the treated patients as compared to placebo (22). Telbivudine, a L-nucleoside analogue, was approved by FDA in 2006 for children ≥16 years. In comparison with adefovir and entecavir, resistance rates for telbivudine have proved to be higher, increasing with the duration of treatment.

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HEPATITIS C

Epidemiology and Natural History

With the availability of HCV treatments in the early 1990s, the incidence rate of HCV infection has significantly decreased in the last 2 decades, nevertheless the number of deaths per year due to HCV liver disease (cirrhosis, hepatocellular carcinoma and liver failure) is constantly increasing. Eleven million of infected people are younger than 15 years of age, of whom 5 million are viremic. Up to now, 7 genotypes (1–7) have been reported, with genotype 1 the most prevalent worldwide (46.2%, 83.4 million), counting for the majority of HCV infections in developed countries. After the universal screening of blood products, vertical transmission is the most common route of acquiring HCV in infants and children in developed countries, while in developing countries contamination through transfusion or health care procedures is still common. The prevalence of HCV infection in children in developed countries ranges between 0.1% and 0.4%, while it is lower in high-income countries (0.05%–0.36%) (23–25). The rate of perinatal transmission from an infected mother to her child ranges from 2% to 5%. Among vertically infected children, HCV infection is shown to chronize in 80% (26–27). Children with HCV infection differ from adults in several ways including modes of transmission, rates of clearance, progression of fibrosis, and the duration of potential chronic infection when acquired at birth. Infected children are usually asymptomatic, with a low risk of progression of the disease, but almost 5% of them develop significant liver disease in childhood.

The incubation period for HCV infection can range from 2 weeks to 6 months. More than three-quarters of HCV-infected children and adolescents are asymptomatic, with normal or only mildly increased serum ALT levels. Nonspecific signs and symptoms (hepatomegaly, hyperpyrexia, lethargy, anorexia, nausea, vomiting, abdominal colic, deep-coloured urine, light-coloured faeces, arthralgia, and yellowish discoloration of skin and sclera) can occur in approximately 15% of paediatric population.

Treatment

In 2012 ESPGHAN/NASPGHAN guidelines on “Diagnosis and Management of Hepatitis C Infection in Infants, Children, and Adolescents” suggested to start treating children with hepatitis C who demonstrate persistently elevated serum aminotransferases or those with progressive disease (ie, fibrosis on liver histology). PegIFN and ribavirin were approved by the FDA (2008) and the EMA (2009) for children aged more than 3 years. The rate of SVR is lower in case of genotype 1, the most prevalent HCV genotype globally, which 48 weeks-treatment results in a sustained virologic response (SVR) in <50% of children (28). In the case of genotype 4 SVR rate is achieved in 40% to 69% of children after 48 weeks of therapy (29). ESPGHAN/NASPGHAN guidelines recommend treatment of patients with genotype 1 and 4 for 48 weeks, patients with genotype 2 and 3 for 24 weeks. However, this regimen is burdened with consistent adverse effects: pyrexia, headache, gastrointestinal symptoms, depression, neutropenia and haemorrhagic anaemia, including deleterious effects on growth (30–33). Furthermore, the use of IFN for the treatment of HCV has been traditionally contraindicated in decompensated cirrhosis, leaving these patients at even greater risk for the development of end-stage liver disease. Given these assumptions, additional treatment options are still needed to eradicate the infection, with better SVR, especially for genotype 1, and less adverse effects. For this purpose, in 2011 an ESPGHAN committee published the “Guidance for Clinical Trials for Children and Adolescents with Chronic Hepatitis C” (28).

Modern direct antiviral agents (DAA) have revolutionized therapy of HCV infection and are now preferred for treatment in adults. The combination multiple classes of HCV antivirals is shown to reduce the development of viral resistance and improves SVR rates. The fixed dose once-daily single-tablet regimen of sofosbuvir (an inhibitor of the NSSB RNA-dependent RNA polymerase) and ledipasvir (an inhibitor of the NS5A protein) has been approved for the treatment of chronic HCV genotype 1 in patients aged ≥18 years in December 2013. This combination is shown to lead to SVR rates of >95% in HCV-genotype 1–infected patients, not only treatment naïve but also with prior treatment experience. Phase II and III trials of combination DAAAs, including the fixed-dose combination sofosbuvir and ledipasvir, for children aged 3 to 17 years with chronic HCV is currently ongoing (34). Safety results have shown comparable pharmacokinetics parameters and safety profiles between adult and adolescent populations with HCV
infections, and first patients treated confirm similar pharmacokinetic and efficacy before and after paediatric liver transplantation (35). Mild and inconstant adverse effects are reported in adults, not affecting the final outcome (36).

CONCLUSIONS
HBV and HCV infections are still a major issue worldwide. Current treatments available for paediatric population are partially efficient in curing the diseases and burdened with several adverse effects. New treatment options, such as new drugs blocking viral entry via the NTCP receptor and modern DAA need to be designed for HBV for HCV-infected children respectively. Long-term studies remain a must to better apprehend the natural history of these infections, along with the treatments’ impact.

REFERENCES
Chapter 6.2. Immune Function-related Liver Disease and ESPGHAN’s Contribution to the Advancement of Science in the Last 3 Decades

Anil Dhawan, Giorgina Mieli-Vergani, Diego Vergani, Nedim Hadzic, and Giuseppe Maggiore

Over the last 3 decades ESPGHAN has been at forefront of clinical research in liver disease of immune dysregulation and also immune phenomena developing in children with liver disease, including post-transplant complications. Several ESPGHAN members (Prof Giorgina Mieli-Vergani, Prof Diego Vergani, Prof Nedim Hadzic, Prof Giuseppe Maggiore) have been world leaders. The following document highlights some of theirs and ESPGHAN’s achievements.

LIVER DISEASE IN PRIMARY IMMUNODEFICIENCIES (PROF HADZIC)

For a long time liver disease in primary immune deficiencies (PIDs) has been underdiagnosed with significant impact on mortality and success of haematopoietic stem cell transplantation (HSCT). We have been first to report that liver transplantation (LT) is possible in children with primary immune deficiencies with a good outcome (1). We have also noted that around 20% of children with PIDs develop liver disease (2), often in the form of chronic cholangiopathy (3) associated with Cryptosporidium parvum (4). Our group has suggested that these patients need to be considered for an early haematopoietic stem cell transplantation (HSCT) if the liver disease is not too advanced (5,6). We have established that peri- and early post-HSCT complications are proportional to degree of underlying liver damage. Furthermore, we have demonstrated that if the liver disease is severe a novel concept of sequential liver and HSCT could potentially be curative (7). Transplanted liver can tolerate conditioning and hepatotoxic drugs required post-HSCT (7). In addition, we have published novel observations on humoral immunity in children with syndromic form of biliary atresia, where abnormal spleen is unable to mount adequate responses relevant for prevention of cholangitis, which is the commonest early complication in management of biliary atresia (8). We have described treatment of giant cell Coombs positive hepatitis of infancy and its overlapping features with some other autoimmune conditions (9).


IMMUNE-MEDIATED PHENOMENA AFTER LIVER TRANSPLANTATION

King’s College Hospital has international reputation for management of acute liver failure (ALF). We have described diagnostic approach and management of one of the commonest post-ALF complications—aplastic anaemia (10–12). This condition is life-threatening, but our clinical experience showed successful evolution from complete immune ablation in absence of haploidentical donor to effective HSCT in the presence of one. Furthermore, we have reported other immune mediated post-LT complications, including de novo autoimmune hepatitis (13,14), post-transplant lymphoproliferative disease (15–17), immune-mediated glomerulonephritis (18) and suboptimal immune responses to immunisation after LT (19). For post-transplant lymphoproliferative disease (PTLD) we have been able to gather a massive clinical experience, which provided a bulk of the UK national data on diagnosis and management of this potentially fatal condition.


HEPATIC COMPLICATIONS AFTER HAEMATOPOIETIC STEM CELL TRANSPLANTATION

For a number of years our centre has been providing support in managing children after HSCT developing complications such as graft-versus-host-disease, sinusoidal obstructive syndrome and drug hepatotoxicity. Given our extensive experience we have been asked to join a national panel to develop guidelines for management of hepatic complications. This UK national activity has resulted in several frequently cited publications helping prevention and management of these life-threatening conditions. Some of these children have been referred for consideration of LT, which have been successful in some, but not in all children (20–22).


LANGERHANS CELL HISTIOCYTOSIS

About one third of children with Langerhans cell histiocytosis (LCH) develop hepatic complications of this rare systemic disease, previously known as histiocytosis X. Typically, these children develop progressive cholangiopathy, which occasionally can respond to chemotherapy. Ensuing portal hypertension can be severe, requiring repeated upper gastrointestinal endoscopies and management of oesophageal varices. The most severe forms require LT on the basis of progressive cholangiopathy and biliary cirrhosis. However, this procedure could only be effective in the absence of signs of ongoing LCH activity. Additional immunosuppression required may facilitate potentially fatal opportunistic infections. Interestingly, these children remain at high risk of developing PTLD after LT. We have reviewed King’s experience (23), including a seminal observation that the condition could recur in liver grafts after LT, when re-LT may be required (24).


JUVENILE AUTOIMMUNE LIVER DISEASE (GIORGINA MIELI-VERGANI, DIEGO VERGANI)

Autoimmune liver disorders are inflammatory liver diseases characterized histologically by a dense mononuclear cell infiltrate in the portal tract that invades the surrounding parenchyma (intercellular hepatitis), biochemically by increased levels of transaminases, and serologically by the presence of circulating autoantibodies and high levels of immunoglobulin G (IgG), in the absence of a known aetiology. If left untreated the prognosis of these disorders is severe, while they generally respond well to immunosuppression, which should be instituted as soon as the diagnosis is made, because best results are obtained with early treatment. These conditions can present insidiously or with a picture of acute hepatitis. The juvenile forms of autoimmune liver disease, whose prototype is autoimmune hepatitis (AIH), have a more aggressive course than their adult counterparts. Pathogenic and clinical aspects of juvenile autoimmune liver disease have been the focus of intense research by 2 groups within the ESPGHAN society: the French group at the Hôpital Le Kremlin-Bicêtre in Paris and the British group at King’s College Hospital in London. Both groups have published seminal papers on the presentation, management and outcome of juvenile autoimmune liver disease (1–6). A close collaboration between clinicians and basic scientists within tertiary paediatric hepatology centres has led to the elucidation of immune mechanisms involved in the pathogenesis of autoimmune liver disease and in the discovery of novel disease entities. The results of the past 4-decade research in this field are summarised below.

AUTOIMMUNE HEPATITIS

Two forms of AIH are recognized according to the type of autoantibody present in the serum. Type 1 AIH (AIH-1) is
seropositive for smooth muscle antibody (SMA) and/or antinuclear antibody (ANA) (7,8), while type 2 AIH (AIH-2) for liver/kidney microsomal type 1 (anti LKM-1) (9) and/or anti liver cytosol type 1 (anti-LC-1) (10) antibody. Both AIH types affect mainly females. AIH-1 accounts for two-thirds of the cases and presents often around puberty, whereas AIH-2 tends to present at a younger age, also during infancy, and more acutely than AIH-1.

**Pathogenic Mechanisms**

The typical histologic picture of AIH, characterized by a dense mononuclear cell infiltrate eroding the limiting plate and invading the parenchyma (interface hepatitis), first suggested that auto-aggressive cellular immunity might be involved in its causation. Immuno-cytochemical studies have identified the phenotype of the infiltrating cells. T lymphocytes mounting the alpha/beta T-cell receptor predominate. Among the T cells, a majority are positive for the CD4 helper/inducer phenotype, and a sizable minority are positive for the CD8 cytotoxic phenotype. Lymphocytes of non–T-cell lineage are fewer and include (in decreasing order of frequency) natural killer cells (CD16/CD56 positive), macrophages, and B lymphocytes (11). A powerful stimulus must be promoting the formation of the massive inflammatory cell infiltrate present at diagnosis. Whatever the initial trigger, it is most probable that such a high number of activated inflammatory cells cause liver damage. The different possible pathways that an immune attack can follow to inflict damage on the hepatocyte are summarised in Figure 1. Over the past 4 decades, different aspects of this pathogenic scenario have been the focus of intense investigation by the King’s group. An impairment of immunoregulatory mechanisms has been described in AIH. Both children and young adults with this condition have low levels of T cells expressing the CD8 marker, and impaired suppressor cell function (12) which segregates with the possession of the HLA haplotype B8/DR3 (formerly B8/DR3), and can be corrected by therapeutic doses of corticosteroids (13). Furthermore, patients with AIH have been reported to have a specific defect in a subpopulation of T cells controlling the immune response to liver-specific membrane antigens (14). Further evidence for an impairment of immunoregulatory function in AIH has been obtained in the last decade (15–17). Amongst T cell subsets with potential immunosuppression function, CD4+ T cells constitutively expressing the interleukin 2 receptor (IL-2R) alpha chain (CD25) (regulatory T cells, T-regs) have emerged as the dominant immunoregulatory population (18). These cells, which represent 5% to 10% of the total population of

**FIGURE 1.** Autoimmune attack to the hepatocyte. An autoantigen is presented to uncommitted T helper (Th0) lymphocytes within the HLA class II molecule of an antigen-presenting cell (APC) either in the regional lymph nodes or within the liver itself. Activated Th0 cells differentiate into Th1 or Th2 cells in the presence of interleukin (IL)-12 or IL-4, respectively, and according to the nature of the antigen. This triggers a series of immune reactions determined by the cytokines they produce. Th1 cells secrete IL-2 and interferon (IFN)-γ, which are cytokines that stimulate cytotoxic T lymphocytes (CTL), enhance expression of class I HLA molecules, induce expression of class II HLA molecules on the liver cells and activate macrophages. Macrophages (M) release IL-1 and tumor necrosis factor (TNF). Th2 cells secrete mainly IL-4, IL-10 and IL-13, and stimulate autoantibody production by B lymphocytes. Regulatory T cells (Treg) are derived from Th0 in the presence of transforming growth factor (TGF)-β. In the presence of defective Treg, hepatocyte destruction ensues from the engagement of damaging effector mechanisms, including CTL, cytokines released by Th1 and by activated macrophages, complement activation, or adhesion of natural killer (NK) cells to autoantibody-coated hepatocytes through their Fc receptors. Th17 cells produce the inflammatory cytokine IL-17 and derive from Th0 cells in the presence of TGF-β and IL-6. They are the focus of current investigations.

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peripheral CD4+ T lymphocytes, control the innate and the adaptive immune responses by preventing the proliferation and effector function of autoreactive T cells. Their mechanism of action involves mainly a direct contact with the target cells, and to a lesser extent the release of immunoregulatory cytokines, such as interleukin 10 and tissue growth factor beta 1.

A numerical Treg impairment affects both children and adults with AIH. This defect is more evident at diagnosis than during drug-induced remission, although even then circulating Treg frequencies fail to reach the levels seen in health (15,19,20). The percentage of T-reg inversely correlates with biomarkers of disease severity, suggesting that a reduction in regulatory T-cells favours autoimmune liver disease. Importantly, several studies from King’s show that Tregs from AIH patients at diagnosis are impaired in their ability to control the proliferation of CD4 and CD8 effector cells compared to Tregs isolated from AIH patients at remission or from healthy subjects (19). What causes Treg impairment in AIH remains unclear. The King’s group has recently observed that Tregs in AIH are defective in the expression of CD39, an ectonucleotidase that initiates an ATP/ADP hydrolysis cascade culminating with the generation of immunosuppressive adenosine. CD39+ Tregs from AIH patients are therefore defective in their ectoenzymatic activity and inhibition of Th17-cell pro-inflammatory function. CD39pos Tregs from AIH patients are also unstable upon pro-inflammatory challenge (21), suggesting that defective immuno-regulation in AIH might result not only from reduced Treg number and function, but also from increased conversion of Tregs into effector cells.

The same group has also reported that effector CD4 T-cells isolated from patients with AIH are less susceptible to the regulatory control exerted by Tregs. This defect is linked to reduced expression of the inhibitory receptor T-cell-immunoglobulin-and mucin-domain-containing-molecule-3 (Tim-3), which upon ligation of galectin-9 expressed by Tregs, induces effector cell death (22). Hepatocytes from patients with AIH, in contrast to normal hepatocytes, express HLA class II molecules (23), and, although lacking the antigen-processing machinery typical of APCs, they may present peptides through a bystander mechanism. Given the impaired regulatory function and the inappropriate expression of HLA class II antigens on the hepatocytes, it is conceivable that an autoantigenic peptide is presented and recognized, as yet that an autoantigenic peptide is presented to the helper/inducer cells, leading to their activation. Although there is no direct evidence as yet that an autoantigenic peptide is presented and recognized, activation of helper cells has been documented in AIH (11,24). These activated cells possess the CD4 phenotype, and their numbers are highest when the disease is most active.

Most advances in the study of T cells have occurred in AIH-2, since the knowledge that cytochrome P4502D6 (CYP2D6) is the target antigen of ant-LC1 antibody in AIH-2 (41). The same group have also reported that effector CD4 T-cells targeting this cytochrome. One study has shown that CD4 T cells from patients with AIH-2 positive for the predisposing HLA allele DRB1*0701 recognize 7 regions of CYP2D6 (CYP2D6) is the main autoantigen (25) has enabled the characterization of both CD4 and CD8 T-cells targeting this cytochrome. One study has shown that CD4 T cells from patients with AIH-2 positive for the predisposing HLA allele DRB1*0701 recognize 7 regions of CYP2D6 (26), 5 of which have later been shown to be also recognized by CD8 T cells (27). A high number of interferon-gamma producing CD4 T cells and CD8 T cells is associated with biochemical evidence of liver damage, suggesting a combined cellular immune attack. What triggers the immune system to react to an autoantigen is unknown. A lesson may be learned by the study of humoral autoimmune responses during viral infections. Thus, studies aimed at determining the specificity of the LKM-1 antibody, present in both the juvenile form of AIH and in some patients with chronic HCV infection, have shown a high amino acid sequence homology between the HCV polyprotein and CYP2D6, the molecular target of anti-LKM-1, thus implicating a mechanism of molecular mimicry as a trigger for the production of anti LKM-1 in HCV infection (28,29). It is therefore conceivable that an as yet unknown virus infection may be at the origin of the autoimmune attack in AIH.

Titres of antibodies to liver-specific lipoprotein, a macromolecular complex present on the hepatocyte membrane, and to its well-characterized component asialolipoprotein receptor, correlate with the biochemical and histological severity of AIH (30,31). Antibodies to alcohol dehydrogenase, a second well-defined component of liver-specific lipoprotein, have been described in patients with AIH (32). Immunofluorescence studies on monodispersed suspensions of liver cells obtained from patients with AIH showed that these cells are coated with antibodies in vivo (33). A pathogenic role for these autoantibodies has been indicated by cytotoxicity assays showing that autobody-coated hepatocytes from patients with AIH are killed when incubated with autologous (34) lymphocytes. The effector cell was identified as an Fc receptor–positive mononuclear cell (34). T-cell clones obtained from liver biopsies of children with AIH and expressing the gamma/delta T-cell receptor have been shown to be cytotoxic to a variety of targets but to preferentially kill liver-derived cells as opposed to cell lines derived from other organs (35).

The establishment of cell lines and clones has shown that the majority of T-cell clones obtained from the peripheral blood and a proportion of those from the liver of patients with AIH are CD4 positive and use the conventional alpha/beta T-cell receptor (35–38). Some of these CD4-positive clones were further characterized and were found to react with partially purified antigens, such as crude preparations of liver cell membrane or liver-specific lipoprotein (36), and with purified asialolipoprotein receptor (36,39) or recombinant CYP2D6 (37) and to be restricted by HLA class II molecules in their response. Because CD4 is the phenotype of Th cells, T cell clones were investigated for their ability to help autologous B-lymphocytes in the production of immunoglobulin in vitro (36,39). Indeed, their co-culture with B-lymphocytes resulted in a dramatic increase in autoantibody production.

The possible role of Th17 cells in the pathogenesis of AIH is under investigation. Th17 cells contribute to autoimmunity by producing the proinflammatory cytokines IL-17, IL-22, and TNF-α, and inducing hepatocytes to secrete IL-6, which further enhances Th17 activation. Th17 cells have been shown to be elevated in the circulation and liver of patients with AIH (40).

**Animal Model**

Animal models of human disorders help in the understanding of mechanisms of disease and in devising novel modes of treatment. Though several models of AIH have been published, none of them recapitulates faithfully the human disease. The King’s group, in collaboration with groups in Yale and Montreal, have recently developed a model based on the HLA-DR3 transgenic mouse by immunization with a DNA plasmid coding for human CYP2D6/FTCD fusion protein. FTCD (formiminotransferase cyclodeaminase) is the target antigen of anti-LC1 antibody in AIH-2 (41). Importantly, immunization with CYP2D6/FTCD fusion protein leads to increased transaminase levels, development of autoimmune bodies and to a histological picture mimicking the human disease—including interface hepatitis and fibrosis—more closely than other published models, supporting a strong association between HLA and AIH (42).

**NOVEL DISEASE ENTITIES**

The exposure to unique clinical material in tertiary Paediatric Liver Centres, together with a keen interest in trying to unravel the immunopathogenesis of liver disease, has led to the description of 3 novel entities: autoimmune sclerosing cholangitis, de novo
autoimmune hepatitis after liver transplantation and giant cell hepatitis with Coombs’ positive haemolytic anaemia.

Autoimmune Sclerosing Cholangitis

Sclerosing cholangitis is an uncommon disorder, characterized by chronic inflammation and fibrosis of the intrahepatic and/or extrahepatic bile ducts. In childhood, sclerosing cholangitis may occur as an individual disease or may develop in association with a wide variety of disorders, including Langerhans’ cells histiocytosis, immunodeficiency, psoriasis, cystic fibrosis, and chronic inflammatory bowel disease. In a retrospective study of paediatric sclerosing cholangitis in the 1980s the King’s group observed that 40% of the patients had initially been diagnosed as having AIH because they had clinical, biochemical, immunologic, and histologic features indistinguishable from AIH (43). In these patients cholangiography was performed during follow up because of the appearance of biochemical and/or histological changes of cholestasis/bile duct disease. The sequence of diagnoses was then interpreted as an evolution from AIH to sclerosing cholangitis, when, in fact, the concurrence of these diseases had not been excluded by cholangiographic studies performed at presentation.

In an attempt to assess the relative incidence of juvenile AIH and ASC, a prospective study was initiated at King’s College Hospital in 1984 and patients enrolled over a period of 16 years (5). Interim results were published in 2001 and the patient cohort is being followed up to date. In this study, all children with increased transaminase levels, and associated serological (ie, positive autoantibodies, high IgG levels) and histological (ie, interface hepatitis) features of autoimmune liver disease underwent a cholangiogram at the time of presentation, independently from the presence of biochemical or histological evidence of cholestasis. Surveillance endoscopy to investigate for possible IBD was performed in all cases, independently from symptoms. Approximately 50% of the patients enrolled in this prospective study had alterations of the bile ducts characteristic of sclerosing cholangitis, although they were generally less advanced than those observed in adult primary sclerosing cholangitis. These patients were diagnosed as having autoimmune sclerosing cholangitis (ASC). A quarter of the children with ASC, despite abnormal cholangiograms, had no histological features that suggested bile duct involvement, and the diagnosis of sclerosing cholangitis was only possible because of the cholangiographic studies. Virtually all ASC patients were seropositive for ANA and/or SMA. In contrast to AIH, which had a clear female preponderance, ASC was diagnosed in a similar proportion of boys and girls. The mode of presentation of ASC was similar to that of AIH-1. IBD was present in 45% of children with ASC compared to 20% of those with typical AIH, and 90% of children with ASC had greatly increased serum IgG levels. At the time of presentation, standard liver function tests did not help in discriminating between AIH and ASC, although the alkaline phosphate/aspartate amino transferase ratio was significantly higher in ASC. Peripheral anti-nuclear neutrophil antibody (pANNA), which are seen in adult primary sclerosing cholangitis and in inflammatory bowel disease, were present in 74% of patients with ASC compared with 45% of patients with AIH-1 and 11% of those with AIH-2. HLA studies show that in the UK susceptibility to ASC is conferred by the possession of HLA DRB1*1301 (44). Evolution from AIH to ASC was documented in one patient in the published prospective series (5) and has been observed in 2 further patients during follow up (45), suggesting that AIH and ASC are part of the same pathologic process. Imaging of the biliary system by magnetic resonance cholangiopancreatography (MRCP), followed by endoscopic retrograde cholangiography if MRCP is not informative, as well as colonoscopy, should be part of the evaluation of all children with liver disease associated with autoimmune features to be able to distinguish ASC from AIH.

Children with ASC respond usually well to the same immunosuppressive treatment used in AIH, that is, prednisolone induction, followed by prednisolone and azathioprine maintenance (5), with resolution of liver test abnormalities within a few months in most patients. Ursodeoxycholic acid is usually added at a dose of 15 to 20 mg/kg per day. However, the medium- to long-term prognosis of ASC is worse than that of AIH because of progression of bile duct disease despite treatment in some 50% of patients, with 20% of them eventually requiring liver transplantation (5,45). Reactivation of the liver disease often follows flares of the intestinal disease in ASC patients with IBD. It is therefore essential to control the bowel pathology to avoid progression of liver disease.

De-novo Autoimmune Hepatitis After Liver Transplantation

In the late 1990s, the King’s group observed that AIH can arise de novo after liver transplantation in children who had not been transplanted for autoimmune liver disease (46). Characteristic of this condition is a histological picture of interface hepatitis and multilobular collapse associated with increased IgG levels and positive autoantibodies (46). These include ANA, SMA, and classical anti-LKM-1, but also atypical anti-LKM-1, staining the renal tubules but not the liver. After the original report, de novo AIH following liver transplant has been confirmed by several studies both in adult and paediatric patients (47,48) and has been reported to be more frequent in steroid-free antirejection regimens (49,50). Importantly, treatment with prednisolone and azathioprine using the same schedule for classical AIH, concomitant with reduction of the calcineurin inhibitor dose, is highly effective in de novo AIH, leading to excellent graft and patient survival. It is of interest that these patients do not respond satisfactorily to the standard anti-rejection treatment schedule, making it essential to reach an early diagnosis to avoid graft loss.

Giant Cell Hepatitis With Coombs Positive Haemolytic Anaemia

In 1981, the French group reported for the first time a rare form of systemic autoimmunity characterised by giant cell hepatitis and Coombs-positive haemolytic anaemia of the immunoglobulin G-positive C type (51). Of the original 4 children reported, 3 died of liver failure, while one responded to immunosuppressive treatment with prednisone and azathioprine. Several case reports, totaling 18 patients, followed the original description. The disorder presents in early childhood, usually between one month and 2 years of age, and affects both boys and girls. Liver histology is characterised by extensive giant cell transformation, while interface hepatitis is rare. A family history of autoimmunity is present in 30% of cases and some 20% of affected children have circulating autoantibodies similar to those of classic AIH (52).

The evolution of the haemolytic anaemia is often independent of the evolution of the hepatitis. At times it is the presenting symptom; at other times it may not be clinically apparent during the investigation of hepatitis; relapses of the anaemia may occur even when the hepatitis is under control. Occasionally autoimmune thrombocytopenia complicates the clinical picture (52,53). Giant cell hepatitis with Coombs positive haemolytic anaemia has variable severity and variable response to immunosuppressive treatment. First line treatment consists of prednisolone and azathioprine, but a long period of high-dose steroids is necessary.
to achieve a response. Relapse during early steroid withdrawal is very frequent. Cyclosporine and intravenous immunoglobulin G have been used to obtain a more rapid control of the disease (52). In refractory cases, anti-CD20 monoclonal antibody therapy has been used with success (52,54). A particularly severe case, refractory to all other modes of treatment, has shown complete resolution of the disease with alemtuzumab therapy (55). The reported mortality/liver transplant rate is 39%. The disease can recur after liver transplant (56). The largest long-term series published to date comes from the French group, and shows that after a median of 21 years of follow up, 12 of 16 patients were alive, one after liver transplant, and 6 had successfully stopped immunosuppressive treatment (52).

CONCLUSIONS
Over the past 4 decades, researchers within the ESPGHAN community have elucidated several clinical and pathogenic aspects of juvenile autoimmune liver disease, which have resulted in improved disease recognition and management. They have played a major role in the establishment and running of the International Autoimmune Hepatitis Group (IAIHG), which has established the criteria for the diagnosis and management of AIH (57–59), and which meets twice a year during the major international European and American conferences, where various aspects of autoimmune liver disease in adults and children are discussed. The next task of the IAIHG is the creation of an international registry to collect patient data from all centres willing to participate. Such registry will foster a fruitful collaboration leading to a better definition and management of the various forms of autoimmune liver disease and to designing clinical trials in large patient cohorts. The registry will also provide a unique platform for research.

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Chapter 6.3. Studies on Hepatic Metabolic Disorders Driven by ESPGHAN Members: The Case of Alpha1-Antitrypsin Deficiency, Cystic Fibrosis, and Urea Cycle Defects

Giulia Paolella, Giovanna Alfano, and Pietro Vajro

Cystic fibrosis (CF), alpha1-antitrypsin deficiency (A1ATD), and urea cycle defects (UCD) are well known inborn metabolic disorders characterized by specific abnormalities that may severely affect one or more organ systems, including the liver. Hepatic involvement may be and/or become the overriding problem burdened by difficult management. As there are not completely effective medical therapies, it may require sooner or later liver transplantation. In the last 3 decades many efforts have been made by ESPGHAN members in getting further insights and improved clinical management of these rare hepatic metabolic disorders.

Cystic Fibrosis

CF (OMIM #219700) is a genetic multiorgan disorder caused by mutations in the CF conductance regulator gene (CFTR), located on chromosome 7. The identification of CF gene was published for the first time in 1989. CF manifestations are related to the disruption of exocrine function of the pancreas, intestinal glands, biliary tree, bronchial glands, and sweat glands; infertility occurs in males and females (1). Biliary obstruction and progressive periportal fibrosis resulting from lack/dysfunction of the CFTR at the apical membrane of bile duct cells determine a focal biliary cirrhosis. Extension of the initially focal fibrogenic process may lead to multilobular biliary cirrhosis, portal hypertension and eventually liver failure. Why some patients develop liver disease (LD), sometimes with progressive outcome is currently still uncertain (2,3).

CF-related Liver Disease

In a cohort of 241 CF children, Thierry Lamireau and colleagues showed that cystic fibrosis-related liver disease (CF-LD) occurred mainly in the first decade of life (prevalence 41% at age 12 years) (4). Although LD does not influence the clinical course of CF, in some patients it may progress rapidly and require LT. In an Italian series of 177 CF patients without LD, Carla Colombo described during a 14-year follow-up, 48 patients (mainly with history of meconium ileus, male sex, or severe genotype) that developed subsequent LD, 5 with cirrhosis (5). In 1990, an Italian study coauthored by Pietro Vajro, demonstrated that the gallbladder hypokinesia with impaired/slower emptying predisposes CF patients to gallstones even in early childhood (6). Based also on these clinical premises, 3 recent studies, conducted on CFTR knockout Cfrt−/− mice and wild-type controls, shed light on the pathogenetic mechanisms of impaired biliary function in CF. Dominique Debray demonstrated that Cfrt−/− and CfrtΔF508 mice have defects in gallbladder emptying that disrupt enterohepatic circulation of biliary acids (BA) and create a cholecystohepatic shunt that restricts the amount of toxic secondary BA entering the liver (7); in 2 studies coauthored by Henkjan Verkade it has been shown that LD in Cfrt−/− mice is not related to increased bile hydrophobicity but probably to alterations in intestinal bacterial biotransformation of bile salts; smaller quantity of faecal Bacteroides bacteria found in Cfrt−/− suggest Cfrt dependent alterations in intestinal bacterial biotransformation of bile salts (8). Furthermore, prolonged cholate exposure did not induce CF-LD in Cfrt−/− mice (9). Further studies in Cfrt−/− mice authored by Dominique Debray have suggested that a high fat diet has a critical impact, mainly via gut dysbiosis, on the emergence of CF-related bile duct injury (10).

Cirrhosis in CF patients has been shown to be significantly associated with either homozygous or compound heterozygous mutations in the MBL2 gene encoding mannose-binding lectin (11,12). In a 2-stage case-control multicentric study coauthored by Carla Colombo, Dominique Debray and Florence Lacaille, it has been shown that SERPINA1 Z allele is a risk factor (odds ratio = approximately 5) for LD in CF with portal hypertension (13), adding therefore an important piece of jigsaw by clarifying that a rare variant with large penetrance (such as the Z allele) may be more useful than a common variant with low penetrance in screening for genetic polymorphism.

Diagnosis and Management of Advanced CF-LD

In the last 25 years the paediatric hepatology research made important progress in the evaluation and management of CF-LD. An interesting collaborative study coauthored by several ESPGHAN members (14) led to recommend an updated clinically useful diagnostic workup (including the more recent fibroscan assessment) and the therapeutic and surgical management of oesophageal varices, integrating previous guidelines (15). Surgical portosystemic shunting may be considered to relieve portal hypertension in CF-LD patients without progressive liver failure and severe lung disease as an alternative to LT (15).

Pietro Vajro proved that correct diagnosis of cirrhosis in CF patients may be difficult unless liver biopsy is made under laparoscopy control (16). Among serological markers of advanced CF-LD persistently high GGT levels (17), and serum hyaluronic acid concentrations (18), have shown quite specific features of increased risk of cirrhosis and/or hepatic fibrogenesis. These studies were
coauthored by Henkjan Verkade (17), Anil Dhawan and Giorgina Mieli-Vergani (18), ESPGHAN members.

In a multicenter study coauthored by Carla Colombo, severe LD was shown to significantly increase the risk of developing CF-related diabetes thus representing a red flag for earlier diabetes screening to identify and possibly treat glucose intolerance (19).

UDCA exerts in mice a choleretic effect and influences the bile salt fractional turnover rate and profile with a more hydrophilic bile salt pool independent of the presence of functional CFTR (20). Early UDCA treatment revealed beneficial in patients at risk of developing CF-LD, eg, those with meconium ileus (21). Based on results of a large double-blind multicenter trial conducted by Carla Colombo, UDCA appeared to improve clinical and biochemical parameters. Brigitta Strandvick group in Sweden demonstrated the efficacy of 2 years UDCA treatment with liver biopsies and liver function tests in 10 CF-LD patients aged from 8 to 28 years. This study showed that UDCA modulates inflammation in CF-LD and improves liver morphology (22). Three retrospective studies conducted or coauthored by a number of ESPGHAN members (23–25) revealed that the common indications for LT in CF patients are hepatic failure and/or severe portal hypertension with well-prepared pulmonary function. In these conditions, LT is also associated with long-term beneficial effects on the nutritional status and seems to favour bone mineralisation. (26). Deirdre Kelly and Carla Colombo coauthored the first European large survey on LT in patients with advanced CF-LD. This study highlighted that liver failure, hypersplenism, gastrointestinal bleeding and malnutrition represented the major indications for LT and that most European liver centres perform LT before the development of end-stage liver disease or overt pulmonary or other clinical decompensation (27). Furthermore, in bloc liver-pancreas transplantation could be an appealing option since it concurrently restores exocrine function and prevents insulin-dependent diabetes (25). In January 2016 during the ESPGHAN CF monothematic conference in Paris it has been discussed the need for a universal consensus on the definition of CF-LD to clarify disease stage and to identify relevant biomarkers (eg, biomarkers of intestinal bile salt malabsorption) to assess disease severity. Future medical treatment approaches have been also evaluated. CF-LD drug candidates other than drug targeting the causative CFTR (ie, CFTR potentiator ivacaftor and combination therapy with lumacaftor, a CFTR corrector) are: bile acid analogues, Farnesoid X receptor (FXR) agonists, fibroblast growth factor 1, and vitamin D receptors (28).

ALPHA1-ANTITRYPSIN DEFICIENCY

A1ATD (OMIM #613490) is not a rare disease but a disease that is rarely diagnosed (29). It is an autosomal recessive disorder characterised by both liver and lung injury. Pulmonary manifestations become evident in adults, whereas LD occurs already in the second common indication to LT (8.1%), preceded by biliary atresia (41.9%) (40). This study was coauthored by Loreto Hierro and Paloma Jara. Based on results of a large retrospective study at King’s College coauthored by Giorgina Mieli-Vergani and Nedim Hadzic, LT resulted to have significantly improved the prognosis of LD associated with PiZZ A1ATD. Duration of jaundice, severity of histological features and biochemical abnormalities predict outcome in early stage of the disease (43). In PiZZ patients with portal hypertension, oesophageal varices, or deterioration of hepatic function, LT should not be delayed, as reported in a single centre retrospective study (n = 59 children homozygous for A1ATD) coauthored by Pietro Socha, ESPGHAN member (44).

UREA CYCLE DISORDERS

UCDs result from several defects in the metabolism of waste nitrogen derived from the breakdown of protein and other nitrogen-containing molecules. Severe deficiency or total absence of activity of any of the first 4 enzymes in urea cycle or the cofactor producer results in the accumulation of ammonia and other precursor metabolites. The incidence of UCD is estimated to be at least 1:35,000 births; partial defects may make the figure much higher (45,46).

Hepatic involvement, for example, liver steatosis initially, is a frequent finding (47) with more frequent severe damage in...
argininosuccinate lyase (ASL) deficiency (48,49) and Ornithine transcarbamylase deficiency (OTCD). Episodes of hepatocellular injury, liver dysfunction, and acute liver failure have been identified in a high proportion of children with symptomatic OTCD. Two recent studies both coauthored by Etienne Sokal, described the initial presentation (48) and the evolving clinical phenotype (49) of 343 UCD compared to 452 patients with Organic acidurias (OA). It was found that neurological impairment is common in OAD and UCD, whereas the involvement of other organs follows a disease-specific pattern. Hepatic involvement was more frequent in UCD patients, in particular in ASL.

Methyl malonic aminoacidemia and propionic acidemia are the 2 main Organic Acidurias which present also hyperammonemia. Their clinical neonatal presentation is very similar, with neonatal period onset, when feeds containing protein have been started. If not recognized and treated promptly, OA patients progress to severe brain damage and death. Those presenting in the neonatal period have a worse prognosis. Immediate treatment is based on removal of toxic metabolites. Long-term treatment is dietary protein restriction and essential amino acid supplementation. Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (Mitochondrial Ornithine Transporter Deficiency) (OMIM #238970) is an autosomal recessive disorder caused by a defect in ornithine translocase. The clinical presentation is variable, including episodic hyperammonemia, chronic neurological manifestations and hepatic derangement which may appear as a fulminating hepatitiss-like condition. Its early recognition in the scenario of hepatic failure is important due to possible recovery without resorting to LT as reported by Pietro Vajro, in a case series of 3 children with fulminant hepatitis (50).

Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) also known as Neonatal-onset type II citrullinemia (OMIM #605814), is caused by homozygous or compound heterozygous mutation in the SLC25A13 gene (1). Mutations have a carrier rate of 1:65 in Japan and China, whereas they are much less frequent in the Western world. The same gene is involved also in the adult-onset phenotype (citrullinemia 2, OMIM #603471) which is mainly characterized by fatty liver and late recurrent hyperammonemic neurological disturbance due to the decreased associated liver-specific argininosuccinate synthetase (ASS) enzyme activity.

NICCD typically presents as a self-limiting neonatal intrahepatic cholestasis. Fatty liver, and increased serum citrulline may make it resembling an UCD. However, NICCD patients show a unique carbohydrate aversion in contrast to protein dislike seen in the adult-onset phenotype (citrullinemia 2, OMIM #603471) which is mainly characterized by fatty liver and late recurrent hyperammonemic neurological disturbance due to the decreased associated liver-specific argininosuccinate synthetase (ASS) enzyme activity.

Transplantation in Urea Cycle Defect

In patients with severe types of UCD, LT also in case of normal liver function remains the most effective means of preventing further hyperammonemic crises; it is associated with excellent survival rate if performed before irreversible brain damage. Auxiliary partial orthotopic LT has shown encouraging results in UCD. Apart from neonatal onset of OTC deficiency which is a clear indication for LT, in all other UCD conditions the indication is based on the failure to maintain metabolic compensation with medical treatment as discussed in the article coauthored by Lorenzo D’Antiga (54,55). Hepatocytes transplantation represents a more and more promising therapeutic approach for patients with liver-based metabolic disorders. Anil Dhawan and Etienne Sokal have pioneered in ESPGHAN the concept of hepatocyte transplantation as an alternative to LT in patients with liver-based metabolic disorders, focusing on protocols (isolation of human hepatocytes with collagenase perfusion, preparation in clean GMP conditions with cells meeting criteria of function and lack of microbial contamination, infusion of cells intraportally into the patient’s liver) and on aetiologies of liver disease in which this technique has been used (including UCDS) (56). The Brussel’s cell transplant program has further demonstrated the long term engraftment of hepatocytes with de novo enzyme activity following hepatocyte transplantation (57), and has pioneered the second generation of cell therapy, using in vitro expanded liver derived stem cells as a new source of cells to treat patients with inborn errors of the urea cycle (58,59).

Even if LT has an excellent survival rate this is not exempt from peri- and post-operative complications. Hepatocyte cell transplantation instead avoids the risks of major surgery and can help bridge a patient to whole-organ transplantation or leave the option of gene therapy, if and when it becomes available in future.

The ability to reproducibly generate a well-characterized source of engraftable and functional liver cells remains a challenge. In this regard, the use of metabolic profiling (NMR spectroscopy of urine and plasma) could be a promising method for evaluating the efficacy of cell infusions and the capability for the early detection of response to therapy in real time. In 2009 it has been published the first successful hepatocyte transplantation as a bridge to auxiliary partial orthotopic LT in a child antenatally diagnosed with severe ornithine transcarbamylase deficiency. In this single patient study coauthored by Anil Dhawan, NMR spectroscopic profiles of urine and plasma has been used for the first time for evaluating the efficacy of cell infusions. NMR profiles indicated that the disrupted urea cycle could be normalized by hepatocyte cell infusion and this was confirmed using orthogonal partial least-squares-based chemometrics (60).

The limited availability of donor tissue implies the search for new resources of liver tissue for isolation of high-quality hepatocytes. The group of King’s College with Anil Dhawan and Giorgina Mieli-Vergani suggested the use of segment IV with or without the caudate lobe obtained from split-liver procedures. Tissue-derived stem/progenitor cells and pluripotent stem cell-derived cells represent now a new opportunity to remove/reduce challenges of hepatocyte cells transplantation. (61).

Finally, cryopreserved cells have proved to allow short- to medium-term metabolic control and urea synthesis while waiting for OLT (62).

CONCLUSIONS

Several ESPGHAN members’ studies in this group of metabolic based liver diseases have substantially contributed to shed light on several disease-mechanisms, understanding why some affected patients develop a progressive outcome and other do not, and evaluating old and new medical therapies.

For CF, A1ATD, and some UCD, LT has become an accepted treatment capable of correcting totally or in part, the metabolic defect while replacing the diseased organ, and sometimes may even improve pulmonary function (eg, in CF-LD). Correct timing for organ replacement has been an issue largely explored. In UCD, and in some OA it may be more difficult in phenotypes with a
(still) little or even absent liver injury, and potential involvement of other organ system. Ideally, LT should be considered as soon as possible when dietary and medical treatments cannot reliably prevent metabolic decompensation and damage of severe extrahepatic organs (eg, CNS) (63–65). Auxiliary partial orthotopic LT, and hepatocyte cells transplantation appear feasible alternatives.

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Chapter 6.4. Diagnostic Progress in Cholestasis

Roderick Houwen

The causes of neonatal cholestasis were largely an enigma in the 1960s. Of course it was clear that some infants presenting in the neonatal period had an anatomical obstruction of the bile ducts: (extrahepatic) biliary atresia. In most patients, however, a nonspecific histological picture was seen on liver biopsy: ‘‘neonatal hepatitis,’’ characterized by ballooning multinucleated hepatocytes and accumulation of bile pigment in hepatocytes and bile canaliculi (Fig. 1). Some of these patients had a congenital infection, or a metabolic disorder like galactosemia or tyrosinaemia, but in most no definitive diagnosis could be made. Similarly the differential diagnosis in older children presenting with cholestasis was limited to infectious agents, anatomical obstruction (eg, choledochal cyst), toxic agents or some diseases that were obviously genetic, like Wilson disease and Summerskill disease (benign recurrent intrahepatic cholestasis, BRIC), while the cause in a large proportion of children remained unknown. Resolving this puzzle and improving diagnosis was made possible by dedicated clinicians, many of them ESPGHAN members, who were able to discern patterns amongst children with cholestasis, initially aided by histological techniques, and towards the end of the millennium deploying more and more the ever-increasing possibilities that genetics and cell biology had to offer.

At the end of the 1960s it was already noted that some children with neonatal hepatitis had a deficiency of α1-antitrypsin deficiency (1), a protein that at that time had only recently been identified. Clumps of this glycoprotein could also be visualized with special staining techniques in the hepatocytes of these patients, establishing α1-antitrypsin deficiency as a frequent cause of neonatal cholestasis. Daniel Alagille at the Hôpital Bicêtre in Paris first described hypoplasia of the intrahepatic bile ducts, in combination with specific extrahepatic features that included pulmonary-artery lesions (2), followed by other descriptions of arteriohepatic dysplasia, now commonly known as ‘‘Alagille syndrome.’’ From this same hospital ESPGHAN member Giuseppe Maggiore described a subgroup of patients with low GGT (Gamma Glutamyl Transferase) cholestasis, children who obviously did not have a good prognosis (3). Another cholestatic disease characterized by a low serum GGT and generally fatal in the first years of life was described amongst the Amish: Byler disease (4). Other rare diseases causing intrahepatic cholestasis were also described or better defined in the first decades after the founding of ESPGHAN: Aagenaes disease, Greenland Eskimo childhood cholestasis, North American Indian childhood cirrhosis, renal tubular insufficiency combined with cholestasis and arthrogryposis (ARC syndrome), as well as others.

The pathogenesis of these supposedly heterogeneic disorders remained a mystery. As many, but not all, of them had a fatal course, with unreleenting cholestasis, cirrhosis, and ultimately death, the need for better categorisation became pressing, especially in those patients that did not have distinguishing extrahepatic features. To this end the concept of progressive intrahepatic familial cholestasis (PFIC) was introduced (5), to describe this specific subset, which could be subdivided subsequently, initially into those with a high GGT and those with a low GGT. Peter Whitington then described partial biliary diversion, a surgical procedure that delays or prevents progression in some of the patients with low GGT PFIC (6).

Yet the pathogenesis of PFIC, and most of the other diseases mentioned, remained unclear. However in a large Dutch kindred with BRIC, biochemically characterized by low GGT cholestasis and clinically by episodes of severe itching, ESPGHAN member Roderick Houwen in Utrecht and Nelson Freimer in San Francisco demonstrated that all patients shared a stretch of DNA, originating from a common ancestor, on which the causative gene should reside (7). With the human genome project in its early stages, the actual identification of the gene needed far more patients however. To this aim DNA of additional patients was collected in several countries, such as the remote Far Oer islands, where Niels Tygstrup had described a cluster of patients with BRIC (8) (Fig. 2). Low GGT cholestasis was also a prominent feature in Byler disease, a form of PFIC. Alex Knisely, then in Pittsburgh, had collected DNA of several patients with Byler disease in the eponymous kindred. Using these samples the—yet unknown—gene involved in Byler disease was shown to be allelic to the—yet unknown—gene causing BRIC in the patients from Holland (9); some years later the same group identified the causative gene, FIC1, now named ATP8B1 (10). The actual function of its protein product is still not totally clear however, but is probably necessary to stabilize the canalicular membrane of the hepatocyte. Bile canaliculi are ultrastructurally remarkable in ATP8B1 deficiency: microvilli are missing and coarsely granular material is observed in the canalicular lumen (11). Not all patients with low GGT PFIC, however, shared this feature, and in some without it their disorder did not map to the ATP8B1 locus (11). Through genetic studies in patients with this second form, ESPGHAN member Richard Thompson from King’s College in London, working with Laura Bull in San Francisco, identified the locus and subsequently the gene involved, ABCB11,
which turned out to encode BSEP, the long sought bile salt export pump (12). Further work showed that both entities, ATP8B1 deficiency and ABCB11 deficiency have severe progressive forms, respectively PFIC type 1 and PFIC type 2, and mild, recurrent forms, respectively BRIC type 1 and BRIC type 2, with progression from the mild to the more severe form being seen in some patients. Solving the riddle of the high GGT variant of PFIC, that is, type 3, was done by more old-fashioned techniques. Deficiency of the mouse orthologue of multidrug resistance protein 3 (MDR3), identified while researching resistance to cytotoxic drugs, was known to cause cholestasis, through insufficient phosphatidylcholine transfer into the canalicular lumen. This disturbed the delicate balance between phosphatidylcholine and bile salts, with nonchaperoned bile salts causing damage to small bile ducts. ESPGHAN member Emanuel Jacquemin at Bicêtre demonstrated the absence of MDR3 in the liver of some patients with high GGT cholestasis (13), and working with Ronald Oude Elferink in Amsterdam, subsequently identified mutations in ABCB4, encoding MDR3, in PFIC type 3 patients (14).

With the completion of the human genome project and the development of automated sequencing, genetic techniques progressively became more sophisticated and efficient. Using these opportunities it was increasingly simple to dissect the genetic background of specific cholestatic syndromes. While at the end of the millennium still hundreds of patients were necessary to identify ATP8B1 and ABCB11, described above, as well as Jag1, the gene mutated in most patient with Alagille syndrome, for identifying VPS33, the gene mutated in ARC syndrome, 6 years later, only 29 patients were necessary (15), and for the recent linking of TJP2 mutations to another form of low GGT cholestasis no more than twelve patients were sufficient (16).

Low GGT cholestasis can also be caused by defects in the bile acid synthesis pathway (17). Each disorder is extremely rare with only a few cases published. For some time it was customary to use the term PFIC4 for these defects, or for some of these defects, but this should be avoided, as it is imprecise. It also overlaps with the more recent habit to label TJP2 deficiency as PFIC4, which should be avoided for the same reason. Over time the use of PFIC1, 2 and 3 will also be less common, as it will be replaced by ATP8B1 deficiency, ABCB11 deficiency and ABCB4 deficiency respectively. Given the long history of the term PFIC it is to be expected that this will take some time.

Identification of the genetic background of many of these defects and the elucidation of its pathophysiology has dramatically changed the diagnosis of cholestasis in neonates and older children. While diagnostic possibilities in neonatal cholestasis were very limited 50 years ago, now the number of different diagnoses to be considered in an infant with neonatal cholestasis can exceed 100. For older children the list is even longer. However by using clinical reasoning, based on the presence of extrahaepatic features (eg, typical facies, renal or cardiac abnormalities, etc), some basic biochemical results (eg, GGT, alpha-1-antitrypsin level, etc), serology for identifying common infectious agents and histopathologic findings in the liver, the number of diseases that should be considered in a particular case can be reduced considerably. Using the tools that biochemistry presently has to offer an underlying metabolic disease can generally be identified, although the diagnostic process can be long and cumbersome. Similarly a genetic diagnosis can be made by sequencing the genes that might be involved in a particular patient. To this aim, Sanger sequencing, which was ideal when only 1 or 2 genes had to be considered, is gradually being replaced by next generation sequencing (NGS) and whole exome sequencing (WES). With these methods all genes, whether 5, 50, or 150, that might cause cholestasis in a particular patient are being scrutinized for pathogenic mutations (18). As this technique is still relatively new its exact place with respect to metabolic investigations in urine and/or blood has still to be defined.

For many of these diseases a diagnosis is mainly important for determining prognosis and genetic counselling, as available therapeutic options, apart from liver transplantation in end stage
liver disease, are very few so far. For patients with low GGT PFIC a partial biliary diversion can be performed, with the better results generally obtained in patients with mild mutations and thus some residual function of the canalicular transporter, either ATP8B1 or ABCB11. Using an alternative pathway to excrete the toxic bile acids, by giving rifampicin, will reduce serum bile acid levels in some, while ursodeoxycholic acid (UDCA) may have a favourable effect (19). UDCA also reduces liver damage in ABCB4 deficiency by protecting the membranes of cholangiocytes against bile deficient in phosphatidylcholine. In these patients too the effect of UDCA is more pronounced when some residual function of the ABCB4 transporter is present (19).

Additional therapeutic options for genetic diseases in which single genes are mutated, and no structural damage to the liver is present, are likely to become available in the next decades, although it is impossible to predict which technique(s) will be commonly used. Gene therapy for liver disease, using adeno-associated virus vectors, is now possible for small genes like F9, encoding coagulation factor IX, while for other diseases human trials are being planned after successes in animal models. CRISPR-Cas gene editing technology, if proven safe in humans, might also be widely used. Small molecules (proteostasis regulators) can often induce or enhance the level of functioning protein in patients with missense mutations in a specific gene, while agents also have been, or are being, developed to permit protein transcription or translation in patients with stop or splice site mutations (20). Liver cell transplantation, now hampered by limited availability of hepatocytes and rather low efficiency, might benefit from new techniques to obtain large numbers of hepatocytes, either through induced pluripotent stem cells or through organoid technology (20).

In conclusion, the last 50 years have seen a tremendous increase in knowledge regarding common and less common causes of cholestasis in infancy and in older children. ESPGHAN members have made important contributions to these developments. It is to be expected that in the next 50 years this knowledge will be capitalized into better therapy for these children.

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Chapter 6.5. Paediatric Liver Transplantation

Martin M. Burdelski

In the late 1960s there was a remarkably sad experience in adult and paediatric hepatology. In acute and chronic end-stage liver disease medical treatment was just palliation without any curative effect. Despite every effort, these patients were bound to die very soon from liver coma, variceal bleeding, sepsis and organ failure. In Denver an American surgeon with an Austrian background, Thomas Starzl, was the first to make a switch from medical therapy to surgical cure. A liver disease, which did not respond to medical therapy anymore, was treated by liver transplantation. In 1968 the first successful liver transplant was performed in a child suffering from extrahepatic biliary atresia. This patient survived almost 1 year demonstrating a proof of principle (1). This experience could only be gathered by a surgeon, who dared to go beyond established frontiers. Thomas Starzl was such a person.

Some years later Sir Roy Calne in England, Henri Bismuth in France and Rudolph Pichlmayr in Germany, and later Jean Bernard Otte in Belgium started liver transplantation in adults and in children (2–4). The success rates in the seventies and early 1980s of the last century were limited, due to lack of effective immunosuppression and only slow progress in surgical experience. One must keep in mind that liver surgery in these days was not commonly performed.

In 1985 Sir Roy Calne, Henri Bismuth, and Rudolph Pichlmayr initiated a central registry for liver transplantation which has collected so far information about more than 110,000 liver transplants in Europe in both adult and paediatric recipients. This registry provides us with actual numbers and results of liver transplantation gained in all Europe (5). There has been an exponential increase in numbers of children and adults undergoing liver transplantation after the pioneering days in the early 1980s until 2008, thereafter the curve is flattening (Fig. 1). The reason for this rise is the steady extension of indications and the reduction of possible contraindications at the same time. The plateau is caused by the increasing lack of suitable donor organs in the last 10 years. With regard to paediatric liver transplantation there was always a lack of suitable donor organs of appropriate size and blood group stimulating transplant surgeons and the hepatologists to invent innovative techniques and strategies.

INDICATIONS AND CONTRAINDICATIONS FOR LIVER TRANSPLANTATION IN CHILDREN

Indications

Indications for liver transplantation in children nowadays are heterogenous. At the beginning of transplantation it was only extra hepatic biliary atresia, but now almost 40 years later cholestatic, noncholestatic liver disorders, metabolic cirrhotic disorders or noncirrhotic ones are accepted. Due to the availability of organs even acute fulminant liver failure is an important indication. The percentage of individual indications varies with the age of children:

Below the age of 2 years there is a predominance of cholestatic diseases, whereas in older children cirrhosis, acute hepatic failure, metabolic diseases and cancer have an increasing frequency (Fig. 2). This development has been enabled by the use of technical variants of liver transplantation, which are described in the next section. Technical variants are used today in about 24% of all transplants, in contrast to the late 80s, where only less than 5% were performed in this modification (5).

Contraindications

Contraindications for liver transplantation have reduced significantly. Today, only active bacterial or viral infections are accepted contraindications. Vascular malformations, as seen in syndromic extra hepatic biliary atresia with preduodenal portal vein, aplasia of the infradiaphragmatic vena cava, azygos or hemiazygos continuation, situs inversus and polysplenia syndrome have been regarded as contraindication for liver transplantation until the end of the 80s but now are accepted. Even systemic disorders such as cystic fibrosis or mitochondrial disorders in some manifestation are indications today. But the extent of indications and disregard of many contraindications enhanced the lack of donor organs. These developments have been made possible by the work of many ESPGHAN and NASPGHAN members.

TRANSPLANT TECHNIQUES

Full Size Organs

Using a full size liver was only possible if the size of the donor organ and the liver of the recipient was almost identical. The blood group had to be at least compatible. Progress reports from transplant centres in Cambridge/Kings College, Paris, Brussels, and Hannover (2,4,6) showed slowly improving results which was mainly due to improved immunosuppression by Cyclosporin A. The ESPGHAN members involved in these activities were Alec Mowat in Kings College, Daniel Alagille in Paris, Etienne Sokal in Brussels, and Martin Burdelski in Hannover.

In small patients, such as children below 10 kg body weight, there were almost no suitable donor organs available. The most frequent indication for liver transplantation in those days was biliary atresia. Without Kasai procedure, life expectancy of these children was almost below 1 year. By consequence, most of these transplant candidates died before a transplantation could be performed. Thus, mortality on the waiting list was up to 30% in almost every European transplant centre. Since this was unacceptable, innovative surgery was needed.

Reduced Size Organs

The concept of this technique aimed to reduce the size of the donor organ to fit the need of the recipient. This was made possible by the improved knowledge of the surgical anatomy of the liver as described by Couinod (7). The rest of the organ was discarded. Surgeons actively working on reduced size liver transplantation were Henri Bismuth in Paris (8) Jean Bernard Otte in Brussels (4) and Rudolph Pichlmayr in Hannover (6). Even in Australia, this type of
liver transplantation was performed (9). Shortly after, in USA reduced size liver transplantation was used by Christoph Broelsch, a pupil of Rudolph Pichlmayr. However, discarding the rest of the donor organ induced a shortage of donor organs for adult recipients.

Split Liver

The idea of split liver transplantation was born out of experience with reduced-size liver transplantation. The technique of splitting 1 donor liver into 2 parts had to follow the module principle. Both parts should have hepatic artery, portal vein, hepatic vein and bile duct. This aim was achieved by dividing the liver into the left lateral segment (segments 2 and 3) and the right lobe plus segment 4. By doing this, 1 donor liver was used to provide 2 grafts, 1 for an adult and 1 for a child. Teams in Hannover and Paris were the first to publish the technique (10,11). Two years later, the Chicago team published an analysis of this innovative surgery of split liver grafting (12). This procedure was extremely demanding: because cold ischaemia time had to be kept below 12 hours, 2 surgical and 2 anaesthetic teams had to work in parallel using 2 operating rooms. Blood bank supply had to be organized. All this happened mostly during nighttime because of logistic reasons. Later, the split liver technique was modified and used even to provide 2 organs for 2 adult recipients. Using right and left lobe or extended right (segment 1, 4–8 and 2–3) according to the need of the corresponding recipient. Since the results of the adult recipient initially were worse compared to the paediatric ones, the idea of in situ splitting was initiated (13) which helped to improve the results of the adult recipient to the same level as in the recipient of the left lateral segment. This technique then was used throughout the world.

Living Related Liver Transplantation

Despite the use of full size, reduced size and split liver transplantation the lack of donor organs forced transplant surgeons to extent the frontiers once again. By gaining experience in reduced-size and split liver transplantation and in liver resection for benign and malignant liver disease, the idea of living related liver transplantation was generated. The first surgeons to dare take this step were in Brazil and Australia, forced to do so in desperate situations.
A first series after establishing an ethical approval and based on surgical experience was performed in Chicago by Christoph Broelsch, who was supported by Peter Whittington, a member of NASPGHAN and his coworkers. Two years later, Broelsch started a living related paediatric liver transplantation program in Hamburg, Germany where he was supported by an ESPGHAN member, Martin Burdelski (14). This living related liver transplantation in Hamburg was the first to be done in Europe. In Japan, Tanaka and colleagues published the first series of living related liver transplantation in 1991.

Using all these technical variants in paediatric liver transplantation world wide, acute and chronic end stage liver disease in children can be treated effectively.

**Results of Paediatric Liver Transplantation**

To acquire meaningful results of paediatric liver transplantation it makes sense to analyse statistics in large series rather than to look for results of individual centres. Such statistics are presented by ELTR (European Liver Transplant Registry) in Europe and even better by SPLIT (Studies of Pediatric Liver Transplantation Research Group) in North America. Experienced single centres may have less complications and better results, but the efficacy of a method such as liver transplantation has to remeasured in multicentre reports.

**Survival**

Factors which may determine the outcome of liver transplantation are indication, age of the recipient, type of transplant, cold ischaemic time and of course skills of the individual surgeon and experience of PICU und paediatric transplant team.

With regard to the age of the paediatric recipient, there is no difference to be observed in children below or above the age of 2 years (Fig. 3). The ELTR report shows no significant difference in the 10-year survival rate for these age groups in 4270 and 5414 patients, respectively. The 10-year patient survival in children below and above 2 years are 78% and 77%.

However, there is a significant influence of the underlying disease on survival in the paediatric transplant population. The 10-year transplant survival in metabolic and cholestatic disease is with 82% excellent. Children with acute hepatic failure and non-classified cirrhosis do less well and have a 10-year transplant survival of only 68 and 70% respectively (Fig. 4).

There is a trend towards better results in the 10 year survival for patients receiving living donated organs compared to all other technical variants: 60% versus 57%, 55%, and 54%. This analysis includes both paediatric and adult recipients (Fig. 5). Death or retransplantation is reported predominantly in the first 6 months after transplantation in both adult and paediatric patients. A second peak in mortality is observed in more than 5 years after transplantation, most probably caused by adult patients with either high-risk comorbidity or malignant disease. Since the prevalence of organ rejection has been significantly reduced by using improved immunosuppression protocols (see Chapter 6.6) it is infection under the current immunosuppression which is the major cause of morbidity and even mortality in the first year after transplantation. This finding may indicate that the actual immunosuppression is still too intense and that this policy has to be reconsidered.

**Complications After Pediatric Liver Transplantation**

There are surgical and medical complications encountered after paediatric liver transplantation. Surgical complications and strategies to prevent them are mostly reported by surgical teams in single centre reports. The use of intraoperative Doppler-ultrasound examinations reduced the vascular and biliary tract complications significantly. In contrast to North America, multicentre studies have been rarely performed in Europe (see SPLIT). The first multicentre trial in paediatric liver transplantation was initiated by ESPGHAN members (15).
This study compared immunosuppression with tacrolimus and steroids with Ciclosporin microemulsion in combination with steroids and azathioprine. There is still a great deficit with regard to these multicentre studies in ESPGHAN although only these studies can give useful informations.

Apart from early complications the main interest today is on the long-term outcome and quality of life after paediatric liver transplantation. The complications causing trouble are calcineurin-inhibitor induced renal impairment, arterial hypertension, malignancies, diabetes mellitus, bone disease, chronic viral infections and liver fibrosis. Of major concern is further the transition time, where paediatric patients have to accept the different attitude of adult hepatologists when they have grown-up to young adults. During this time many patients start to be non-compliant with medical advice and are at risk of damaging the transplant.

These complications are affecting the quality of life in children after liver transplantation even after reaching adulthood. The importance of these complications makes it an ideal subject for ESPGHAN driven multicentre studies. It will be a major task of the
hepatology committee of ESPGHAN to inaugurate such studies in the near future.

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Liver transplantation has transformed the lives of many children by providing treatment for patients with fatal acute or chronic organ failure. The success of liver transplantation is related to the development of innovative surgery, but also the discovery and development of immunosuppressive agents. ESPGHAN’s role in establishing safe and effective immunosuppression in children post transplant is as follows:

- Educational role in discussing and debating the risks and benefits through numerous postgraduate courses and Hepatology Summer Schools.
- Research and clinical trials led by ESPGHAN members.
- Establishment of the Chilsfree network (through the Hepatology Committee), which led to the network accreditation EnPrema.

**DEVELOPMENT OF IMMUNOSUPPRESSION**

Early immunosuppression (1) consisted of a combination of anti-thymic globulin (ATG), azathioprine (AZA) and prednisolone, but it was not until the discovery of cyclosporine (CsA) (2) that the modern era of paediatric liver transplantation (LTx) began (3). The cyclophilin binding CsA was followed by the discovery of FKBP-12 binding tacrolimus (Tac) both inhibiting the calcium-mediated activation of lymphocytes via calcineurin.

**STANDARD IMMUNOSUPPRESSION**

The 2 calcineurin Inhibitors (CNI), Tacrolimus and Cyclosporin became the primary immunosuppressive agents for transplantation of liver and other organs, with rejection-free rates in Paediatric Liver transplant of 55% (Tac) and 40% (CsA) as highlighted by the only prospective randomised clinical trial in paediatric immunosuppression (4) which was a collaboration between 10 European centres, including Professor Kelly (Birmingham), Professor Burdelski (Hamburg) and Professor Jara (Madrid). This clinical trial established the standard immunosuppression regimen not just in Europe but internationally with Tacrolimus gradually replacing Cyclosporin as first line therapy. In view of the long term side effects of immunosuppression which include: renal toxicity, infection, diabetes mellitus, hypertension and hypercholesterolemia (5), the focus has changed to the use of induction therapy, addition of combination therapy to reduce the dosage of the more toxic CNI inhibitors and the evaluation of steroid free regimens.

The use of induction immunosuppression with monoclonal antibodies (IL-2 inhibitors) such as daclizumab, a humanised antibody and basiliximab, a chimeric antibody has allowed reduction of CNI doses in the first instance (6) while the use of maintenance immunosuppression with renal sparing drugs such as mycophenolate mofetil or Sirolimus (Rapamycin) may reduce long-term renal dysfunction (7,8). A more recent approach is the development of steroid free immunosuppressive regimens, which reduce hypertension, stunting and the cosmetic side effects of steroid therapy (9).

In 2012, 7 major ESPGHAN paediatric liver transplant centres combined their scientific efforts and created the ChilsFree study, which examines the functional degree of immunosuppression after paediatric liver transplantation. Immune monitoring data are correlated with clinical events, such as the occurrence of acute cellular rejection or infection. Data documentation is accomplished via a purpose-built web-based database, the creation of which was supported by ESPGHAN (10).

The ChilsFree study is now embedded in the framework of the European Paediatric Liver Transplantation Network EPLTN. This network of European specialist centres is dedicated to promoting both clinical and scientific excellence in paediatric hepatology. The EPLTN has been recognized by the European Medicines Agency EMA as a member of Enpr-EMA, the European Network of Paediatric Research at the EMA. Besides the ChilsFree study, EPLTN facilitates a number of other studies including work on risk factors of cardiovascular disease after paediatric liver transplantation, and on health-related quality of life after paediatric liver transplantation.

The need to take immunosuppression long term presents a challenge in adolescents who have a high rate of anon- adherence partly related to teenage risk behaviour and partly due to the cosmetic effects of immunosuppression (11). Identifying adequate strategies to resolve these issues urgently need identification. Currently, it is thought that immunosuppression should be life long as there have only been anecdotal accounts of safe withdrawal of therapy, although many ESPGHAN led units advise immunosuppression minimisation (prope tolerance) (12). A large prospective study of post-transplant withdrawal is in progress in The US and may provide valuable information. In the meantime, there are a host of new biological agents whose clinical role is still being defined (13) and ESPGHAN led units continue to work with the pharmaceutical industry to carry out safe trials of new therapy in children.

The combination of surgical and pharmacological progress has made paediatric LTx the success story it is today, when patient 5 year survival rates for paediatric LTx recipients are from 73.0% to 89.4% in the US, depending on age at PLT.

**REFERENCES**


Chapter 7. The Contributions of the ESPGHAN Committees on Nutrition to Paediatric Nutrition

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ABSTRACT

The first Committee on Nutrition (CoN) was founded in 1974. Two years later nutrition (N) was added to the society’s name, which then became ESPGAN. The Committee systematised compositional and quality criteria for breast milk substitutes and food for special medical purposes, the first of many examples on how recommendations and comments published by the Committees on Nutrition to Paediatric Nutrition (CsoN) were adopted by the European Economic Community, later the European Union and also influenced the World Health Organization/Food and Agriculture Organization of the United Nations Codex standards. A second CoN focusing on preterm infants was established in 1979 and its recommendations on nutrition of these infants were widely implemented. The third and standing CoN, established 1986, started to organise high-quality symposia at the annual meetings appreciating the need to enhance the expertise in nutritional research. From 1991 the CoN has organised Summer Schools in paediatric nutrition for young colleagues further emphasising its educational interest and more recently an annual, more specialised Nutrition Masterclass. Successively the interest of the CoN has expanded to other areas, such as ethical dilemmas and uncertainties in the field of nutrition including the design, choice of outcomes and statistical analysis of trials in infant nutrition. The work of the CsoN have had great impact on paediatric nutrition and the committee will continue its important role by writing commentaries and systematic reviews and revising guidelines on how recommendations and comments published by the Committees on Nutrition to Paediatric Nutrition can be harmonised internationally.

Key Words: children, feeding practice, infants, nutrition

(JPGN 2018;66: S144–S153)

The 1960s and 1970s were burgeoning times in the internationalisation of science and medicine which stimulated the formation of clinical subspecialties and interest groups, among which were ones in nutrition, such as substrate metabolism, inborn errors of metabolism, malnutrition in public health, and clinical care, especially hepatogastrointestinal disease. These were interdependent entities and socio-economic improvements fostered better professional communications and international collaborations to exploit and advance the knowledge base which underpinned clinical developments. In due course the professionals involved coalesced into international organisations which supported strategic research and the translation of new knowledge into diagnosis and management of disorders of paediatric nutrition.

Several new techniques including tissue (especially gastro-intestinal) biopsies, the use of radioactive tracers, initially, and then of stable isotopes, developed our understanding of substrate and nutrient metabolism and enhanced the quality of public health and clinical nutrition alike. This was a time when deficiencies of micronutrients, such as zinc and copper and of essential lipids were being recognised in preterm neonates and in children on parenteral nutrition. In adult medicine, gastroenterology had developed into a separate specialty, and had enabled improvements in parenteral nutrition in adult medicine and surgery, which served as exemplars for paediatric practice.

In gastroenterology and nutrition for both age groups, there was a vast array of challenges, many of which persist, particularly those concerning quantitative nutrient requirements in the context of changing lifestyles and treating certain diseases. It is significant that besides in the first 4 to 6 months there is still no harmonised international or intercultural approach to feeding infants in general as well as those with specific needs, such
as the management of malnutrition affecting one or more essential nutrient, the infection malnutrition cycle, inborn errors of metabolism and consensus on growth standards, encompassing not only linear and ponderal growth, but also body composition.

Advances in obstetrics and neonatology generated a need for skilled nutritional support and management of preterm and, increasingly, low birthweight infants. Peculiar nutritional needs distinct to and dependent on the stages of development of preterm infants fostered research on the maturation of the gastrointestinal tract including hepatopancreatic function, impacting on the efficiency of digestion and absorption of macronutrients coupled with the functional role of breast milk, also beyond providing nutrition, as well as on systemic effects of substrate metabolism on other organs, such as the kidney, body composition, and even psychomotor development.

All this generated a unique and critical portfolio of information that needed to be systematised so that it could be used effectively to inform the development of appropriate enteral and parenteral nutritional regimens for preterm infants. Proper nutrition is still one of the greatest, if not the greatest challenges in neonatology.

Techniques for parenteral nutrition developed, and simultaneously experience in creating formulas as breast milk substitutes or for inborn errors of metabolism, was applied to enteral nutritional support. At the same time there was an increasing awareness that adverse reactions to food and food components could be a serious problem for many infants and children. Interest in food allergies prompted research on mechanisms and management to achieve immunotolerance and avoid immunosensitisation. Thus, nutrition became a clinical subspecialty of its own, and the ESPGHAN Committee on Nutrition has, in many ways, initiated and sustained this important paediatric discipline.

**EUROPEAN SOCIETY FOR PAEDIATRIC GASTROENTEROLOGY (ESPGA) 1968**

The Committee of Nutrition (CoN) is the oldest, and a major committee within ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology and Nutrition). Its origin can be traced back to Paris in 1968 with the founding of the European Society for Paediatric Gastroenterology (ESPGA) initiated by H.A. “Dolf” Weijers from Utrecht, The Netherlands, Bertil “Jotte” Lindquist from Lund, Sweden, and Jean Rey from Paris, France (Fig. 2) (1). The initial idea was not to create a large, formal scientific organisation but rather an informal platform where colleagues from all over Europe could meet as friends to present and discuss common problems as well as new scientific ideas of mutual interest. Everyone with an interest in paediatric gastroenterology, clinical nutrition, or both (which was the rule rather than the exception at that time), was welcome to attend the annual meetings of the Society, either as a member or as an invited observer. Thus, all the initial 36 members of ESPGA had specific interests in pediatric gastroenterology and nutrition with, between them, skills in inborn errors of metabolism, clinical biochemistry, developmental physiology, substrate metabolism, and clinical nutrition as far as it was needed to tackle nutritional problems prevalent at that time. One agreed mission, which has persisted over the years, was the responsibility to disseminate knowledge within Europe, including to those countries which were then behind the Iron Curtain.

**THE BIRTH OF THE COMMITTEE OF NUTRITION 1974**

In 1974 Bertil Lindquist (Fig. 3) had identified the need for a CoN. Particularly pressing issues were the quality and standards of infant formula composition, foods for specific medical purposes (FSMP), and diversification of the diet in early life. In 1974, at the seventh annual meeting of the society in Verona, the ESPGA Council approved his proposal to establish a CoN. This importance of this new committee was highlighted in 1975 by the publication of a paper addressing the need for “standards and indications for industrially produced infant formulas,” which catalogued the principal issues concerning the composition of infant formulas: that is, characteristics relating to energy density, fat and individual fatty acids, protein and amino acids, carbohydrate, and individual micronutrients (2). There was an obvious need to establish quality standards and, because this was a public health issue, there was a need to collaborate with industry, industrial associations, and
regulatory and legislative authorities at national and international levels. This set the framework for an important role of the CoN in the systemisation of compositional and quality criteria for breast milk substitutes and for food-specific medical purposes. As is mentioned later these criteria were taken up by the European Economic Community (EEC).

Subsequently, in 1976, when he was ESPGA President, Bertil Lindquist proposed including Nutrition in the name of the society. Thus, the European Society for Pediatric Gastroenterology and Nutrition (ESPGAN) was born, and the initially strong and continuously increasing impact of nutrition within the society was acknowledged (1). The first meeting of the CoN (Chairman Bertil Lindquist, Secretary Jarmo Visakorpi, members: Beat Hadorn, Sergio Nordio, Jean Rey, Otto Wolff and the 2 invited permanent advisors June Lloyd and Eberhardt Schmidt) took place on June 29, 1974 in Trieste. The following year Angel Ballabriga, Wolfgang Plenert and Eberhardt Schmidt became members of the CoN (3). The struggle of the members to find the time for all their undertakings is symbolised by Beat Hadorn’s drawing (Fig. 4) (3).

Initially the roles of the committee were seen simply as advising and commenting on (1) nutritional needs of infants and children; (2) guidelines on the feeding of infants and children; and (3) supporting education and research in nutrition during early life and childhood (1). At that time the Committee had no standing orders or defined constitutional status within the ESPGAN. It had no dedicated funding either. The first task of the CoN was to consider the need and composition for a single formula for healthy babies throughout infancy until 12 completed months. This concept had been endorsed in 1976 by the American Academy of Paediatrics (4). The recommended composition was then adopted by the Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Codex Alimentarius Committee with a slight modification of the maximum acceptable protein content. The discussions and debate engendered by these recommendations inspired the ESPGAN CoN to consider early life nutrition in the context of new insights on the maturation of infants’ physiology, biochemistry, and substrate metabolism and the interaction of these with the compositional and functional characteristics of human breast-milk (eg, lipids and fatty acids, protein, amino acids and non-protein nitrogen, digestive enzymes, and hormones). The committee developed an alternative concept of developing a formula suitable for the first 3 months or so of life, and another for the latter part of infancy. Thus, Bertil Lindquist and the first CoN could be credited for devising “adapted infant formulae” and “follow-up formulae” (Fig. 5).

These deliberations and guidelines were published in the first 3 commentaries produced by ESPGAN CoN ((5–7) and Table 1) between 1977 and 1982. The recommendations were well received, and were acknowledged for the responsible use of available evidence, and the effective synthesis of contemporary knowledge to achieve reasoned recommendations which embraced evolving concepts and practices in the countries of the participants. Collectively this series of reports established the reputation and authority of the ESPGAN CoN.
TABLE 1. Topics of position papers and comments published by the Committees on Nutrition and related subgroups

<table>
<thead>
<tr>
<th>Topic</th>
<th>Year</th>
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<tbody>
<tr>
<td>Guidelines on infant nutrition. I. Recommendations for the composition of an adapted formula</td>
<td>1977</td>
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<td>Guidelines on infant nutrition. II. Recommendations for the composition of follow-up formula and Beikost</td>
<td>1981</td>
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<tr>
<td>Guidelines on infant nutrition. III. Recommendations for infant feeding</td>
<td>1982</td>
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<tr>
<td>Nutrition and feeding of preterm infants.</td>
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<td>Comment on the composition of cow’s milk based follow-up formulas</td>
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<tr>
<td>Comment on the composition of soy protein based infant and follow-up formulas</td>
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<tr>
<td>Comment on the content and composition of lipids in infant formulas</td>
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<td>Comment on antigen-reduced infant formulae.</td>
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<td>Response to comments on antigen-reduced infant formulae</td>
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<td>‘Recommended Dietary Allowances (RDAs), Recommended Dietary Intakes (RDIs), Recommended Nutrient Intakes (RNIs), and Population Reference Intakes (PRIs) are not ‘recommended intakes’’</td>
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<td>Comment on the vitamin E content in infant formulas, follow-on formulas, and formulas for low birth weight infants</td>
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<td>The nutritional and safety assessment of breast milk substitutes and other dietary products for infants</td>
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<td>Probiotic bacteria in dietetic products for infants</td>
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<td>Annotation: antireflux or antiregurgitation milk products for infants and young children</td>
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<td>Prebiotic oligosaccharides in dietetic products for infants</td>
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<td>Supplementation of infant formula with probiotics and/or prebiotics: a systematic review and comment</td>
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<td>Role of dietary factors and food habits in the development of childhood obesity</td>
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<td>Donor human milk for preterm infants: current evidence and research directions</td>
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<td>Iron requirements of infants and toddlers</td>
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<td>Arsenic in rice: a cause for concern</td>
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<td>Intravenous lipid emulsions and risk of hepatotoxicity in infants and children: a systematic review and meta-analysis</td>
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<td>Prevention of vitamin K deficiency bleeding in newborn infants</td>
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<td>Complementary feeding: a position paper</td>
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<td>Sugar in paediatric nutrition</td>
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<td>Young child formula</td>
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<td>Dietary products used in infants for treatment and prevention of food allergy. Joint Statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition</td>
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<td>Pesticides in dietary foods for infants and young children. Report of the working group on pesticides in baby foods of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)</td>
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<td>Global standard for the composition of infant formula: recommendations of an ESPGHAN coordinated international expert group</td>
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<td>Guidelines on paediatric parenteral nutrition of the European Society of Paediatric gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR)</td>
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<td>Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)</td>
<td>2009</td>
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<td>Documentation of functional and clinical effects of infant nutrition: setting the scene for COMMENT</td>
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<td>Core data necessary for reporting clinical trials on nutrition in infancy. Consensus group on outcome measures made in paediatric enteral nutrition clinical trials (COMMENT); Early Nutrition Project</td>
<td>2015</td>
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<td>Gluten introduction and the risk of coeliac disease: a position paper by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition</td>
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<td>Attrition in long-term nutrition research studies: a commentary by the ESPGHAN Early Nutrition Research Working Group</td>
<td>2016</td>
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The guidelines on “Recommendations for the composition of an adapted formula” influenced the WHO/FAO Codex CoN and Foods for Special Dietary Uses regulations during the late 1970s and during the 1980s. There was a discernible concordance between the ESPGAN CoN’s recommendations and the decisions of CODEX. This was not that surprising: in fact, Bertil Lindquist, Jean Rey, Eberhard Schmidt, and Jarmo Visakorpi participated in the drafting panel for the “Codex Standard for Infant Formula” (Codex Stan 72–1981). Several countries were convinced to adopt the concepts of follow-up, or follow-on, formulas as an alternative to cows’ milk, and the “Codex Standard for Follow-up Formula” was adopted in 1987 (Codex Stand 156–1987).

THE SECOND COMMITTEE ON NUTRITION 1979

The next challenge was to address the nutritional needs of the preterm and low birthweight infant. By the end of the 1970s there was more insight, much of it acquired from research on animal models in support of animal husbandry, into the maturation of the hepatopancreatic system and the gastrointestinal tract, and of the subtle interactions between micronutrients and substrate metabolism, energy utilisation and body composition. Much of this work had been shared with paediatricians through the auspices of societies dedicated to neonatology. Complementary expertise had also become available from experience in the nutritional rehabilitation of malnourished children, particularly in the developing world.

These skills were utilised when, in 1979, the ESPGAN CoN decided to establish a CoN of the Preterm Infant (Chairman: Brian Wharton (who had appreciable experience in East Africa with nutritional rehabilitation), members: Hans Bremer, Oliver Brooke, Marcello Orzalesi, Guy Putet, Niels Raihâ, Jacques Senterre, Jonathan Shaw (Fig. 6). After a preparatory meeting on “Nutrition of Low Birthweight Infants” organised in 1981 by Bertil Lindquist in Lund, this group started to systematise the available information and to produce recommendations for good practice in feeding the preterm infant. The Committee’s report, produced in 1987, was appreciated and acknowledged as an outstanding review of the topic, and its recommendations for the nutrition of low birth weight infants were widely implemented. The report, which was published as a supplement of Acta Paediatrica Scandinavica (8) and as a stand-alone hardback book (9), still stands as a superb resource for anyone who wishes to specialise in the nutrition of the low birthweight and preterm infant as well as infants in general.

THE THIRD AND STANDING COMMITTEE ON NUTRITION 1986

While the CoN of the Preterm Infant was deliberating, Alexander (Sandy) McNeish, during his presidency (1983–1986), proposed the inception of a new standing CoN which was convened during the subsequent presidency of Salvatore Auricchio (1986–1989). Initially the work of the “new” CoN (Chairman Jean Rey, secretary Peter Aggett, members, Ferdinand Haschke, Willi Heine, Olle Hernell, Kari Launiala, Armido Rubino, Gerhard Schöch, Jacques Senterre, and Ramon Tormo), focused on issues concerning the composition of infant formulas and dietetic products within the European Community. The latter had established its Scientific Committee on Food (SCF) in 1974, and Jean Rey, Sergio Nordio, Eberhart Schmidt, and Jacques Senterre participated in the working group which prepared the European Commission’s SCF’s first report on the essential requirements of infant formulas and follow-up milks based on cow’s milk proteins in 1983. In 1989 the EC produced a Directive (89/398/EEC) on the approximation of the Member States’ various guidelines on food composition of Foodstuffs for Particular Nutritional Uses (PARNUTS) which included the standards, composition and use of formulas and dietetic products for infants and young children. This Directive, and improved understanding of infant nutrition since 1983, was an opportunity for the EC to update its guidance on Infant Formulae. The consequent

FIGURE 6. The Second CoN. Left to right: Oliver Brooke (London), Jacques Senterre (Liege), Guy Putet (Lyon), Marcello Orzalesi (Sassari, Sardinia), Brian Wharton (Birmingham), Hans Bremer (Dusseldorf), and Jonathan Shaw (London). Niels Raihâ (Malmo) could not attend the meeting when the photo was taken. Photo courtesy of Brian Wharton.
drafting and revision of European Directives on formulae and follow-on formulae (eg, 91/321/CEE) were both anticipated and strongly informed by the reports and commentaries of the earlier CoN and those of the “new” CoN on infant formulae on cows’ milk-based follow-up formulas (10), soy protein-based infant and follow-up formulas (11), lipids in infant formula (12).

The CoN also prepared a commentary on antigen reduced infant formulae, including consideration of nomenclature, diagnosis, management, and prevention of allergy in infancy and later life (13,14) topics for which scientifically based recommendations were largely absent at the time, particularly because of uncertainties about the pathogenesis of allergic sensitisation. Many uncertainties remain, but the debate stimulated by this commentary contributed to the SCF’s draft on this difficult topic, and additionally stimulated a collaborative commentary with other specialist societies in Europe (15).

The experience of CoN members drafting guidelines for the composition of formulas, along with that of several, who, in the late 80s and early 90s served on national (eg, Germany, France, UK) and international panels (FAO/WHO, DACH, Nordic Countries, and the SCF of the EEC) on setting and observing the use of “population dietary reference values,” highlighted a number of problems. The quality and quantity of data available for setting dietary or nutrient reference values for adults and, particularly, for children beyond infancy were limited. Furthermore, CoN members were disappointed that health practitioners, including paediatricians, treated the published values as definitive indices for diagnosis and therapy. Thus, after the SCF Working Group had reported on “Population Reference Intakes” for the European Union (EU) population in 1993, the CoN decided to comment on the use, misuse, and misunderstanding of Dietary Reference Values. This report “Recommended Dietary Allowances, Recommended Dietary Intakes, Recommended Nutrient Intakes, and Population Reference Intakes are not ‘recommended intakes’” was published in 1997 (16); it stimulated much discussion, and subsequently a United Nations University working group funded by the FAO, WHO, and EC met to comment on ways to harmonise approaches to setting Dietary Reference Values at an International level, particularly in the increasingly complex context of free trade and world trade agreements (17).

Other important aspects concerning the composition of formulae and reference values were ambiguities and uncertainties in the definitions of lipids and fatty acids, and carbohydrates, and in the assessment of children’s needs for these in general as well as their specific components. Lipids were addressed relatively soon after the commentaries on composition of infant formulae, as mentioned above. This was followed by a comment, the first by the CoN, addressing the impact of early nutrition on health in later life, in the form of a report on the effect of childhood diet in the reduction of the risk of coronary heart disease in adulthood (18).

The commentary on carbohydrates took longer, principally because of the variability in their classification and analytical quantification and the need to produce a succinct commentary on what remains a complex topic (19). Additionally, the CoN prepared a critical review of the knowledge base and research needs relating to iron supply and the actual amounts that young children probably need. The reference values for iron were, and probably still are, cautious (20).

In the late 1990s, the CoN realised that, given the increasing interest in early feeding and short- and long-term outcomes, it would be beneficial to have an agreed common approach to the nutritional and safety assessment of infant formulas. In particular the CoN emphasised the need for a rigorous approach to assessing the impact and outcomes of dietary practice in infancy, and encouraged further constructive critical thinking in the practice of nutritional science as applied to infants and children as well as pregnant women (21). This was followed by a proposal for the collection of core data in studies on early life nutrition, so that data from individual studies would be suitable for aggregation and review for long-term outcomes (22). This is an ongoing topic within ESPGHAN (Fig. 7).

The status and authority of the ESPGHAN CoN was recognised and internationally acknowledged in 2003 when it was
granted formal observer status as an independent member in the Codex Alimentarius process and meetings. This led to the Codex CoN and Foods for Special Dietary Uses asking the ESPGHAN CoN to initiate a consultation process with the international scientific community to provide a proposal on nutrient levels in infant formulae, based on scientific analysis and taking into account existing scientific reports on the subject. ESPGHAN accepted the request and, in collaboration with its sister societies in the Federation of International Societies on Pediatric Gastroenterology, Hepatology and Nutrition formed an International Expert Group (IEG) to review the issues raised. The group, chaired by Berthold Koletzko, arrived at recommendations on the compositional requirements for a global infant formula standard. The report, which to a large extent was based on the ESPGHAN CoN’s publications and commentaries and the recent SCF report on revision of Essential Requirements of Infant Formulae and Follow-on Formulae (23) with Berthold Koletzko, Olle Hernell, and Dominique Turck as working group members (24), impacted substantially on the revised Codex standard that followed.

THE ESPGHAN COMMITTEE ON NUTRITION FROM 2005 AND ONWARDS

The CoN evolved in a number of ways from 2005. Whereas in the early days, the Committee was instrumental in driving the development of nutritional recommendations and setting compositional standards for infant formulae, these roles have been taken over by regulatory bodies such as the European Food Safety Authority (EFSA). Set up in 2002, following a series of food crises in the late 1990s, EFSA was established under the EU General Food Law (Regulation 178/2002) which created a European food safety system in which responsibility for risk assessment (science) and for risk management (policy) are kept separate. EFSA is responsible for the former area, and also has a duty to communicate its scientific findings to the public. The EFSA Panel on Dietetic Products, Nutrition & Allergies (NDA) is responsible for issues related to infant and child nutrition, including providing scientific opinions on nutritional requirements, the compositional requirements for infant formulas, complementary feeding and assessing health claims for nutritional products. While participation in the NDA Panel and related working groups is by individual invitation, many current and former members of the CoN have participated or continue to participate in EFSA activities (Fig. 8). Notwithstanding the changing regulatory climate, the CoN has maintained its high level of productivity, publishing 16 position papers or comments on topics ranging from infant feeding to nutritional issues in older children, including obesity and clinical nutrition (Table 1). As in previous years, many of these papers have had a considerable impact on clinical practice and public health across Europe and beyond. Indeed, 3 papers are categorised as “highly cited” by Web of Science (in the top 1% of papers in their field): vitamin D in the paediatric population (2013; 45 citations); enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition (2010; 254 citations); and Complementary Feeding: a commentary by the ESPGHAN Committee on Nutrition (2008; 285 citations). The impact and influence of these papers is testament to the combination of a systematic approach to reviewing the literature with the collective knowledge and experience of CoN members, resulting in a scientifically rigorous and yet pragmatic approach to each topic. This is particularly important since, as recognised by committee members in the late 1980s and early 1990s, for many areas of infant and child nutrition the evidence-base is still somewhat limited in quality and quantity. As discussed in the Committee’s 30th anniversary paper (1), the format of Committee papers—specifically whether they should be narrative reviews or formal systematic reviews—is an issue of ongoing discussion, which is particularly relevant since many topics in the field are not suitable for formal clinical guidelines. The consensus of CoN members is that a combination of literature review using a systematic approach with narrative review and expert opinion remains appropriate for many topics.

The fact that the CoN no longer has a primary role in regulatory aspects of nutrition has enabled it to expand its focus on other areas, such as highlighting ongoing dilemmas and uncertainties in the field including the design, choice of outcomes, and

statistical analysis of trials in infant nutrition with a recent position paper on attrition in long-term follow-up studies (25). It also has increasing involvement in influencing the research agenda in paediatric nutrition, including participation in EU platforms on Healthy Diet & Healthy Lifestyle; and Obesity.

Over the last 10 years, a number of nutrition working groups and special interest groups have been established under the auspices of the CoN which allow a wider group of ESPGHAN members to participate and to produce guidelines and position papers in specific areas. Current working groups cover Clinical Malnutrition; Infant Nutrition Research; Pre and Probiotics; Newborn Immunity, Gut and Brain (NEOMUNE); and, following on from the earlier commentaries on Core Outcomes in Nutrition trials, COMMENT. The objective of the latter working group is to identify and agree on core outcome measures for use in infant nutrition research projects, with the eventual aim of facilitating the pooling of trials in systematic reviews and meta-analyses. To date, 4 papers have been published by these working groups (Table 1). In addition, Committee members increasingly participate as representatives in working groups under the auspices of other ESPGHAN Committees, producing joint papers on topics such as nutrition in children with cerebral palsy; updated guidelines for the introduction of gluten; and jejunal feeding. In collaboration with the European Society for Clinical Nutrition and Metabolism (ESPEN) and European Society for Paediatric Research (ESPR), the CoN has coordinated a revision of the guidelines for parenteral nutrition in infants and children, originally published in 2005.

EDUCATION AFTER THE CREATION OF THE STANDING COMMITTEE ON NUTRITION IN 1986

Immediately after its creation in 1986 the Committee Secretary started to organise high-quality symposia at annual meetings. The committee appreciated that there was a need to enhance the expertise in nutritional research both within the society and more widely. It took the opportunity to foster nutrition and metabolic research among young members and, for that matter, other members of ESPGHAN. Now the CoN designs the scientific programme for nutrition at the annual ESPGHAN meetings; currently running 3 scientific symposia plus a keynote lecture and clinical practice session. The latter, introduced at the 2014 annual meeting in Jerusalem, has proven extremely popular, providing a more practical approach to nutrition issues including breast-feeding, complementary feeding and feeding disorders; and complementing the scientific sessions.

In 1991 Peter Aggett and Ferdinand Haschke organised a Summer School on “Methodology in nutritional and metabolic research” at La Tour de Peilz, Switzerland. This was a valuable exercise in pre-competitive co-operation between industry, some national government initiatives, and the society. Industry clearly appreciated the potential benefits of having available in the community of paediatricians, some who were well trained in nutritional science and in the essential skills of metabolic and nutritional research. The course was a great success, largely thanks to the quality of the faculty; many of the participants established collaborations with well-founded and internationally recognised research groups in North America and Europe, and have become prominent investigators in their particular fields thereby raising the standards of nutrition within the society. There followed a series of Summer Schools, “Physiological and Metabolic Foundations of Infant Feeding” (Warsaw, Poland 1992; Organizer Jerzy Socha), “Lipid Metabolism and Nutrition” (Irséi/ Munich, Germany 1993; Organizers Berthold Koletzko, Olle Hernell, and Kim Michaelsen) to mention the first in a long series. The Nutrition Summer Schools now take place every 2 years. In addition to providing education on broad aspects of infants and child nutrition and related research, these courses offer a unique opportunity for young colleagues to interact with Faculty; indeed many current CoN members were students at one of the schools. Recent summer schools have taken place in Ameland (The Netherlands, 2011), in Prague (2013), in Cambridge (UK, 2015), and, most recently, in Bari, Italy (2017) (Fig. 9). As a result of receiving support from the ESPGHAN EPP
and from UEG, the CoN was able to offer greatly subsidised fees for attendance at the 2015 and 2017 schools, increasing the opportunity for young trainees to attend from all over Europe and beyond and greatly increasing the number of applicants.

The level of demand for educational activities in the field that is apparent, and the availability of funding from the EPP, has prompted plans to increase the number of such activities with the aim to hold at least one more specialised Nutrition Masterclass annually; to date, topics have included Parenteral Nutrition in the Intensive Care Unit and Clinical Trials in Paediatric Gastroenterology, Hepatology & Nutrition. A further recent initiative instigated by the CoN is to assist the development of nutrition research in Africa. Building on ESPGHAN-facilitated courses run 2012 to 2015 in South Africa with students attending from a variety of African countries, the aim of the initiative is to provide basic training and guidance in simple research methods with initial work focussing on complementary feeding.

COMMITTEE GOVERNANCE AND TERMS OF REFERENCE

Improved governance of the society and the need to rejuvenate the CoN as well as the other standing committees of the Society has become increasingly important especially given the global move towards greater transparency. In the late 1990s, in part at the instigation of the CoN, and as a result of the formation of other Standing Committees and Working Groups, ESPGHAN Council started to formalise the accountability and governance of its working groups and committees. ESPGHAN set specific rules for the Terms of Reference, skill portfolio, and duration of committee membership, including that of the Chair and Secretary. This also provided an opportunity to review the achievements and challenges that the CoN had experienced since its inception in 1986.

The standing CoN specified its terms of reference or mission statement as promoting child health through good nutrition by:

- Writing and publishing authoritative commentaries of clinical and scientific relevance on pertinent questions in the area of paediatric nutrition in health and disease,
- Providing advice on matters related to paediatric nutrition to ESPGHAN and other scientific societies, regulatory bodies, non-governmental organisations, industry and other interested parties,
- Contributing to the exchange of scientific information in promoting high-quality research and training in paediatric nutrition by organising workshops and scientific meetings, training courses, and other suitable approaches, and
- Providing guidance on teaching in paediatric nutrition, the organisation of nutritional care and education, practical approaches to nutrition, the quality of nutritional products and their use and other questions of relevance.

Producing high-quality position papers and comments relies on the ability of the Committee to attract suitably experienced and enthusiastic colleagues. Members can now serve for a maximum of 6 years, renewable once, to ensure a supply of new ideas and perspectives. The need to provide a future supply of suitably trained colleagues who value the work of the Committee and who wish to participate links to another essential component of the Committee’s work—educational activities.

The potentially wide impact of Committee papers necessitates a rigorous and transparent approach in the conduct of the committee’s affairs. This has been aided by the agreement in 2014 of the new ESPGHAN Code of Conduct, which provides specific guidance to both members and committees, especially regarding sponsorship and relationships with Industry. Further progress has been made by the founding in 2015 of the Educational Partners Programme (EPP), initiated by Berthold Kolletszko as a result from the ESPGHAN Code of Conduct, in which industry partners who wish to support the educational ventures of the Society contribute to a central fund which is then administered by Council to support selected activities.

PUBLIC AFFAIRS

This paper has outlined how the CoN historically had a major influence on infant and child nutrition practice and research via its societal papers, educational activities and by its presence at the CODEX (described previously). All of these are ongoing. In addition, with the formation of the ESPGHAN Public Affairs Committee in 2014, there is greater emphasis on raising the profile of the Society, especially in terms of lobbying for greater European Investment in research in the fields of paediatric gastroenterology, haematology, and nutrition. This initiative has some urgency given the low priority given to paediatric research in the EU Horizon 2020 programme to date. The Committee is also represented on EU platforms (eg, Diet, Physical activity and Health Lifestyle), offering further opportunities to provide input to EU policy and funding decisions.

THE FUTURE

Training in paediatric nutrition is still lacking in many settings. This is an important issue for CoN given its reliance on a supply of suitably trained and experienced colleagues, ideally covering a range of disciplines (not all gastroenterologists or neonatologists, for example). One arm of this undertaking should be to develop standard curriculums and clinical guidelines across Europe and to continue to promote the building of nutritional support teams. A second aim is to promote increased funding for infant and child nutrition research within the EU. Appropriate interaction with Industry will continue to be an important issue, both in terms of the exchange of scientific information and Industry support for ESPGHAN’s educational activities.

Although progress has been made in many areas of paediatric nutrition, there are still important gaps and issues, for example, relating to lipids, proteins, amino acids, micronutrients (especially iodine) requirements, and nutrient and food additive risk assessments. Thus, the CoN will continue its important role in writing commentaries and systematic reviews and revising guidelines when required to inform and stimulate discussion among colleagues.

REFERENCES

Chapter 8. 50 Years of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN): Captivating Witness Reports of a Success Story

ABSTRACT

Since the conception of an idea of a few paediatric gastroenterologists in Europe to create a society for Paediatric Gastroenterology in 1967, and its foundation in 1968, half a century has passed. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) now celebrates its 50th anniversary and its utmost success in combining clinical and scientific expertise in the fields of paediatric gastroenterology, hepatology, and nutrition. To describe this success story 14 of the still living presidents of ESPGHAN recount their impressions of the steady growth of ESPGHAN with all the historical facets from their own points of view. This historical view of ESPGHAN over the last 50 decades provides personal accounts of the development of all activities and creations of this great European Society. The Society started as a small family of experts in the field into a global working open society involved in a large variety of activities within the subspecialties, becoming a leading organisation in Europe and beyond. This unique view provides a wonderful insight into the famous clinicians and researchers from all over Europe who have helped in the growth and development of ESPGHAN. By describing all these activities and collaborations it becomes clear that this astonishing pan-European enterprise was achieved by people who put considerable effort and time into the development of this society. Their statements serve as a historical source and reference for future evaluation of the first 50 years of ESPGHAN. In depicting different time episodes, and by assembling all the historical pieces of a puzzle together, the statements help to illustrate how a highly structured society such as ESPGHAN has evolved over the last 50 years, for what it stands for today and what is to be expected in the future.

Key Words: ESPGHAN, 50 year anniversary

(JPGN 2018;66: S154–S171)

Raanan Shamir

Current President (2016–2019) (Fig. 1).

It gives me great honour and pleasure to write the introduction to the ESPGHAN Presidents’ statements that are published as part of the 50th Anniversary celebrations of our organisation.

This article provides an insight to the life of our Society from the days of its creation and carries with it the memories wishes and achievements of many individuals that worked with devoted teams and a family of members to bring ESPGHAN to where it stands today.

From ESPGA to ESPGAN and lastly ESPGHAN, we have become a large organisation that encompasses full members, young-trainee members, corresponding members, allied health professional (AHP) members, emeritus members, and low-income countries members. Together, this group, reaching soon more than 900 members is part of a complex structure (Fig. 2) that not only represents paediatric gastroenterologists, nutritionists, liver experts and AHP in Europe, but also has active members worldwide with an annual meeting that, in 2016, brought together delegates from 103 countries.

With so many functions and activities it is important to stop for a minute and reflect on our history. When reading through the various reports one learns to appreciate the long road, we have taken and the huge achievements of individuals, committees, groups, networks, and the all ESPGHAN organisation over the years. This is nicely illustrated by the first report by Jean Rey who was the President from 1977–1980. It helps us meet the founding members that created this society 50 years ago and how this all came to life at the first meeting in 1968. The pivotal role of celiac disease in ESPGHAN returns in a few statements, reminding once again the importance of European scientists in establishing the role of gluten...

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in causing celiac disease when American journals found it impossible to believe that bread is related to celiac disease, leading to multiple European publications and to the first paediatric diagnostic criteria (the 1969 Interlaken Criteria). Reading through we realise how important ESPGHAN was and is in establishing nutrition guidelines and reinforces our position as the representative body of Paediatric Gastroenterology, Hepatology and Nutrition (PGHAN).

Currently ESPGHAN has an Executive Committee (President, Secretary, and Treasurer), a council (Executive Committee, Past president for 1 year or President Elect, Education Secretary, International Affairs Representative, Scientific Secretary, Chairs of the 3 Committees, Gastroenterology, Hepatology, and Nutrition), Chair of the Local Organizing Committee of the next Annual Meeting, Chair of the Young ESPGHAN Committee and the Chair of the AHP), and multiple active working groups. Some Committees (International Affairs, AHP, and Young ESPGHAN) are represented in Council and some (Ethic, Finance, History, National Societies, Public Affairs, and Publication Committees) report to Council and we are all in debt to the huge voluntary work of all individuals. Now that we have an active website (www.espghan.org) all individuals working for ESPGHAN can be found there including their specific role. Finally, in addition to a European Editor and Editorial Board for our Journal, we have an e-learning editor and growing e-learning activities.

As the current president, most of the actions that brought us to where we are now can be found in the various reports. This history brought us to be a Society with more than 900 members, having more than 20 very active working groups and special interest...
groups and our vivid Society continue to have the largest Annual meeting in PGHAN and in the last Annual meeting (Prague 2017) we had a record attendance of 4770 delegates from 96 countries.

I would like to add that our vision is to reinforce ESPGHAN’s position as the leading organisation for clinicians, educators, scientists, and health care professionals in Europe and beyond. In parallel, we are committed to continue and assist ESPGHAN committees, working groups, and individuals in achieving their goals, while maintaining the family spirit of our organisation.

ESPGHAN should continue to be a worldwide leader in the field of PGHAN, to increase the membership base and be the voice of all professionals in PGHAN in Europe and beyond and to help our journal improve its scientific value and impact.

ESPGHAN will continue to strive for high-quality education and dissemination of knowledge, setting the best clinical standards and guidelines and promote high-quality paediatric research in the fields of gastroenterology, haematology, and nutrition. This should include basic, translational, and clinical research. We should act with European Union scientific and regulatory bodies to set the research priorities and facilitate them. With the help of all members, we should continue to be the source for clinical guidelines and provide updated education material. We will work to ensure that anyone interested in having a voice, will be heard while structuring our guidelines.

The main role of ESPGHAN is to improve the care of children with gastrointestinal, nutritional, and liver disorders. I am proud of being an ESPGHAN member and humbly hope that I can steer this boat to even larger achievements in years to come and hope that ESPGHAN members and all paediatric gastroenterologists, nutritionists, and liver experts will find time to read and reflect on this publication since history is the best guide for planning the future.

Jean Rey, France 1977–1980

(Fig. 3)

The European Society for Paediatric Gastroenterology was born in Utrecht in 1967 from a common initiative of Dolf Weijers (Netherlands) and Bertil Lindquist (Sweden). I met Dolf in Paris in 1963 during a meeting where I was presenting a report on coeliac disease. He invited me in Utrecht to discuss the methods we had developed in Paris to study and treat these children, methods largely inspired from Weijers and Van de Kamer papers. We spent 2 or 3 days examining several of my cases and discussing the interest of intestinal biopsy they had not yet used. Weijers’ conclusion was “You may come as much as you wish in our laboratory and consider which methods you would like to use in Paris.” That year I spent a week in his home and later on I returned to Utrecht every year, alone or with my wife Françoise.

As you know it is Dolf Weijers, who in the 50s with Jan van de Kamer, a pharmacist with a vast knowledge in musicology, had demonstrated the harmful effect of gluten in this disease. As an anecdote, I recall that the first paper submitted to an American paediatric journal was refused as it seemed unthinkable to the reviewers that bread could be responsible for the disease. This is why all their later publications (except one 10 years later in Paediatrics asked by this prestigious and faulty journal) were published in Acta Paediatrica Scandinavica (1).

Dolf used to take days off the hospital to guide us through Holland, to chat, to drink Sherry at 5 pm—“its Sherry time”—he used to say before having dinner with his wife Carla and their 2 daughters. The family visited us in Paris at our home, in a hot month of May. We spent together 2 or 3 days in Burgundy. During these trips and meetings together he talked to me of his project of organising a yearly meeting of paediatricians interested in gastroenterology from all over Europe. He had also submitted this plan to Bertil Lindquist. Bertil was in charge of writing the Constitution of this new Society, the European Society for Paediatric Gastroenterology (ESPGA). I had to organise the first meeting in Paris in October 1968. Nutrition and haematology were out of the focus of ESPGA, even though we had interests in these matters.

Bertil Lindquist insisted that paediatricians from Eastern Europe—it was the time of cold war—should be invited at this first meeting, and colleagues from Hungary and German Democratic Republic could attend. I will always remember Kerpel Fronius from Budapest who recited in French large extracts from Anatole France to Françoise before kissing the hollow of her elbow! The idea of the meetings was to exchange in the most informal way possible, as Dolf and I did, and to try to make progresses in this new discipline. I went myself several times to Lund in Bertil and Anna-Brita’s family and he spent 2 weeks at our home to improve his French, but his progresses were limited to say “Monsieur Guillotine” (the French anatomist who invented the guillotine) every morning while cutting his boiled egg.

ESPGA was the first European society of paediatric subspecialty to be founded, before the societies of nephrology, endocrinology, and others. However, it had been preceded by the European Club of Paediatric Research, which later became the European Society for Paediatric Research (ESPR) founded by Pierre Royer (Paris), Ettore Rossi (Bern), Andreas Prader (Zurich), and other famous paediatricians. In fact, we had a first common meeting of ESPR and ESPGA in Interlaken in 1969. It is in Interlaken that the first diagnostic criteria of coeliac disease were worked out.

Dolf Weijers was the President, Bertil Lindquist the Secretary and we used to meet in Holland at Dolf’s house with Charlotte Anderson (Melbourne, then Birmingham) for the first meetings of the executive Committee of ESPGA. Dolf had insisted that the Society organise a session on paediatric gastroenterology during the coming meeting of the International Paediatric Association (IPA) in Vienna in 1971. However, shortly after, Dolf Weijers had a severe myocardial infarction complicated by a few weeks long coma. He was slowly recovering and we had regular phone calls in English—he spoke French very well but used to say that conversation was easier in English for him. We had planned to meet in Utrecht in early June 1972. The day before my departure I learned he had

FIGURE 3. Jean Rey.
suddenly died while painting the door of his garden. I spent 3 days in his family until his funeral. I was the only ESPGA member attending the ceremony.

As President, I had the occasion to remember these memories during the ESPGAN meeting in Utrecht (our logo had been enriched by an N after the 1974 meeting when Bertil Lindquist founded the Nutrition Committee and proposed this new name). It was in 1979. Half of the audience had known Dolf and mourned during my talk recalling Dolf’s qualities, his intelligence and his understanding of others. At that time, we were a small group nearby Bertil Lindquist: Charlotte Anderson and Sandy McNeish, Salvatore Auricchio and Armindo Rubino, Jamo Visakorpi, Beat Hadorn, Eberhard Schmidt, Ann Ferguson, and John Harries, who left us too early. This group was in some way the soul of ESPGA, then ESPGAN.

The Nutrition Committee used to issue guidelines (1977–1981), which still form the basis of European and international rules for infant food. We were all or nearly all able to discuss the various items during our early meetings. May be we knew nothing about everything. Time passing, with increasing specialisation, only few people still can take part in all discussions. In a certain way, young members know everything about nothing. Long life to ESPGHAN.

Jarmo Visakorpi, Finland 1980–1983

(Fig. 4)

As the fourth president of ESPGHAN, in 1980–1983, I have been invited to write my memories of the time of my presidency. However, my memories from that period are rather scanty partially therefore that my own academic interest on that time was quite different than research and gastroenterology.

My main contributions to the society were acting as secretary 1971–1976 and secretary of the Nutrition Committee 1974–1981 as well as organiser of 2 annual meetings, in Helsinki 1973 and in Tampere 1984. In these duties it was easy to learn to know personally members of the society and even many invited guests working in the field especially from US sister organisation due to joint meetings. Organising meetings by nonprofessional way with assistance of own team, which was possible on that time when the number of participants was relatively limited, was challenging but also interesting and gave familiar feelings to the meetings. Therefore, networking of European paediatric gastroenterologists was very close from beginning, even without Facebook.

During my presidency in the early 1980s the growth and development of the society were quite steady, since beginning the number of members was doubled and the number of admitted papers increased even more. Therefore, the poster sessions were included in the meeting program in Madrid 1982 according to the model of joint meeting with ESPR in Berne in 1981. Reviewing the admitted papers for oral and poster presentations became more and more difficult task for council members. Especially difficult was this process when handling papers coming from eastern European countries, which we otherwise wanted support in research according to our objective of “missionary” function presented often strongly by Bertil Lindquist.

My really strong memories on ESPGA, which was the original name of society, are, however, bound to the early years, may be therefore that my own research activities with a group of young and active colleagues, Kari Launiala, Pekka Kuittinen, and Erkki Savilahti, all later ESPGA members, started in Helsinki at about the same time during 1960s. We were studying malabsorptive diseases, including coeliac disease, but we had no plans to develop a new subspecialty. I had also rather early 1 international contact: Bertil Lindquist, who became my mentor for whole my career and close friend also at family level. He connected me also by many ways to the activities of ESPGA.

The main topic in the second annual meeting of ESGA in 1969 in Interlaken, Switzerland, was panel discussion on coeliac disease and especially the diagnostic criteria of it. The idea of this program was launched by our first president Dolf Weyers, whose own research career was based as a member of the team of W.K. Dicke on study of this disease. He invited me to prepare this panel discussion by conducting an international inquiry concerning the topic of the planned discussion. The results of this inquiry showed clearly that some kind agreement on coeliac disease concerning both diagnosis and treatment was on that time really needed. The conclusions of this panel meeting gained great popularity and they become known as the “Interlaken Rules.” The knowledge of these rules spread also among the gastroenterologists for adults, for example, Sir Christopher Booth organised similar discussion at the 2nd International Coeliac Symposium in Leyden at 1973.

Although Interlaken criteria were well accepted, the development of research in this field has required continuous follow-up. Therefore, several follow-up round-table discussions and committees have been organised during the whole 50 years existent of ESPGA/ESPGHAN and will be certainly organised also in future.

The name of the society was changed at 1976 by adding the word nutrition in the title. Thus, ESPGA became ESPGAN. This was strongly supported by Bertil Lindquist, the president on that time, who was also one of the main persons creating the society. By his suggestion a committee on nutrition was established in 1974. I was invited to be secretary of this group obviously therefore that I had good connections to Bertil, although I did not have any scientific basis in nutrition. This became a real demanding task for next 7 years including 20 committee meetings mainly in central Europe and writing recommendations, which led to 3 supplement publications in Acta Paediatrica Scandinavica (2–4) on recommendations of compositions of different types of infant formulas and additional food as well as infant feeding in generally. After this committee a new one was appointed in 1981, during my presidency, for creating guidelines on enteral feeding of low-birth-weight babies.

I think that ESPGA was established just in right time in late 1960s for supporting the establishment of paediatric gastroenterology in Europe. Earlier according to a common belief, GI diseases such as diarrhoeal disorders, including coeliac disease, prolonged vomiting, and the like were essential part of general paediatrics. Development of new methodology for clinical investigations such as small intestinal biopsy and fiberoptic endoscopies were the practical motives for establishment of a new subspecialty in the framework of paediatrics following the model of Internal medicine. This topic was not so much discussed during the first years in the

FIGURE 4. Jarmo Visakorpi.
Society because all agreed that the main aim was to develop research. Therefore also basic scientists were invited as full members of the society. But during these first years it became also evident that paediatric gastroenterology is developing as its own subdiscipline, which will be a core substance of the Society.

The plans for the program of the Society were already from its beginning very ambitious. The routine to be a forum for scientific presentations and related discussions was not enough, but it was wanted to see the impacts of scientific expertise in clinical gastroenterology and clinical nutrition. The 2 examples, which I have described above, are good examples of this intention. The discussions and committee work around the coeliac disease have influenced much on the diagnosis and treatment of this disease and the committee work on infant nutrition has contributed much on the nutrition of the children. As far I have been able to follow the operations of the society the same line has been continued and strongly developed.

Alexander S. McNeish (Sandy), United Kingdom 1983–1986

(Fig. 5)

It was with great pride that I took over the Presidency from Jarmo Visakorpi at the end of the Graz meeting in 1983, on the very day of the 50th birthday of our host in Graz, Beat Hadorn. Now, 33 years later, what do I remember? What are my thoughts and feelings about what I continue to think of as “our dear Society”?

It has always been an unwritten but generally known rule that candidates for our Presidency should be active in the science and practice of paediatric gastroenterology, haepatology, and nutrition (haepatology was, rightly, added to the Society’s title after my practice of paediatric gastroenterology, haepatology, and nutrition of the children. As far I have been able to follow the operations of the society the same line has been continued and strongly developed.

FIGURE 5. Alexander S. McNeish.
was held over 2 weeks in Birmingham, UK. Thirty-three delegates were selected from over 70 applicants. The feedback was positive, and Council embraced the concept of Summer Schools. [It is noteworthy that all the arrangements necessary to organise and present the course were made at the desk of my splendid secretary, Mrs Janet Garlick.] At the completion of our course, I thought naively that we in Birmingham may consider repeating the exercise in, perhaps, 3 years’ time. I completely underestimated the drive and ingenuity of future Presidents and Councils in steadily driving forward postgraduate education and training for health care professionals to the stage where, in 2015, the ambitious ESPGHAN Education Partner Programme has been launched, with multiple sponsorship. Again, I extend my congratulations to all concerned.

With hindsight, the growth of ESPGHAN was predictable. The burgeoning of modern science, which cross cuts any organ, system, or clinically based definition of a subject, has made this inevitable. In addition, the exponential growth of our educational activities, frankly astonishing in their scale to my eyes, has been truly remarkable. Our converts now number in thousands. This has meant, however, that the Annual Meeting has become more impersonal. The friendships within the Society that were, and are, so valued by members of my generation, are, I suspect, more difficult to make and retain—but seeking them will be as important as ever.

I should like to add a few words about colleagues who were contemporaries, and who were, and are, “le vrais ESPGHAN” to me. I served as Secretary under 3 great Presidents: Bertil Lindquist, Jean Rey, and Jarmo Visakorpi. I learned so much from them-collectively they taught me to be a European. As some know, I also slept once with Jean Rey, but that is another story. Two Secretaries, Armido Rubino and Jacques Schmitz, supported me unsparingly and did not hesitate to tell me when I was wrong. Council members Birgitta Strandvik and Sammy Cadranel, deservedly progressed to lead our Society. I am fortunate to have retained their friendship. Salvatore Auricchio followed me as President, but I have always thought of him as my senior—a great scientist and a true friend.

This leaves 2 names, both dear friends, who never held office in our Society but who both influenced us all greatly before dying young (far too young): John Harries (1935–1983) and Anne Ferguson (1941–1998). I have written about John previously. A young giant of paediatric gastroenterology, we remember his science, his superb mentorship of trainees, his infectious friendship and his superb Welsh singing voice. With the death of Anne Ferguson at the tragically early age of 57, medicine lost a remarkable intellect and a major star in clinical research in gastroenterology. A gut immunologist and adult gastroenterologist of international distinction, she attracted research fellows from every corner of the world. Her early animal studies in cell-mediated immunity proved that immune reactions in the gut could produce severe enteric damage. In Edinburgh, Anne developed what was her greatest professional skill, of investigating directly in her patients the concepts generated by her basic research and using the results to formulate new diagnostic methods and therapies for their benefit. She travelled widely, and was in constant demand for her lectures, which she delivered without notes and with a restless energy and infectious enthusiasm. Somehow she found time to co-host with me our (I believe successful) Annual Meeting in Edinburgh in 1986. She even arranged for the sun to shine throughout the Meeting in what can be a grey city. Most of all, in the present context, Anne loved ESPGHAN and we loved her.

In conclusion, I can only hope that the reader may detect in these few words the affection which I continue to feel for our dear Society, and the wish that I have for its continued good fortune in the next 50 years.
Chairman. At the 1988 AGM in Copenhagen on behalf of Jean Rey, ESPGHAN President. On that occasion Jean Rey was acclaimed at the Edinburgh AGM in 1986, by A.S. McNeish, the then significantly to the organisation of the new ESPGHAN activities and to the contribution of the Secretary Peter Aggett. It contributed significantly to the organisation of the new ESPGHAN activities and to the atmosphere of warm and fruitful relationship between the ESPGHAN council members. This committee was officially established at the Edinburgh AGM in 1986, by A.S. McNeish, the then ESPGHAN President. On that occasion Jean Rey was acclamed Chairman. At the 1988 AGM in Copenhagen on behalf of Jean Rey, Chairman, Peter Aggett presented the members of the committee (Ferdinand Haschke, Willi Heine, Olle Hernell, Kari Launiala, Armido Rubino, Gerhard Schöch, Jacques Senterre, Ramon Torno, and Peter Aggett as Secretary). He described the role of the Committee as follows:
- to give advices for future main topics in nutrition for annual meetings,
- to issue short "state of the art" papers or "editorials" that would present the position of the Society on "hot topics" in Paediatric nutrition,
- to organise Summer School in nutrition, alternating them with similar schools in gastroenterology.

This program was effectively realised and the Committee published various important reports.

As a matter of fact, the ESPGHAN birth was due to a series of studies in the 1960s mainly on malabsorption syndromes, with the identification of different forms of congenital and acquired defects of the digestive and absorptive functions of the digestive system. Our knowledge at that time on the molecular basis of these functions was quite scarce. That was a fruitful period, in which the clinical studies paved the way to basic studies, increasing our knowledge in this new field of gastroenterology. The ESPGHAN members were very close to each other thanks to common interests in research and to friendship: the ESPGHAN indeed, during the first years, with a limited number of members, was essentially a club of friends sharing common scientific interests.

The following developments of gastroenterology, and in particular the influence of the knowledge acquired thanks to the techniques of "adult" gastroenterology, together with the growing number of members, led to the creation of a larger society of Paediatric Gastroenterology, a specialist branch of Paediatrics. However, since the beginning, the importance that the promotion of the research had in the society was very clear and it was the basis for the creation of the working groups. Anyway, I have to say that the ESPGHAN (and more generally Paediatric Gastroenterology) has still a lot to do in this direction. More than 20 years ago, in a booklet realised by the Society in occasion of its 25th Anniversary, I recalled the attention on this: "Paediatric gastroenterology has not enough contact with other areas of internal medicine and basic research, in this respect behaving differently from other society such as the American Gastroenterological Association. The biggest challenge for the future of ESPGHAN is the role of the society in promoting the research in Paediatric Gastroenterology and Nutrition."

Today, as it is well known, the problem has become much more complex; in fact, basic and clinical research is able to produce an enormous amount of results, thanks to the new global approach methods (omics) and to cellular and animal models, necessary to the comprehension of complex biological phenomena. At the same time, the work of the clinical scientist is becoming increasingly difficult. In this context, ESPGHAN is called to give its contribution to these epochal challenges. I am optimistic the Society will be able to continue to play a significant role.


(Fig. 7)

I had the great honour to give my first presentation at ESPGA in Interlaken 1969. I remember it as a very small club and I was young and extremely nervous but very proud to have my paper accepted for oral presentation. I could then not attend for some years because I had to be invited as a guest, since ESPGA was open for
members who at a meeting could bring only 1 guest, expected to present research in the front of gastroenterology or nutrition. Since 1973, I have probably attended all meetings, have served on the Board, and 1989–1992 honourably acted as the first female President of ESPGAN. The late Charlotte Anderson was one of the founders of the Society but unfortunately it took decades until the glass roof was again broken through and yet after 50 years there have only been 2 female Presidents of the Society.

I have especially appreciated the club feeling during the first decades which made the Society grow slowly so all knew each other well and the quality of the presentations as well as the activities was the overwhelming goal; to gain the development of gastroenterology, including haematology and pancreatology, and nutrition. Later also to extend science in Paediatric Hepatology motivated an H in the acronym for the Society. A recent expanding interest in pancreatology has made discussions how this can be included as well. During the latest 30 years working groups gathering about different subjects have grown and expanded, starting cooperation in science, initiatives for summer schools and promoted friendships, and contributed to prevail the old club spirit. These activities have counter-balanced the impersonality the huge present annual meetings express. Personally I feel a little sad that the economic struggles have open up the Society to everyone interested to join. The thousands of attendees at the meetings have of course made it much appreciated that the Newsletter is still living as a separated issue of the journal. However, the informal information was so important of our Society. The decision to start a special journal related to ESPGAN has begun before my presidency and contained several problems. A delicate one was that starting a completely new journal would take long time to get indexed, and it had to compete with many other journals in gastroenterology and haematology, and especially the journal of Paediatric Gastroenterology and Nutrition, which Emanuel Lebenthal had started many years before. I had long discussion with Blackwell Publishers but at the end the Council, and finally the AGM, decided after some agony that it would be better to take over from Emi Lebenthal than start a competition—a decision that John Walker-Smith never has forgiven me, as the acting President, because he absolutely wanted a new journal. The decision to take over the journal from Emi Lebenthal also strengthened the bond with NASPGAN, with which we had started to have common meetings during the leadership of Sandy McNeish. After electing editors for the western and eastern hemispheres to run the journal all contracts were signed and the cooperative work for the journal started officially in the beginning of 1991.

Another important issue was to decide if we should join the United European Gastroenterological Federation (UEGF), which was just to be founded during these years. Gastroenterology had developed rapidly and successfully in Europe and the goal was to start a corresponding federation to the American Gastroenterological Association, which ran the well-known AGA meetings. The idea was to have a yearly meeting comparable to the AGA week, called the UEGW (United European Gastroenterological Week). During several meetings we discussed the format and gradually the UEGF emerged, the constitution being based on that of ESPGAN. The ESPGAN Secretary during this time, Isabel Polanco from Madrid, and I had many meetings and I remember with great affection how nice our cooperation was in the struggle with all the men from the other societies. The first UEGW meeting was held in Athens in September 1992 with a small impact of ESPGAN. Unfortunately, this imbalance has persisted. I gave a presentation at the UEGW in Oslo 1994 and the interest from the attendees representing adult gastroenterologists was great, which indicated that we probably would have an impact. However, in practice the UEGW has to compete with many other subspecialties, which probably has contributed to relatively less visibility of ESPGHAN in the UEGW.

To keep members informed I felt we needed a communication forum and suggested that we should start a Newsletter, written by the President and the Secretary. This idea was approved by Council in February 1990. From the beginning it was decided that the Newsletter should not be delivered until JPGN was fully established as the voice of ESPGAN and then be included in each issue of the journal. However, the informal information was so much appreciated that the Newsletter is still living as a separated message to all members.

The ESPGHAN annual meeting has always attracted researchers from outside Europe and they could be elected members on the basis of the same criteria as the Europeans but called “corresponding” members without the right to vote. In 1988, a Pan Pacific Paediatric Society for Gastroenterology and Nutrition was founded and that started the discussion of extending to triple joint meetings, including ESPGAN, NASPGAN, and PPSGAN. It was suggested that the joint meeting with NASPGAN was to occur
every fourth year and the triple meeting was suggested to occur less frequently, and so it proceeds since many Asians in the field will continue to attend our meetings.

I have been very proud to belong to ESPGHAN and happy to see and to some extent have the possibility to contribute and take part of the development of our Society. Despite my expression of some nostalgia, this should mainly be taken as a sign of the joy and friendship the Society stands for. I hope that the claim for quality will never be in question since the sign of quality will keep our Society in the front line also for the future.


(Fig. 8) «I had a farm in Africa...» Karen Blixen 1937

It was the time of balance studies so brilliantly used by Dicke, Weijers, and Van de Kamer to demonstrate the harmful effect of gliadin in coeliac disease and later by Weijers and colleagues to describe congenital sucrose-isomaltose intolerance; it was the time of the spreading of intestinal biopsy, performed for the first time in children in 1957, and of the elucidation of the structure and functions of the intestinal brush border, of the emerging concept of glucose/sodium cotransport. Among the more than 20 inborn errors of metabolism affecting the intestinal digestion and absorption, 9 had been described between 1960 and 1964. It is in the context of this extraordinary blossoming of knowledge that it was the time of the spreading of intestinal biopsy, performed for the first time in children in 1957, and of the elucidation of the structure and functions of the intestinal brush border, of the emerging concept of glucose/sodium cotransport. Among the more than 20 inborn errors of metabolism affecting the intestinal digestion and absorption, 9 had been described between 1960 and 1964. It is in the context of this extraordinary blossoming of knowledge that the ESPGAN Society for Paediatric Gastroenterology (ESPGA).

At that time, I just had joined Jean Rey’s laboratory (INSERM U 12, J. Frézal, Director) and clinical unit as resident working on dipeptidase activities, then a black box. Jean was friendly enough to invite me, and my wife Françoise, to the historical first meeting of the Society in Paris in 1968. It was so exciting to get to know all the already famous individuals in addition to the 3 founding fathers: Charlotte Anderson, Salvatore Auricchio, Beat Hadorn, who soon after would describe enterokinase deficiency, Jarmo Visakorpi, Gunnar Meeuwisse, and others! This was my first encounter with ESPGA, when I got the virus. Then: first oral presentation in Interlaken, member in 1975 after returning from Robert Crane’s laboratory in Rutgers University (New Jersey), secretary from 1984 to 1988; my life in paediatric gastroenterology was entirely shaped by ESPGAN. This deep involvement was also due to the extremely friendly atmosphere during these meetings. We were young and enthusiastic and it was not uncommon that a member stayed at another member’s home, as ‘‘the founding fathers’’ had done.

It seemed thus normal to me to wish to continue as President to serve ESPGAN as I did with great interest and pleasure as Secretary of Sandy McNeish and Salvatore Auricchio. I presented my candidacy to become President after Birgitta Strandvik at the AGM during the Brussels meeting in 1992. However, that year Samy Cadranel and John Walker-Smith were also running for President. ‘‘After careful consideration, the Council decided to propose a democratic election instead of endorsing one particular candidate.’’ It was the first time that the Society elected its President, usually proposed by the Council and accepted by the AGM. I was elected with a small majority, but democracy worked very well later on.

When I took the presidency, ESPGAN was already a rather large and well growing Society. Membership had grown from 39 in 1968 to 232 in 1993. Number of abstracts received had increased up to more than 250. Workshops introduced after 1982, working groups after 1989 witnessed the vitality of the Society. My intention was to confirm or increase the scientific level and promotion of the Society without affecting his friendly atmosphere.

With regard to promotion, the development of Summer Schools was impressive. After the success of the first ones in gastroenterology in Birmingham in 1990, and in Nutrition in Vevey in 1991, a Summer School was organised by Isabel Polanco, near Madrid in September 1993 with the project of ‘‘learning by doing.’’ A second Nutrition Summer School planned by Berthold Koletzko in 1994 had to be postponed to October 1995 because of funding problems. The first Hepatology Summer School was organised by Deirdre Kelly and Martin Burdelski, in Germany in 1995. Finally, facing the political upheavals of Europe, making Eastern Europe more accessible to us, I proposed to the Council in 1993 to organise Travelling Summer Courses in Eastern Europe to bring ESPGAN senior members close to a local audience. This proposal was enthusiastically received and in 1994 we (Deirdre Kelly, Erika Isolauri, Salvatore Cucchiara, Stefano Guandalini, Jan Taminiau, and I) went to Bialystok (Poland), thanks to the organising proactivity of Hania Szajewska, and to Budapest with the help of Hedvig Bodanski. In 1995, the Travelling Summer School welcomed by Pr Georgescu visited Bucharest but sadly had to cancel the Novi Sad course proposed by Tamara Vukavic because of the escalating and widening conflict in Yugoslavia. The kindness and enthusiasm of our audiences were our rewards.

With regard to our scientific activity, the creation under the impulsion of Hans Büller and Deirdre Kelly of the Research Forum for young investigators was an excellent proposition. It was aimed at bringing together around 20 young researchers from all over Europe to present at length their ongoing work in the presence of Michael Lentze, the organisers and myself during the first Forum held in the Netherlands in June 1994. It was a great success both on the scientific level and for the friendly atmosphere. This Forum was repeated in January 1996 in the same place, organised by the same team, with the same success.
These developments were made possible by the financial support of the industry, MILUPA for the Travelling Course and of NUTRICIA for the research Forum. This support was visibly acknowledged as a response to the concern of some members regarding our financial dependence on NESTLE for our Council Meetings in Vevey.

The scientific quality of our Society was appreciated by adult gastroenterologists, who had welcomed ESPGAN into the United European Gastroenterology Federation (UEGF) in 1991. As President, I served during 3 years as a member of UEGF Council together with our Secretary (Isabel Polanco, then Peter Milla). It was a constant concern for us to convince our members to attend the annual UEGI Week, and to avoid a loss of our identity.

During my presidency, 3 Annual Meetings were organised. In 1993 Birgitta Strandvik welcomed us in Göteborg where the 25th Anniversary of the Society was cheerfully celebrated. The trip to Marstrand and the closing dinner marked by a paper plane shooting were memorable events. In 1994 our 27th Annual Meeting was also the 4th ESPGAN—NASPGN Joint Meeting in Houston Texas. William Klish, helped by Carlos Lifshitz, was our active host. The science was excellent with 2 innovations: a Post-Graduate Course of Paediatric Gastroenterology organised by Bill Balistreri and a state of the art symposium on mucosal biology by Michael Lentze and Bufford Nichols, both well attended. I remember particularly my uncomfortable opening of a rodeo on the back of a longhorn, fortunately very quiet, and the farewell banquet at the fantastic NASA Space Center. Our 29th Annual Meeting organised by Serem Freier was convened in Jerusalem. Prior to the meeting a Postgraduate Course was once again, organised on “HLA from structure to function.” I remember with pleasure the Son et Lumiere presentation within the walls of the old city. At that meeting Samy Cadranel was elected President; the Society was going forward.

Eleven years later I organised the 25th annual meeting in Brussels, which coincided with the election of a new president to succeed Birgitta Strandvik. For the first time in our society, there was an election between 3 candidates: John Walker-Smith, Jacques Schmitz, and myself. Although I was “playing at home,” to my great disappointment eventually Jacques won with only one vote difference. The next election in Jerusalem inaugurated the concept of the candidates presenting their program and I openly pleaded for enhancing ESPGHAN’s influence by promoting fellowships among young researchers from Europe but also from other continents.

In 1981 I had the ballot I was conducting new younger members and this was probably one of the reasons why the president Sandy McNeish proposed me as Council member. Although I was “playing at home,” to my great disappointment eventually Jacques won with only one vote difference. The next election in Jerusalem inaugurated the concept of the candidates presenting their program and I openly pleaded for enhancing ESPGHAN’s influence by promoting fellowships among young researchers from Europe but also from other continents.

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Samy Cadranel, Belgium 1995–1998

(Fig. 9)

To be elected as president of ESPGHAN represents a considerable hallmark on the CV of any paediatric gastroenterologist and I had this honor in 1995, more than 20 years after becoming a member. Since my ESPGAN journey started in 1970, I considered that to be part of such a prestigious scientific society was a must and a privilege and I have been lucky to attend all but one of 46 annual meetings, usually rewarding, sometimes disappointing but always the occasion to meet colleagues who eventually become good friends.

In the early years of our ESPGAN (gastroenterology was considered wide enough to contain all aspects of our specialty) coeliac disease, brush border membrane, mechanisms of diarrhoea were the running high profile subjects of our meetings. At the 1972 Hamburg meeting, we presented an original paper on Campylobacter jejuni, a brand “new” intestinal infectious agent that did not receive any attention and not a single question from the audience or chairpersons.

Very disappointed, we decided to visit Olympus in Hamburg and convinced them to produce a slim endoscope suitable for children. We became the pioneers of paediatric GI endoscopy. The “new” diagnostic tool, rapidly adopted throughout Europe allowed our centre in Brussels to become the first paediatric gastroenterologist with an endoscopy unit attended by many fellows from all over Europe. Only 3 years after, endoscopy was the main topic of the 1975 Brussels-Leuven ESPGAN meeting.

The first workshop accepted by the Council at the joint meeting in Bern 1981 concerned paediatric endoscopy and inaugurated the concept of specific workshops that are nowadays routinely organised but then unauthorised. Michael Lentze’s organising talents saved this first workshop from a programmed disaster. I wish to thank him even after so many years. I was accepted as one of the youngest member (together with Pierre Rodesch and Jacques Schmitz, the former president) and regularly pleaded for introducing new younger members and this was probably one of the reasons why the president Sandy McNeish proposed me as Council member. During those 3 years I learnt how to manage what was then a relatively small but emerging society.

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My presidency was the occasion of important decisions for ESPGHAN’s future: signature of the JPGN contract with Raven Press, participation as one of the 7 founding societies of the United European Gastroenterology Federation (UEGF) and promotion of UEG Week and also joining the European Academy of Paediatrics (EAP). In all these moves, I continued the work of my predecessors, especially Birgitta Strandvik, with whom I share many ideas and, needless to say, friendship because it was not easy to resist the conservatism of some influential members. In the end the success of JPGN, UEGF and to a lesser extent EAP proved we were right.

The 1997 meeting in Thessaloniki was chaired by Sanda Nousia Arvanitakis, who had visited us in Brussels. Her daughter has become a prominent assistant professor in the adult gastroenterology teaching hospital of my University in Brussels. Further happy memories, with the final meeting of my term in Toulouse 1998, chaired by Jean Pierre Olives, a dear friend with whom, since the early years of endoscopy, we had exchanged perspectives. However, the end of my presidency was not the end of action and it was my council that enthusiastically proposed Warsaw 1999 because we were convinced that young Hania Szaejewska would do an excellent job. Together with Dominique Belli, the treasurer, we negotiated the financial terms, insisting in passing contracts at the central level of ESPGHAN (another novelty). No doubt that for the Marriott a payment in Swiss francs in Geneva was more attractive than zlotys (even if the literary translation means “golden”).

Whereas today the role of the president of ESPGHAN can be compared to an orchestra director, with numerous soloists in charge of specific tasks, it was not the case in the 1990s and the president relied mainly on the secretary and the treasurer. Dominique Belli was the treasurer before and also after my presidency. Our understanding was excellent because of the similarity in many of our points of view. I shared my term with 2 secretaries. First Peter Milla, whose experience and perfect domination of his English mother tongue was a notable helpful advantage in a multilingual Council. Peter and myself were also active at the levels of EAP (drafting the criteria for a European recognition of our specialty at the tertiary level) and UEGF where Peter continued as treasurer after his term as ESPGHAN President. Markku Maki, the second secretary of my term was straightforward and well organised and his sound common sense allowed a steady progress in our discussions. I still remember how helpful he was in backing my proposition for a new ESPGHAN logo, the very one we are still using now. I feel very proud of our logo with its playful and joyful simplicity, designed by a famous Belgian graphic artist after my suggestions.

Remembering these events I am aware how faithfully all the members I quote served our Society and, not surprisingly, accomplished great things during their notorious career in ESPGHAN: the presidents Sandy McNelis, Birgitta Strandvik, Jacques Schmitz, Peter Milla, Michael Lentze, Deidre Kelly, Ricardo Troncone, Berthold Kolektzko; the secretaries Markku Maki, Peter Milla, Jean-Pierre Olives and currently my friend Geneviève Veereman; Dominique Belli my treasurer but also the following ones, that I consider as friends Jorge Amil Dias, Alan Phillips and currently Anna Maria Staiano; the successive European editors of JPGN John Walker-Smith, Johan Desjieux, Michael Lentze, gentle David Branski who sadly passed away and to whom I paid regular visits in Israel and Raanan Shamir who replaced him before becoming the current president and, of course Hania Szaejewska, the current editor, who fulfils the expectations we placed in her. I would like also to evoke the names of those who shared my adventures in endoscopy, Jean-François Mougenot and Martin Burdeliski and in the study of Helicobacter, Giuseppina Oderda and Sibylle Kolektzko.

My reminiscences would be incomplete without telling of the narrow escape from the terrible car accident we had in 1997. Coming from Paris Dominique Belli joined me at Roissy airport. We were driving in my car towards Brussels at a moderate speed on the highway when I saw in the mirror a car coming behind me at a very high speed. We were lucky to avoid the collision but my car ended upside down with Dominique on top of me in the passenger seat. Miraculously none of us was hurt but we had to get out of the car through the sunroof. The police transported us back to Roissy and we succeeded in booking a flight to Brussels just in time to reach my home where Peter Milla had just arrived and we could hold the scheduled meeting as if nothing had happened. The next morning, still scared but valiantly we took the train for a business meeting in Amsterdam at ESPGHAN’s service!

Finally, in few words, I happily enjoyed serving ESPGHAN.

Stefano Guandalini, Italy 1998–2001

(Fig. 10)

After serving 6 years as Treasurer, I was elected to the Presidency in Toulouse in the annual meeting of May 1998, at the Fifth Joint Meeting of ESPGHAN and NASPGN (in fact, at the time the North American Society hadn’t yet introduced the “H” for Haepatology in its acronym). I delivered my “acceptance speech” during the gala dinner in an enchanted atmosphere in a cathedral, but the acoustics were less than ideal, so I am not sure anyone heard (let alone remember!) any of my words. One thing however my wife Greta still remembers vividly, as she was sitting at the “Presidents’ table”: a spouse of a former President telling her: “Enjoy these three years: you will always be sitting at the honour table, and after that no more!”

At that time, preparations for the upcoming joint meeting with the 3 other international societies of Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN, the North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition; LASPGHAN, the Latin American Society for Paediatric Gastroenterology, Hepatology, and Nutrition; and APSPGHAN, the Asian Pan Pacific Society for Paediatric Gastroenterology, Hepatology, and Nutrition) were under way as the first world congress, an event going beyond the previous few joint meetings with NASPGN, was

![FIGURE 10. Stefano Guandalini.](www.jpgn.org)
planned to take place in Boston in the year 2000. It occurred to me
that this was going to be a tremendous opportunity to seize in order
to create a permanent organisation that will not only oversee every
4 years the organisation of the world congress, but more: a steady
body, similar to UEGF (the United European Gastroenterology
Federation), producing working group reports, position papers
and timely statements on a global scale, thus maintaining alive
throughout the 4 years in between congresses a vivid international
cooperation.

I first presented this vision to the council of ESPGHAN in
February of 1999. Here, on a cold Swiss winter morning in Vevey,
Markku Maki (our Secretary) was open and balanced, but not
enthusiastic as I had hoped; Hania Szajewska was instead quite
cold, as she was of the opinion that a small Society, holding small-
scale meetings, was more conducive to exchange of ideas and
projects, and we were risking losing this when embracing such a
larger audience and scope; a position held by others as well. But I
persevered, being convinced that the times of our small, closed
circle of illumined people were gone, and we needed to open the
doors and be ready to more intense comparison and collaboration
with the rest of the world. Eventually I did get the council’s
endorsement, and was thus ready to export the project of a Federa-
tion to my colleagues who were at the time responsible for the other
Societies: Dick Colletti for NASPGHAN, Geoff Cleghorn for
APPSPGHAN, Ulysses Fagundes Neto for LASPGHAN. I do
remember Ulysses immediate, warm reception of the idea, Geoff’s
similar positive response (he actually brought me later a bottle of a
really outstanding Australian red wine to convince me that their
great wines had nothing to envy to their Italian counterparts—and
he did succeed!); the Americans (Harland Winter was often with
Dick Colletti since he was the local organiser of the 2000 Boston
meeting) took a bit longer to convince, but once they bought into the
idea, their contribution was instrumental in shaping the bylaws and
detailing all the financial aspects of it.

The years of my presidency were characterised for me by a
lot of travelling: in fact, I was elected in Toulouse in spite of the fact
that since about 2 years I was already living in the USA, to me a
great testimonial of the affection and esteem from the ESPGHAN
membership that I will never forget. But as I was extremely
respectful of the fact that ESPGHAN is a European Society, I
made a point of having each and every one of the council meetings
to be held in Europe. So we met in Geneva, in Rome, in Warsaw.
Warsaw, in 1999, was going to be double first: for me, the first
congress as President; and for Hania Szajewska the first congress as
first President of FISPGHAN, I dedicated myself completely at
making sure this will be a smashing success. Specific committees
were created, leaders appointed and charged with specific tasks, and
progress reports were periodically done and reviewed. Olivier
Goulet was a stellar organiser, and I think everybody who was
present in July 2004 will agree that the congress, probably the
largest ever until then for any ESPGHAN event, went extremely
well and was enjoyed by an impressive variety of international
participants. Among many memories of the event, the one that I
cherish the most to this day is the treat Olivier gave me: to start the
opening ceremony by entering the stage with him aboard his own
Fiat 500!! What a moment! We got a prolonged standing ovation
that still resonates in my ears.

Peter J. Milla, United Kingdom 2001–2004

(Fig. 11)
For me ESPGHAN was a large family who were bound together by good science and enjoyed having fun. Like all families there were differences of opinion but these were in the main settled by friendly but rigorous debate. During the 1990s the society was growing in size and changes were occurring around us so that by the time I was elected President it had become clear that our Society was at a crossroads and some of our institutions needed to change but others did not. My abiding memory of my time as President was that it was a period of great change and most of the changes seem over the intervening years to have stood the Society in good stead. Scientific excellence, good fellowship, and friendship remained the cornerstones but the expanding role and increasing size of our Society resulted in alternative and additional routes being required in our endeavour to develop paediatric gastroenterology, haematology, and nutrition in Europe to the standards of ESPGHAN.

The Need for Change: the days of the close familial society of friends were over. The dramatic and continuing increase in the demand to attend the annual meeting prompted changes that would result in a more open society involving all of the membership and which truly represented paediatric gastroenterology, haematology and nutrition in Europe. The Society’s response for the need for change affected all areas of activity of the society from the President, the election of officers, councilors and members, the provision of a permanent secretariat, as well as to the mode of submission of abstracts to the Annual Scientific Meeting of the Society.

Changes to the Society: It was clear that the Presidents responsibilities had increased markedly both in breadth and complexity since the early days of the Society. To such an extent that the Presidents effective 3 year term of office was reduced to 2 years by the time taken to understand all the areas of business which now included ever increasing cooperation with NASPGHAN and the rise of ESPGHAN and a World Congress. For the incoming President “to hit the ground running” was now not possible. The obvious solution was to alter the President’s term of office to include a year’s run-up as President elect together with being available to the Council for a year after his term of office to ensure effective hand over. In addition the officers: President, Secretary General, and Treasurer acted as Executive directors to carry out the day to day business of running the Society between Council Meetings. For this I was ably supported first by Jan Taminiau, then, Jean Pierre Olivier as Secretaries, and Dominique Belli as our long serving Treasurer. It was great fun and increased our friendship. Without them the changes to the society required that I now relate would not have occurred so smoothly.

The Society’s Officers, Councillors, and Members had from the earliest days always been elected at the Annual General Meeting held during the Annual Scientific Meeting of the Society. Usually only one-third at most of the membership attended. This meant that the majority of the Society, as dictated by the Society’s constitution, did not take part in making major decisions concerning the Society. This was not a democratic way of conducting the Society’s business. With the ever-growing society, in order, to involve the whole society and remain within our constitution elections were changed, to be carried out by a postal ballot.

The Committees and Associate Members: The development of specialist within gastroenterology, haematology, and nutrition brought about the Committees of Gastroenterology and Haematology, which were inaugurated in 2004, but development was not restricted to medicine with the growth in some countries in Europe of Nurses and Dieticians with a special interest and expertise in the area. This was largely brought about by the development and growth of nutritional support and a variety of innovative methods that required expertise for them to be successful. Not surprisingly the nurses and dieticians involved felt the need for their own forum and so the Nurses and Dieticians programme as Associate Members of ESPGHAN was born with enthusiastic midwifery from Yigael Finkel, Clare Burnett, and Sarah Macdonald. The Nurses and Dieticians programme became a very much welcomed development and contribution to ESPGHAN’s mission.

A Permanent Secretariat: From its inception the Society had been dependent on the individual Officer’s university departments for administrative and secretarial support. Changes in academic life were making this less and less possible. With the increasing size and complexity of the annual meeting, the growth in size, stature and function of the Society a permanent Society secretariat was required. Eventually after examining a number of different models a tender was put out to companies in the business of Association management and a contract entered into with Colloquium. Industry had supported the development of the Society in a variety of ways both financially and with hospitality. The February Council Meeting since the early years had been generously hosted in Vevey but changes of attitude by governments and NGO’s to the interface between the profession and the medical industry meant that this could no longer continue. The last Council meeting in Vevey was held in 2004 sending a clear signal that the Society was independent of Industry.

Technology had also developed and the rise of the personal computer (PC) had invaded all our lives. The PC made possible data handling which most of us had only previously dreamt of. With the secretariat also came sophisticated electronic means of handling abstracts. Even so, many members of the society preferred to submit their abstracts for the Annual Meeting on paper forms. With the increasing size of the Annual Meeting, by now up to 1500 delegates, submission of abstracts by some electronically and by others on paper forms was making abstract handling cumbersome. Prolonged debates at the AGM resulted in no paper forms for the 2003 meeting and removal of the electronic form by January 2, 2003 made late submission a thing of the past.

JPGN: An important area of change was that involving JPGN. The editors and their editorial teams had worked hard to improve the journal. They were now being rewarded for this by achieving an impact factor of greater than 2. From the time of the Journal’s founder Emi Lebenthal, it was always intended that the journal would be the mouthpiece of both NASPGHAN and ESPGHAN and that eventually it would be solely owned by the two societies; this time was fast coming. The interface that the Societies had with the publisher was far from ideal. In order to improve this we joined forces with our friends in NASPGHAN and formed a joint publication committee to put the Societies points of view to the publisher more effectively. We duly became the owners. Over the recent years we have retained the original publisher so that I believe our negotiations around post ownership changes have been effective.

ESPGHAN and Europe: ESPGHAN as a society was steadily increasing its involvement in European affairs in a number of directions including the UEGF, training via the European Board of Paediatrics of CESP and UEMS, European paediatrics and medicines. The most visible evidence of this was the development of a training syllabus for paediatric gastroenterology, haematology, and nutrition in Europe with notable contributions by John Walker-Smith, Deirdre Kelly, and Peter Milla, which was approved by the EBP and published in JPGN. The existence of a training syllabus and recognised centres for training greatly aided the acceptance in many countries of Europe of paediatric gastroenterology, haematology, and nutrition as a recognised subspecialty. The European Medicines Evaluation Agency (EMEA) of the European Commission recognised the increasing importance of ESPGHAN as the voice of European paediatric gastroenterology, haematology, and nutrition by inviting the Society to collaborate with them in the evaluation of paediatric medicines by its Paediatric Expert Group.
Despite the numerous changes, the expanding role and increasing size of our Society, scientific excellence, good fellowship, and friendship remained the cornerstones. The Annual Meeting still opened with a Welcome Reception at which to meet old friends with a drink in convivial surroundings, dancing was still "de rigueur" at the Farewell Dinner but who knows what the future holds; maybe there will be a return of the ESPGHAN Football Championship or even throwing the Wellington boot!

Michael J. Lentze, Germany 2004–2007

(Fig. 12)

After so many wonderful years of a closed ‘‘family’’ shop, the society ‘‘among friends’’ moved in the beginning of the 21st century more and more into an internationally and globally recognised organisation. Already under the presidency of Peter Milla the milestones for the future development were set and I saw it as the goal during my presidency to extend these footprints together with council into larger future global perspective. It was obvious to foresee that our annual meeting would become larger with extended programs, which led to extensive parallel scientific oral and poster session, workings groups and symposia as well as early morning and late afternoon symposia. The results of these trends were discussed with friendliness, but were often controversial within the council and the AGM when trying to meet the new requirements. Changes in our constitution became necessary in regard to membership. Already 2005 the proposal was made to extend our membership towards nurses and dieticians, which was decided at AGM in Dresden 2006. The election of new members was already decided as a general electronic postal ballot. It was only logical to extend this way of democratic election to the officers of Council as well, and this was institutionalised.

Our relations to industry needed to be rethought. The first step was to hold the annual council meeting, which up to 2006 were held in Vevey, independently on neutral grounds in order to have the liberty for free decisions towards sponsors from industry, which plays an important role for the organisation of our meetings. Thanks to a wonderful council with Jean Pierre Olives as secretary, Jorge Amil Dias as treasurer, Steffen Husby, Andras Arato, Anna-Maria Staiano, David Branski as representative of the GI-committee and Raanan Shamir as representative of the Nutrition committee, we were always able to reach mutual decisions on our ways for future changes in our society.

One cornerstone of our annual meeting was the working groups, discussing various aspects of our subspecialties. The working groups were independently holding meetings within the annual congress or apart from it. After institutionalisation of 2 more committees, that of gastroenterology and of haepatology, in addition to the already 30 years existing committee of nutrition in 2004, the chairmen of these committees became council members for 3 years. The growing number of working groups was allocated to the 3 committees. The working group activities were quite successful. The IBD working group, which was meeting in Porto, were establishing criteria for the diagnosis and therapies of IBD in childhood, published 2005 as ‘‘Porto criteria for IBD.’’ Together with our American colleagues the working group on gastroesophageal reflux disease (GERD) elaborated guidelines of ESPGHAN and NASP•GHAN for the diagnosis and treatment of GERD. The working group of ‘‘acute gastroenteritis’’ together with ESPID published evidence-derived guidelines for the management of acute gastroenteritis in children in Europe 2008.

The 3 committees initiated very well attended summer schools in their subspecialties all over Europe with great success. Many attendants of the summer schools started their career in subsequent years and became well known in academic medicine as prominent members of our society. The Eastern summer schools continued their successful work in Eastern Europe and are now extending their mission globally organising summer schools in the Middle East, Asia, and Africa. As one of the 7 founding sister societies, our relationship with UEGF was becoming an issue while UEGF meeting were growing into very big congresses with more than 10,000 participants. Peter Milla and I were for 3 years attending the committee meeting of UEGF pursuing the interests of ESPGHAN. The impression by our adult gastroenterologist was that the contribution of ESPGHAN was rather limited at their annual meetings. In 2005, Peter Milla and I fought for more representation of paediatric topics at UEGF. Yigael Finkel as representative in the scientific committee of UEGF took the arguments for paediatric gastroenterology, haepatology and nutrition forward into the future organisation of meetings and in subsequent years the input by ESPGHAN into UEGF grew steadily thanks to his hard work and that of the following representatives of our society. Now ESPGHAN is very well represented at UEG meetings with postgraduate courses, symposia, workshops, and e-learning programs.

The issue of ethics in medicine and science was brought up by Sandy McNeish and encouraged by Birgitta Strandvik. Various aspects like collaboration with industry, ethical standards in publishing, plagiarism, and fraud in science were discussed in council and as results the necessity of a Committee on Ethics of ESPGHAN was seen and subsequently decided. Since then the Committee on Ethics became involved successfully in many aspects of our daily society life like in the ethics of publishing as well as in the regulations and relations to industry leading finally into a ‘‘code of conduct’’ put together by Hans van Goudoever.

FIGURE 12. Michael J. Lentze.
After some decades of existence it became obvious that ESPGHAN needed a logo for its recognition value to the public. A logo contest was initiated and among various proposals the one by Samy Cadranel won the contest and since then the “Little Man” in cyan with the curvy gut is recognised very well as a brand of our society on flyers, congress emblems, internet presentations, and letters.

Despite the enormous growth of our society the friendly and familial atmosphere remained in ESPGHAN. The spirit to be among friends, the wonderful annual meetings and the joy to belong to that 50 year old society has never diminished and I am convinced that the future of our society will be as inspiring and sparkling for our subspecialties as the colourful fireworks during the farewell dinner at the annual meeting in Dresden 2006.

**Deirdre Kelly, United Kingdom 2007–2010**

(Fig. 13)

I took over from Michael Lentze, which was a big step and I had very big shoes to fill. Luckily, I had a great Council, with Riccardo Troncone as secretary and Jorge Dias as Treasurer. Raanan Shamir, Annamaria Staiano, Alan Phillips, Alfredo Guarino, Gigi Veereman, Florence Lacaille, Sibylle Koletzko, Dusanka Micetic-Turk, Andras Arato, Yvan Vandenplas, Hania Sajewiska, David Branski and Dominique Turck, all there to help me at one time or another. It was a time of great change for ESPGHAN and we worked hard to create a modern organisation, which maximised the talent in the society and made strong collaborations with industry, national and international societies.

I introduced the annual Council strategy day with our much-loved facilitator, Val Glenny. Although there was a lot of scepticism about the project initially, the time away to allow us to focus on our strengths and think about what to do next was great help in developing our strategy and clarifying our mission to promote care of children with gastroenterological, haepatological, and nutritional conditions through the production of new knowledge and the education of professionals working within Europe and beyond. Our first big task was to change the congress organisation and association management in order to restructure the administration and the governance of the Society. After a competitive tender, we appointed MCI, who worked with us very successfully for many years and I will always have great fondness for our first manager, Maria Phillips and our congress organisers Henry Lushington and Sarah Lawrence.

We also streamlined the rules and regulations for our highly successful committees and working groups and introduced budgets and accountability for their members. A big achievement was the establishment of separate committees for Allied Health representatives and Trainee members and ensuring that they became observers on Council so we could benefit from their ideas and build for our future. The Trainee committee, (now called Young ESPGHAN) headed initially by Ron Brenner is now the largest committee in the Society and a source of most of our new and active members.

We felt it time to honour our long-serving distinguished members, and the first ESPGHAN Distinguished service award was presented to Professor John Walker-Smith in 2010. ESPGHAN has always had a strong reputation for education and building on this tradition, we made partnerships with industry and established a number of overseas postgraduate courses in China, Indonesia, and East Africa, not to mention the successful ESPGHAN Africa diploma course, so well led by Michael Lentze and Jan Taminiau.

Maintaining a clear and ethical relationship with industry was a key priority and we had many constructive discussions and developed guidelines as well as good relationship with our key partners in industry. We also built relationships with other national societies: NASPGHAN, through joint working committees and guideline groups and the joint Publication Committee of JPGN, which successfully re-negotiated a better contract with Lippincott; UEG (much helped by Peter Milla who was the Treasurer of UEGF), EASL, and EPA, through David Branski’s leadership.

These important steps have been strongly consolidated by Bert Koletzko and Riccardo Troncone and it is wonderful to see the development of the Public Affairs Committee strengthening our profile in Europe and the world, making us the influential society we are today. And it was all a great deal of fun, lots of laughs, lots of good times and some wonderful annual meetings with an ever increasing number of delegates, but always the warmth and the friendship for each other which makes ESPGHAN a society like no other.

**Riccardo Troncone, Italy 2010–2013**

(Fig. 14)

I accepted the position of President Elect in 2009 at the end of my term as General Secretary. This has given to me the unique opportunity of being a witness, and to some extent a protagonist, to the life of the Society for a relatively long period. This period has been characterised by rapid growth of ESPGHAN and its arrival on a global scale. This process is still ongoing and it is important to look with great detail to some of its experiences, hoping to better interpret its evolution and to prepare the Society for its next challenges.

The Growth: The Annual Meeting probably represents the most important event in the life of the Society. Nothing more than the number of registrants at the Annual Meeting gives us an idea of the steady growth the Society has undergone in the last decade. That process has had a number of implications, first of all the choice of the venue. Sorrento 2012 was the last meeting organised in a large hotel; since then it has been necessary to hire convention centres.
capable of hosting thousands of attendees. A few know that in Sorrento it was decided that in the last days preceding the meeting to close registration considering registrants had already surpassed the limits of capacity of the structure. The budget of the annual meetings has become remarkable and with it some financial risk to which the Society has become exposed in the case the expected number of participants is not reached. The decision of committing the Society to such large financial enterprises, years in advance, without knowing with certainty if the increase would have been confirmed in the future, was very difficult.

However, the expansion of the Society has caused not only financial concerns, but has challenged the very nature of ESPGHAN. The discussion of the scientific or professional (or even better multiprofessional since the creation of the AHP membership) nature of ESPGHAN had already started in previous years. That debate eventually resulted in a revision of the criteria for membership, with the elimination of the requirement for the new members to have presented at least once an abstract at an ESPGHAN meeting. That change alone has already generated a consistent increase in the number of members, and began to resolve, at least in part, the discrepancy between the number of members (relatively small) and the large attendance at the annual meeting (much more than 10 times the number of members).

The Global Dimension: Another aspect related to this process of growth is the provenience of professionals attending the ESPGHAN annual meeting. The number of those coming from extra-European Countries is impressive, a trend initiated in Istanbul 2010 and confirmed in subsequent meetings. During the period of my presidency the educational offer by ESPGHAN beyond European borders has shown a parallel trend. Examples are the courses organised in Asia (China, Indonesia), and also in Mexico. Of special importance is the attention given to the educational requests coming from Africa. The meritorious initiative, led by Michael Lentze and other ESPGHAN members, that has taken place in South Africa for the benefit of colleagues from the rest of the African continent cannot be forgotten. That is leading to the creation of a group of Paediatric gastroenterologists, that we hope may represent the first nucleus leading to the creation of a continental society, which will help the development of our subspecialty. Going with this momentum a new position on the ESPGHAN Council was created, the International Affairs Council member, to whom the organisation of educational activities outside of Europe has been entrusted. Again, with the intention of favouring the association of colleagues who operate outside of Europe to ESPGHAN, who are interested in participating to ESPGHAN activities, the concept of the corresponding membership, first reserved to paediatric gastroenterologists already members of another society affiliated to FISPGHAN, was revised and expanded. At the same time access (online) to JPGN has been rendered easier.

Beyond these decisions, the increasing global growth and influence of ESPGHAN is evident. A particular example is the prestige acquired by the Nutrition Committee of the Society; the value of the papers produced have in fact led to the general perception of ESPGHAN as the world leader in infant nutrition. The entrance of ESPGHAN on a global scale has also led to an appreciation for our relationships with our North American sister society NASPGHAN. Our most important area of collaboration has been the production of guidelines that have had, because sustained by both societies, an impressive impact (it is sufficient to mention those on gastroesophageal reflux and on constipation).

One other important area of collaboration remains JPGN. The decision to have annual strategic meetings of the 2 editorial committees with the aim of discussing the editorial policy of the Journal has enhanced debate and favored the definition of common strategies.

Relation With Other Scientific Societies: In the years 2010–2013 ESPGHAN has given increasing attention to relations to other scientific societies, NASPGHAN and other FISPGHAN societies having already been mentioned. For strategic importance was the strengthening of our relations with UEG. ESPGHAN is a founding member of UEG and ESPGHAN members, such as Peter Milla our treasurer for many years, have been leaders of UEG. However, the impact of ESPGHAN has not always paralleled its scientific strength. During the first part of this decade our relations have significantly improved. The contribution of ESPGHAN members to the UEG Committees, Scientific Committee (Raanan Shamir, Sibylle Koletzko), Educational Committee (Alan Phillips, Lorenzo D’Antiga), Future Trends (Nikil Thapar), Public Affairs Committee (Gigi Veereman) have been of great impact and very much appreciated. The UEG President was formally invited to the ESPGHAN strategy meeting held in 2012 in Jerusalem. The decision that most tangibly shows how close we have become the with UEG is the choice of Vienna and the House of Gastroenterology as the venue where winter council meetings and ESPGHAN strategy meetings have been taking place since 2013.

Again in the area of relations with other scientific societies of particular importance are those with the National Societies of Paediatric Gastroenterology, Hepatology and Nutrition. Here much has been done, but much more remains to be done. This is important for a Society such as ESPGHAN that aims to become the house of all professionals involved in the care of children affected by gastroenterological, liver, and nutrition diseases. Great progress has been achieved in the educational area with the proposition of syllabi to be adopted in the different European Countries, along with the effort to see paediatric gastroenterology recognised as subspecialty in the Countries where still it is not formalised. And, again, in this educational area of importance are relations with the European Academy of Paediatrics, EAP, the paediatric branch of the UEMS, again in view of rendering homogeneous the teaching programs all over Europe.

Research: The evolution of ESPGHAN to a multiprofessional society does not contradict its main feature that has greatly contributed to its success, its unique blend between friendship and scientific excellence. Production and diffusion of knowledge
remain the mission of ESPGHAN. Special efforts have been made to encourage basic and translational research within the society. With the increased financial availability a significant amount of money has been allocated to awards recognising the scientific merits of members, particularly the youngest, to funds favouring the exchange of experiences, and even most importantly, to scientific networking. In fact, working groups and special interest groups have grown in number and complexity. The Stockholm meeting in 2012 was perhaps the strongest demonstration of enthusiasm and the richness of scientific commitment during my presidency. That year the tradition to not have the ESPGHAN annual meeting during the year of the world meeting was reconsidered due to the amount of requests from members asking that the society meet. This was established on the basis of the activity of working groups, their research and their scientific interests. Thanks to the commitment of Birgitta Strandvik and her colleagues the meeting was highly successful. The Society has further grown since then and this year on the occasion of another world meeting, ESPGHAN will have its second annual meeting. This further demonstrates, if it is necessary, a society that maintains its DNA in the mission of producing and diffusing science in the interest of children affected by digestive diseases.

**Berthold Koletzko, Germany 2013–2016**

(Fig. 15)

It has been a great privilege indeed to serve as president of ESPGHAN—a most impactful European voice on gut, liver, and nutritional health of infants, children, and adolescents, with strong global links and impact. ESPGHAN has steadily become stronger and more active than ever before in the now 5 decades since its foundation. This success is due to the dedicated work of many enthusiastic members. I am particularly grateful for the contributions of the committee and working group members, of the members of the ESPGHAN council which during my term included Mark Benninga, Ulrich Baumann, Lorenzo D’Antiga, Jernej Dolinsek, Mary Fewtrell, Luisa Meairin, Piotr Socha, Yvan Vandenberg, Hans van Goudoever, Gabor Veres, and Nikhil Thapar and for the hard work of the members of the executive council including Sanja Kolacek (secretary 2012–2015), Gigi Veereimens (secretary 2015–2018), and Alan Phillips (treasurer 2012–2016).

Annual Congress: ESPGHAN hosts the largest and most successful congress in the field worldwide, with attendance recently reaching more than 4000 delegates from all 5 continents, which includes a broad spectrum of clinicians, clinical researchers, scientists, AHPs, and trainees. To meet the increasing needs for clinical updates, we introduced in 2014 a new Clinical Practice Track, and in 2015 a new hands-on learning zone in endoscopy (with addition of motility in 2016), both of which have been highly successful. We expanded the use of digital tools such as our interactive congress app for handheld devices, ePosters, the Virtual Meeting Site, and the Website on Demand, to enhance information sharing and convenience for delegates. Since 2015 we are joined by patient and parent organisations with whom we wish to closely collaborate to achieve our goal to optimally support patients and their families. Our members can also enjoy the added privileges of the ESPGHAN Members Lounge and the newly introduced Young ESPGHAN Lounge. With the rapid growth of the congress, the organisational aspect have become more demanding, and hence a new professional congress organisation was appointed in 2015, which resulted in an even more cost effective running of the meeting.

Membership: The criteria for membership were modified in 2014 towards becoming an inclusive association for all clinicians, researchers, AHPs, and trainees dedicated to paediatric gastroenterology, haepatology, and nutrition. As a result, the number of members has markedly increased to now over 900, with a particularly encouraging increase of young members. To meet the demands of a growing and increasingly active society, additional support for professional office management of the association was contracted in 2015.

Code of Conduct: Our council developed the ESPGHAN Code of Conduct and—after consultation with the membership—adopted it in 2015. Our Code of Conduct summarises the ethical foundations of ESPGHAN’s obligation to ensure that paediatricians and allied health care professionals acquire and maintain knowledge, skills, and values that are central to paediatrics and child health without undue bias based on commercial interests. Ethical challenges are addressed that may arise when ESPGHAN members who organise, teach, or serve other roles in medical education have financial relationships with companies that have a direct interest in recommendations. It also illustrates strategies for mitigating the potential of such financial relationships to influence professional education in undesired ways. ESPGHAN’s Code of Conduct also governs the relationship between ESPGHAN and industry representatives involved in the support of research and educational activities in the field of paediatric gastroenterology, haepatology, or nutrition. In addition to identifying the principles of transparency, independence, and accountability, the Code of Conduct also provides a practical approach on how to maintain the independence and integrity of ESPGHAN’s related professional education while promoting a trustworthy relationship between ESPGHAN and commercial companies. It is rather encouraging that our Code of Conduct has since served as a model for similar initiatives of other associations.

Committees, Special Interest Groups and Working Groups: Throughout the year, numerous activities are contributed by the members of ESPGHAN’s main Committees on Gastroenterology, Hepatology and Nutrition, and the many other Committees, Special Interest Groups, and Working Groups. They develop recommendations and guidelines on pertinent issues in the field, facilitate and perform research, and engage in educational and other activities.
We created the new Public Affairs Committee in 2013 to raise awareness for PGHN themes among decision makers, with a particular focus on the European Commission and European Parliament where repeated meetings and events were held to lobby for greater support for child health. The History Committee has been newly formed in 2014 with the goals to compile the history of PGHN and of ESPGHAN, and to build an ESPGHAN archive with records of the foundation of the society, annual meetings and other activities. This publication on the occasion of the 50th anniversary of ESPGHAN in 2018 is a main outcome.

For a number of years, representatives of the national PGHN societies across Europe have met with the ESPGHAN officers at the ESPGHAN Congress to discuss issues of common interest and opportunities for harmonisation. The ESPGHAN National Societies Forum was established in 2015 as a sustainable platform for collaboration and joint activities.

Research Networks and Collaborations Arising out of ESPGHAN: ESPGHAN aims to promote basic, translational and clinical science in PGHN and to enhance financial and other means of support for research, including collaborative and multidisciplinary research. The ESPGHAN strategy on research for promoting child health was formulated and published (7). The strong and active networks of leading experts in different areas of PGHN provide excellent opportunities for scientific collaboration and successful multicentre research grant applications. This strategy has become rather successful as shown by the following examples. The Paediatric European Digestive Diseases Clinical Research Network (http://www.espgan.org/about-espgan/research/paediatric-european-digestive-diseases-clinical-research-network-peddcren/) was established in 2013 with financial support from UEG to form a network of clinical trials for studying and ultimately providing effective medicines for infants, children and adolescents with disorders in the area of PGHN. The European Network Study on Malnutrition and Outcome in Hospitalized Children in Europe supported by the European Society for Clinical Nutrition and Metabolism (www.espen.org) and by ESPGHAN explores the prevalence and effects of undernutrition among 2500 hospitalised children in 12 countries, and it also studies opportunities for nutrition screening. The European Commission (EC) funded the ‘PreventCD’ project (http://www.preventcd.com) which studies the aetiology of coeliac disease and the effects of infant feeding on disease manifestation. The ‘Early Nutrition Project’ also funded by the EC (www.project-earlynutrition.eu) explores long-term effects of early nutrition on later health with a focus on opportunities for prevention of obesity and associated disorders. The EC funded ‘Paediatric Inflammatory Bowel Disease network for Safety, Efficacy, Treatment and Quality Improvement of Care’ (http://cordis.europa.eu/project/rcn/199745_en.html) aims to establish a long term inception cohort of paediatric IBD patients and to perform a randomised clinical therapeutic trial. The European Union-funded regional project ‘Innovative coeliac disease learning model for health care professionals in the Danube region’ (http://www.interreg-central.eu/Content. Node/Focus-IN-CD.html) aims at strengthening knowledge and awareness on coeliac disease among health care professionals and the general public. Many more opportunities exist for successful research activities based on the strong ESPGHAN network.

Education: In 2014, we published an updated European Training Syllabus in Paediatric Gastroenterology, Hepatology and Nutrition to define minimum requirements for training to support recognition as a European Specialist in PGHN, along with a logbook on necessary achievements (8). The ESPGHAN Education Partner Programme (EPP) was launched in 2015 as an up-to-date, independent, high-quality educational programme for health care professionals. It is designed and implemented in full compliance with current professional and Continuing Medical Education (CME) standards and with our Code of Conduct, to promote confidence in independence, integrity and credibility of ESPGHAN and its industry partners. The key target groups include Trainee Members and other young health care professionals (addressed primarily by the ESPGHAN Summer Schools and the Young Investigator Forum), established specialists (addressed by the new Master Classes introduced in 2015 that are open only for ESPGHAN members), as well as health care professionals from less privileged areas (Eastern European Summer Schools, International Schools).

The Way Forward: ESPGHAN needs to continue striving for improving our ability to promote child health, to treat and prevent challenges to digestive health in children and adolescents, and to strengthen the knowledge base that is required to do so. Close collaboration among all health professionals involved in this area, along with patients, families and the many involved stakeholders and decision makers, will be key to achieving our goals. ESPGHAN provides a strong platform and great opportunity for such a fruitful collaboration.

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Chapter 9. Words From Partner Societies


ABSTRACT

On the occasion of the 50th anniversary of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), its close partner associations submitted comments and felicitations which are presented here. These include words from the Latin American (LASP-GHAN), North American (NASPGHAN) and Panarabian Societies (PASP-GHAN) and the Commonwealth Association (CAPGHAN) of Paediatric Gastroenterology, Hepatology and Nutrition, the Federation of International Societies of Paediatric Gastroenterology, Hepatology and Nutrition (FISP-GHAN), the European Academy of Pediatrics (EAP), the European Pediatric Association/Union of National Pediatric Societies (EPA/UNEPSA), the International Pediatric Association (IPA), the European Crohn’s and Colitis Organisation (ECCO), European Society for Clinical Nutrition and Metabolism (ESPEN), the Federation of European Nutrition Societies (FENS), and United European Gastroenterology (UEG).

Key Words: CAPGHAN, ECCO, ESPGHAN, FENS, LASP-GHAN, NASP-GHAN, UEG

COMMONWEALTH ASSOCIATION OF PAEDIATRIC GASTROENTEROLOGY AND NUTRITION

ESPGHAN was formed when I was a medical student, full of medical knowledge but completely lacking in nutritional knowledge. However, I was very aware that hospital patients, who could not look after their own nutritional needs, were dying of starvation. ESPGHAN was not a minute too soon. Later, I spent nearly 2 decades in the Tropical Metabolism Research Unit in Jamaica doing research in and managing young children with severe acute malnutrition. More recently, the scourge of overweight and its consequences, have been occupying us and even our children and throughout the world: but famines and underweight are also still occurring particularly in African and Asian countries where children form the majority of the population. The consequences of malnutrition in surviving children, who are the future of these countries, are lifelong and severe. Thus, thank goodness for the enlightened founders and early members of ESPGHAN who realised that their Society, while advancing interest, research, knowledge, and practice of the closely related topics of gastroenterology, hepatology, and nutrition in Europe, was not enough.

Many Commonwealth and other countries in Africa and Asia suffered and still suffer severe poverty, famines, and childhood malnutrition. Sixteen years after ESPGHAN was founded, in 1984, the ESPGHAN members John Walker-Smith and Sandy McNeil ran a highly successful conference in London on diarrhoea and malnutrition in children in the Commonwealth (CDMCC). This was followed by conferences in Delhi and Hong

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From the CAPGAN, the European Academy of Pediatrics, the ECCO, the EPA/UNEPSA, the ESPEN, the FENS, the International Pediatric Association, the LASP-GHAN, the NASP-GHAN, the PASP-GHAN, the UEG, and the FISPGHAN.
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Kong. At the Hong Kong conference, Commonwealth Association of Paediatric Gastroenterology and Nutrition (CAPGAN) was created and John Walker-Smith and Peter Sullivan were the first Chairman and Secretary, respectively, of its Council. A Constitution was created and accreditation by the Commonwealth Secretariat was received. Thus, CAPGAN was largely an offspring of ESPGHAN. Several other senior ESPGHAN members, Alan Phillips (Past Treasurer of CAPGAN & ESPGHAN), and Bhupinder Sandhu (Past President, CAPGAN) in particular, have contributed freely and willingly to the development of CAPGAN. However, of necessity, CAPGAN has a larger role in advocacy and it tries to be as inclusive as possible when organising conferences, which are now biennial. Thus, CAPGAN is attended by state of the art researchers as well as junior paediatric trainees from very poor areas, and not just limited to Commonwealth countries. Our recent conference in September 2017 was in Lusaka, Zambia, while the next will be held in 2019 in Toronto, Canada.

FISPGHAN was created in 2000 as an umbrella organisation of which ESPGHAN is a full member and CAPGAN is an associate member. CAPGAN has been particularly active in FISPGHAN and contributed to organising the 4 yearly World Conferences (WCPGHAN), from that in Paris 2004 till the next one in Copenhagen in 2020. CAPGAN also contributes to FISPGHAN’s Council meetings and Working Groups. Thus, we are indebted to ESPGHAN and particularly its founder and early members for our existence and development.

We wish ESPGHAN all the very best for the next 50 years and beyond.

Barbara Golden, President of CAPGAN

Dear ESPGHAN and all its members.

It is an honour for the European Academy of Paediatrics (EAP), as the paediatric section of European Union of Medical Specialties (UEMS), to pay a special tribute to ESPGHAN and congratulate you on your 50th anniversary. We especially value the collaborations between the 2 societies and are proud to have ESPGHAN as member of our Tertiary working group where you play an important role and now provide the chair of this group. The EAP/UEMS acknowledge the important work ESPGHAN has been and is doing for children and children’s health, being a leading organisation giving paediatric advice on gastroenterology, haepatology, and nutritional issues. This is much needed in preserving child health, especially with the increasing incidence of obesity and type 2 diabetes in the child-adolescent population. We also acknowledge your continuing efforts to provide guidelines and all your research input. Your work to optimise nutrition for the premature infant has a great reputation in neonatal medicine. We wish you to continue the successful activities in the years to come. We look forward to strengthen our collaboration; together we will make a difference and we will have a stronger political voice when we speak on behalf of all children and their health.

Professor Tom Stiris, President of European Academy of Pediatrics

European Crohn’s and Colitis Organisation (ECCO) joins the scientific community in the celebration of the 50th anniversary of ESPGHAN. The long history of the society is the best testimonial of a fruitful contribution to education and research in the fields of Pediatric Gastroenterology, Hepatology and Nutrition in Europe. ECCO shares with ESPGHAN the objective of improving research, education, and collaboration in the area of inflammatory bowel diseases (IBD) for the purpose of improving the care of patients with IBD. Europe has outstanding specialists in paediatric IBD, the community of paediatricians devoted to the condition has developed initiatives that brought about substantial advances to the field, and there is a growing need of education on the topic among general
paediatric gastroenterologists. ECCO highly values the continued collaboration with ESPGHAN in the development of joint guidelines for the diagnosis and treatment of paediatric IBD, the guidelines for development of clinical trials in the paediatric population together with the European Medicines Agency, as well as the joint collaboration in educational activities. ECCO is willing to continue and expand these joint initiatives for the benefit of all our patients. ECCO congratulates ESPGHAN for the successful trajectory in these 50 years and wishes all the best for the future of the scientific society.

Julián Panés, President of ECCO

The European Pediatric Association/Union of National Pediatric Societies (EPA/UNEPSA) was founded more than 40 years ago and unites today 50 national and affiliated paediatric societies from all over Europe. The main goal of our Association is to gather the efforts of all European paediatric professionals and scientists in order to improve child health care and quality of life. The European Pediatric Association complies with the strategy of building efforts for the better future of European children. One of the main vectors of our Association is cooperation among the leading medical, social and specialized societies—with all who want to improve child health and development by putting children and young people into the centre of their activities. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) is one of the key partners for EPA/UNEPSA. We are proud to have longstanding and fruitful cooperation with ESPGHAN—the multiprofessional organisation whose aim is to promote child health with special attention to the gastrointestinal tract, liver, and nutritional status. Our goals are very close—to spread science-based information, promote the best practice of care and to provide high-quality education. We have a lot of common activities. Leading experts of ESPGHAN are involved in the scientific committees of the EPA biannual Congresses—Europaediatrics to provide high-quality scientific topics in the field of their expertise for European paediatricians. And vice versa, we also cooperate closely on providing publications, educational programs and analytical statements. And we are positively looking forward to our common future—to accept together the challenge and strive for a unified and constructive cooperation for the benefit of the future of our continent—our children! With warm regards.

Leyla Namazova-Baranova, EPA/UNEPSA President

On behalf of the European Society for Clinical Nutrition and Metabolism, its officers and members, I am delighted to congratulate you at the occasion of the celebration of the 50th anniversary of your Society. In many ways our both Societies are sharing the same objectives: improving education, scientific research and clinical practice in the field of medical nutrition. ESPGHAN and European Society for Clinical Nutrition and Metabolism (ESPEN) have the same pattern: multidisciplinarity. During the last decades
ESPGHAN and ESPEN have closely collaborated: joint sessions at the respective Congresses, joint working groups, and collaboration in publishing joint Guidelines. Several eminent ESPGHAN members were involved in ESPEN Committees. Moreover many clinicians and scientists are members of both Societies. Thanks to the efforts of the members of our both societies the importance of clinical nutrition is now highly considered in the medical domain. However, it is the responsibility of our Societies to continue developing the field of Clinical Nutrition. ESPEN is wishing you the best for the next decades!

Andre´ Van Gossum, ESPEN Chairman

The Federation of European Nutrition Societies (FENS) would like to congratulate the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) on its 50th anniversary. It is not easy to remember the time period of the 1970s in which the European idea was restricted to the western countries and transnational collaboration limited to a few of them. It is important to realize that this medical discipline was already following the idea of a united Europe and many common interests among the different national bodies. I have to admit that the nutrition societies started relatively late to be represented within an own organization at the European level compared to ESPGHAN. Nowadays, it is important that the various players in the area of nutrition are working together in order to help science and policy recognizing that nutrition is one of the most important aspects for health, well-being, and also cultural identity. In the past ESPGHAN and FENS can refer to common scientific sessions at the European Nutrition Conferences. In this way, all the input from the many areas of nutrition research is important for the overall picture of a strong common community. In this way, FENS is looking forward for successful collaboration between the 2 organizations also in the future.

Heiner Boeing, FENS President

The global Federation of International Societies for Pediatric Gastroenterology, Hepatology and Nutrition (FISPGHAN) and its member societies congratulate ESPGHAN on its 50th anniversary, and for amazing achievements in the last 5 decades in promoting child health through research, education, and bringing people together. FISPGHAN owes a lot to ESPGHAN. In fact, it was the ESPGHAN president Stefano Guandalini who from 1998 onwards promoted the idea of holding World Congresses Pediatric on Gastroenterology, Hepatology and Nutrition and convinced partner societies that a global Federation should be created. At the first World Congress held in Boston in the year 2000, FISPGHAN was formally established jointly by the Asian Pan Pacific
(APPSPGHAN), European (ESPGHAN), Latin American (LASP-GHAN), and North American (NASPGHAN) sister societies as full members, joined by the Commonwealth Association (CAPGAN) and later the Pan Arabian (PAPGHAN) societies as associate members. ESPGHAN was the co-host of the very successful second world congress in Paris, France, in 2004 with Prof Olivier Goulet as the congress president, and ESPGHAN members provided key contributions the Expert Working Groups of the Federation that offered instructive updates on the approach to and management of key challenges in paediatric digestive health. A further remarkable achievement is that the Young ESPGHAN team won the FISP-GHAN expert team award at the WCPGHAN in Montreal, Canada in 2016 and produced an outstanding teaching video on treatment of acute gastroenteritis, which is now available at www.fispghan.org. FISP-GHAN will need the future active support and contribution of ESPGHAN and its members for its continued success, and it is very much looking forward to co-hosting the next world congress jointly with ESPGHAN in Copenhagen in June 2020!

Berthold Koletzko, FISPGHAN President

On behalf of the International Pediatric Association (IPA), we want to forward our esteemed felicitations and congratulations to the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) for celebrating their 50th anniversary. ESPGHAN’s continued work as a global advocate for advancements in novel research, education, quality of care, and best practices in paediatric gastroenterology, haepatology, and nutrition has been of significant benefit to paediatric practice in Europe and setting standards globally. I and several of my colleagues have had the privilege of working with ESPGHAN, and I can attest to the passion of the engaged members who make up this body. Paediatricians have a responsibility to speak for children in all settings. We are united for education that advances the causes of children, we jointly advocate for policy and action that preserves the right to a healthy childhood. While ESPGHAN serves in one way, we all serve together and have the additional benefit of working together on global task forces and committees. Congratulations ESPGHAN for an astounding 50 years of advocating, educating, and providing a platform for paediatricians to unite for child health. We wish you the best for the 2018 Congress; the IPA enthusiastically supports your work, and wishes you success for the next 50 and beyond.

Zulfiqar A. Bhutta, President of the International Pediatric Association

LATIN AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

The Latin American Society of Pediatric Gastroenterology, Hepatology and Nutrition (LASPGHAN) joins the celebration of the 50th anniversary of the foundation of the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) in 2018. The history of gastroenterology in children starts during the XX century when there was the need of special care for diseases like protracted diarrhoea, inborn errors of metabolism, metabolic diseases of bilirubins, coeliac disease, cystic fibrosis; and the acquisition of specific skills such as small bowel biopsies, parenteral nutrition,
paediatric GI endoscopies and percutaneous liver biopsies in children. The foundation of ESPGHAN in 1968 (ESPGAN at that time) as the first paediatric GI society in the planet was the result of an increase number of paediatricians involved in the care of GI and liver diseases. Since then, ESPGHAN has become one of the cornerstone in our field promoting the development of science, education, and health delivery to sick children. Also ESPGHAN has been a model for the emergence of other societies in the world; always open to collaboration in research, medical education and patient care. We all recognize the social commitment and medical work ESPGHAN offers to the developing world specifically in Africa. Europeans colleagues should be proud for the countless academic, social, and scientific achievements, and the colossal growth ESPGHAN has experienced during the last 50 years. The LASPGHAN congratulates all the ESPGHAN members, especially those who have played an active role on its brilliant history, for their performance and input to build a great example of a medical society. Let us all join ESPGHAN in Geneva 2018 and celebrate 50 years of success.

Armando Madrazo, President of LASPGHAN

NORTH AMERICAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

PAN-ARABIAN SOCIETY FOR PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION (PASPGHAN)

I have attended my first ESPGHAN meeting 13 years ago, since then I attended most of its annual meetings. It is an excellent opportunity not only to hear from my peers about their scientific advances and to share their experience and new insights into different area of interest, it is also an excellent platform to meet colleagues to develop a wide network of friends and contacts, many of whom are willing to give their time to support Training and Sciences around the globe simply just to help others. I have enjoyed being a part of ESPGHAN Regional Meeting in Collaboration with TURKPGHAN and PASGHAN in November 2013 in Istanbul, and

James E. Heubi, MD, President, NASPGHAN
have been honoured to host an ESPGHAN Scientific Session during the 14th PASGHAN Congress in November 2014 in Marrakech, involving many of young researchers and doctors. ESPGHAN is an important and great society with high ethical and scientific standards, its’ opening influence widely on the quality of care and the nature and direction of research all over the world, attending its’ annual meeting is a must.

Prof Nezha Mouane, PASGHAN General Secretary

It is a distinct pleasure to congratulate the ESPGHAN with their 50th anniversary. Your society was among the 7 European gastroenterological societies that decided to join forces 25 years ago and form United European Gastroenterology (UEG). This was evidently excellent strategic planning as UEG and the UEGW are now among the most important meetings for our specialty with around 14,000 participants each year and more than 3000 physicians participating in the postgraduate course. As UEG president I feel it is important to have paediatric gastroenterology in the heart of the UEG. The developments in medicine are going faster than ever before and traditional borders between specialties are disappearing. To keep up with the current developments and provide the best care for our patients, we must know what’s happening “next door” and UEG provides this opportunity. At the same time UEG is trying to influence EU politics and make digestive health one of the priorities and provide more resources for research. And apart from this education and quality are also part of UEG’s target areas where we try to assist our member societies. I wish ESPGHAN a very happy birthday celebration and excellent health for the next 25 years to come!

Yours sincerely,

Paul Fockens, UEG President 2018–2019