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The Historical Roots of Paediatric Gastroenterology, Hepatology and Nutrition

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Abstract

The last fifty 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 three common clinical problems – diarrhoea, jaundice, and milk-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.

Introduction

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 forty 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 PGHAN 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 PGHAN extend back to the work of those who concerned themselves with the digestive ailments of children and wrote about them in the past, but it only came of age as an independent clinical subspecialty in the last half century. It is now one of the foremost fields of paediatrics, as this supplement proclaims.

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Lawrence Weaver, Guest Editor

Chapter 1 outlines the roots of the modern clinical specialty of PGHAN up 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 sub-specialty 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 PGHAN, marked by memorable joint meetings.

The next three 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 research, development and practice. Chapter 5 concentrates on thirteen 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 paediatrics, and chapter 6 addresses six 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 PGH&N in Europe. In Chapter 9 the presidents of our partner societies, with which ESPGHAN shares common goals and members, pay tribute and offer congratulation 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 fifty 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 nine 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 PGHAN, 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 twenty-five years as being

‘a time of growing and finding an identity’ with ‘an optimistic prognosis for the future’. At fifty 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 coeditors of this supplement, five 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.

Introduction

(Fig. 1 Lawrence Weaver)

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 in the prehistory 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 one of the three 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 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 initiate motion and sensation (Fig. 3) (2).

With the decline of the ancient Greek and Roman civilisations, many medical texts were preserved in Arabic translations and infused 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 (1209), Padua (1222) [**Italy, France, England**], these writings, elaborated by commentaries, were the basis of a bedside medicine, taught from books that dealt with diseases *a capitem ad calcem* (from 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 treatment was to promote the flow or restore the balance of the humours.

During the Renaissance humoral 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. 1450-94) [**Italy**] and *Ein Regiment de Jungen Kinder* (1473) (4) by Bartholomew Metlinger (c. 1450-92) [**Germany**]. Such texts generally restated the teachings of the Ancients, broadly under three 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 *Paedotrophia* (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 humoral 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 ‘feebleness of the stomacke and vomitings’, teaching that ‘colyke and rumblings of the guttes cause the child restlessness. He crieth and frettish himself and many times also makes urine by reason of winde that oppreseth the neck of the bladder’.

Scientific Revolution and Enlightenment (1550-1800)

The ‘new anatomy’ of Andreas Vesalius (1514-64) [**Belgium**] ‘corrected ancient errors’ and challenged received ideas of how the body was formed, but offered few insights into the causes of disease. Humoural physiology still served to explain physiological processes, such as digestion, absorption, excretion and lactation. Bartholomew Metlinger (c. 1450-92) [**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 soothe 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 Infantum* (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 endued 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 (1614-72) [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 children were generally cared for at home, by their parents, sometimes attended when seriously ill by a physician or clergyman (to care for the soul as well as body). Healing and recovery from illness might be brought about by Nature (*vis medicatrix naturae*), under the command of God and the assistance of the physician. With the help of the six 'Non-Naturals' – excretion, sleep, food, passions, air and exercise, the 'natural spirits' would expel bad humours and redress their balance. Choice of food reflected the 'chain of being', in which fowls stood higher than meat, than fish, than vegetables in their capacity to restore the 'innate heat' and 'radical moisture', which constituted health.

Herman Boerhaave (1668-1738) [Netherlands] continued to teach that the 'child in the womb has its nourishment and growth from the mother's humours; it seems very probable that in the last months of pregnancy the milk is carried to the uterus and to the fetus' (9). But as a physician Boerhaave collected clinical cases, based on careful questioning, observation and inspection, and shared them with other practitioners by correspondence, through journals and published lecture notes, facilitating the spread of knowledge of children's diseases, albeit within a small network of physicians, with court appointments, university positions, charitable dispensaries or postal practices. Texts on the natural histories of diseases, such as those by Thomas Sydenham (1624-89) [England], were accompanied by classifications of diseases (nosologies), based on symptoms (e.g. itch, gripes, cough) and external signs (e.g. rickets, measles, pox), grouped generically as dolores, spasmi, fluxes, cachexiae etc. Such systematization reflected the organization of information within quasi-Linnaean taxonomies (Carl Linnaeus 1707-78) [Sweden].

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). External 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 1608-79) [Italy], cardiac function (William Harvey 1578-1657) [England], respiration (Robert Boyle 1627-91) [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 1628-94) [Italy], and by human dissection the cerebral, placental and fetal circulations (Thomas Willis 1621-75) [England], (Frederik Ruysch 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 (1706-73) [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 plenty, or from anything preventing the vasa bibula (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 18thC 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 (1719-89) [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 viscera appeared very sound, nor could anything be discovered to account for his complaints, except the above viscid 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 watery gripes, 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 putrid sanies, 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. Floury 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 ‘spiritous’, ‘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 etc. 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 etc. 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 wellbeing. Foods made up of a single substance, such as gelatin (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 infant feeds (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 of 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 humoral 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)

Foundling 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, 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 ('methode numerique'), 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 Chaussier (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

metastasis between them. Based on the records of more than 600 dissections, many prefixed with symptoms, his *De Sedibus et Causis Morborum per Anatomen Ingegnatis* (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 (1800-32), physician at *L'Hôpital des Enfants Trouvés*, who described in his *Traité des Maladies des Enfants Nouveau-Nés et à la Mamelle* (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 organization 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 two physicians, Frédéric Rilliet (1814-61) and Antoine Barthez (1811-91) [**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 five ‘divisions by organ’ are cross-tabulated by eight ‘divisions by nature’. The first four have labels that echo humoral categories – phlegmasies, hydropsies, hémorrhagies, gangrènes, and are followed by névroses, fièvres, tuberculisations (occupying the whole of volume 3), and entozoaires (gut parasites) (Fig. 7).

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). The second edition of Rilliet et Barthez (1861) reflects developments in physiology and experimental medicine, by François Magendie (1783-1855) [France] and Claude Bernard (1813-78) [France], and in the German-speaking states (Wilhelm Camerer, 1842-1909) [Germany], where the chemistry of Justus von Liebig (1803-73) [Germany] formed the basis of physiology, auxology and metabolism. Chapters devoted to particular diseases, eg. Entéro-Colite Chronique, which has sections on anatomie pathologique, symptômes, complications, pronostic, 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 (1743-94) [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 peristalsis, 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

(1803-73) [Germany] who sought to explain how food might 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 four elements, viz. 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 1810-82) [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 (1813-78) [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 1822-95) [France] work on fermentation and moulds. The application of the microscope, laboratory study of moulds (Louis Pasteur 1822-95) [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 characterization 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 1818-65) [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 (1822-95) [Germany] distinguished distinctly different patterns of temperature change in patients with typhoid and typhus, and William Budd (1811-80) [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):

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-René Villermé 1782-1863) [France], Edwin Chadwick 1800-90 [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). Obstetrics, the medicalisation of antenatal and postnatal care, infant-feeding (so critical for infant survival), crèches, and legislation to protect children from dangerous employment, recognized 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). There was a shift

from a primary concern for mothers, to infants and children, who became recognized as patients. Amongst a range of welfare services initiated for babies, consultations de nourissons, 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 (1803-73) [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 two decades. Henri Nestlé (1814-90) [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 popularized 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' (24). 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, without 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' (25). 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 professionalization 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 three 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' (26). Henry Koplik (1858-1927) [USA], in his *Diseases of Infancy and Childhood* (27), 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 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 four volume, multi-author *Handbuch der Kinderheilkunde* (28) edited by Meinhard von Pfaundler (1872-1947) and Arthur Schlossmann (1867-1932) [Germany] (translated into English in 1908), based on physiological and developmental principles, represented the state-of-the-art of paediatrics at the start of the twentieth 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 investigated. However, although the chemist and pharmacist were replacing the apothecary, therapeutics still comprised recipes primarily designed to relieve symptoms. For instance 'Acute Catarrh (diarrhoea) 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':

a thin mucilage, I Gm. (15 gr.) to 100 c.c (3 oz.) water may be given containing zinc sulphate 0.1 Gm. (1.5 gr.), extract opii 0.2 Gm (1/3 gr.) and syrup althaea 10 Gm. (2 dr.), teaspoonful every two hours; or extract haematoxylin 5 Gm. (11/4dr.) 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] (27).

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 digestions 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* (29) says 'avec Rilliet et Barthez nous réservons le terme de dysenterie, à une maladie sporadique ou épidémique caractérisée *cliniquement* par des selles fréquentes, muco-purulentes et sanguinolentes, et *anatomiquement* par des lésions ulcéreuses, siégeant dans le gros intestin. ... Pour établir le diagnostic, il faudra tenir compte des conditions étiologiques, et recourir surtout aux procédés de laboratoire.' L'agglutination due bacilli dysentérique par le sérum du malade a été utilisé pour le diagnostic.'

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* (30) 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).

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' (31). 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 forty 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 of the (via respiratory or gastrointestinal tract) remained unresolved.

Efforts to understand the metabolic disturbances associated with chronic diarrhoea and malnutrition – variously termed *atrophy*, *dystrophy*, *decomposition*, *athrepsia*, *intestinal intoxication* – through competitive and collaborative research during the 1920s and 1930s. In Pfaundler and Schlossmann's expanded five-volume edition of the *Diseases of Children* of 1935, the 'theories of the origin of dystrophy' were summarized 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 maldigestion. Heinrich Finkelstein's (1865-1942) [Germany] in his *Lehrbuch der Säuglingskrankheiten* (32), 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 1804-78) [Austria], bronchiectasis and chronic diarrhoea into the diagnosis of cystic fibrosis.

The diseases of the liver in children are allocated only eight out of more than 600 pages in Henry Koplik's *Diseases of Infancy and Childhood* (27): Jaundice and Congenital Obstruction of the Bile 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 icterus, with calomel, enemas fresh air and daily alkaline baths, no treatments of children's liver diseases were specified.

The aetiology of childhood rickets, long recognized 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 Huldshinsky 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 characterization of a number of vitamin-deficiency diseases.

Conclusions

The enormous advances in our understanding of infectious diseases and nutritional disturbances to the health, welfare, growth and development of children between 1850 and 1950, when paediatrics was born and came of age, made the gastrointestinal tract, as the organ of nutrition, of vital interest to paediatricians (33). Although the aetiology of many children's digestive diseases were determined, and scientifically-based treatments were available, improvements in sanitation, hygiene, nutritional support and food supplementation were the chief contributors to their prevention and better outcome.

International and European organisations, including the International Paediatric Association, WHO and UNICEF, formed in the inter- and post- world war periods championed the

interests of sick children. National societies of paediatrics had GI sections, and international links between fellow clinicians were strengthened through the exchange of trainees, research collaborations and personal friendships. Medical insurance schemes and national health services expanded access to hospital care, and growth surveillance, vitamin supplementation, school health and immunisation programmes improved the health of all children. The discovery and clinical use of antibiotics, corticosteroids, vitamins, new anaesthetics, and rational fluid management transformed the fortunes of many sick children in hospital.

Endoscopy, special feeds and diets, parenteral nutrition, functional diagnostic tests, luminal contrast studies, for instance, all required laboratory support and expertise, stretching the capabilities of general paediatricians. Children's hospitals and paediatric departments facilitated the trend towards clinical specialisation, driven by technological advances, such as the sweat test in 1953 (Paul di Sant' Agnese 1914-2005) [USA] and jejunal biopsy capsule in 1957 (William Crosby 1914-2005) [USA]. The first use of the biopsy capsule in children by Jack Sakula (1908-1982) and Margot Shiner (1923-1998) (34) [England, Germany], 'made a very big difference to intestinal studies and gave paediatric gastroenterology a quantum leap', according to Charlotte Anderson (1915-2002) (35) [Australia], opening the way to tissue diagnosis as well as to the study of the gut mucosa in health and disease (36).

The foundation of ESPGA in 1968 by a small group of European paediatricians 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, multi-professional teams, non-invasive 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. ESPGHAN 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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Fig 1.
Lawrence Weaver

Fig. 2.
The four humours, with their characteristic properties and associated elements.

Fig 3.
Galen's 'physiological system'.

Fig 4.
The Anatomy Lesson, by Frederik Ruysch (1683).

Fig 5.
Ospedale degli Innocenti (foundling hospital) in Florence, Italy.

Fig 6.
Paris Hospitals in 1804.

Fig 7.
Tableau Synoptique du Plan de L'Ouvrage, from Rilliet & Barthez's *Traité Clinique et Pratique de Maladies des Enfants* (1843) (19).

TABLEAU SYNOPTIQUE DU PLAN DE L'OUVRAGE.					
Division par NATURE.	Division par Organes.				ORGANES EXTERNES.
	ORGANES INTERNES.				
Classes.	I. Poitrine.	II. Fosses nasales. — Bouche. — Col.	III. Abdomen.	IV. Encéphale. — Ra- chis.	—
1 ^{re} Classe. PHLEGMASIES, ETC. PRÉLIMINAIRES.	CHAP. 1 ^{er} . Bronchite. Ch. 2. Pneumonie. Ch. 3. Emphysème. Ch. 4. Pleurésie. Ch. 5. Pneumothorax. Ch. 6. Péricardite. Ch. 7. Endocardite. — Hy- pertrophie du cœur.	Ch. 8. Coryza. Ch. 9. Stomatite. Ch. 10. Pharyngites. Ch. 11. Laryngites.	Ch. 12. Phlegmasies et ramollissements de la membrane muqueuse gastro-intestinale. — Étude anatomique. Ch. 13. Phlegmasies et ra- mollements de l'esto- mac. Ch. 14. Phlegmasies et ra- mollements des intes- tins. Ch. 15. Périlonite. Ch. 16. Hépatite. Ch. 17. Néphrites. — Pyé- lite, etc.	Ch. 18. Méningite simple. Ch. 19. Maladies des sinus veineux de la dure-mère. Ch. 20. Congestion céré- brale. Ch. 21. Ramollissement cé- rébral. — Encéphalite. Ch. 22. Hypertrophie et in- duration du cerveau. Ch. 23. Méningite rachi- dienne. Ch. 24. Ramollissement de la moelle. Ch. 25. Induration de la moelle.	Ch. 26. Rhumatisme arti- culaire aigu. Ch. 27. Inflammations de la peau. Ch. 28. Endurcisse- ment du tissu cellulaire. Ch. 29. Œdème.
2 ^e Classe. HYDROPIQUES. PRÉLIMINAIRES.	CHAP. 1 ^{er} . Œdème du pou- mon. Ch. 2. Hydrothorax. Ch. 3. Hydropéricarde.		Ch. 4. Ascite.	Ch. 5. Hydrocéphalie.	Ch. 6. Anasarque.
3 ^e Classe. HÉMORRHAGIES. PRÉLIMINAIRES.	CHAP. 1 ^{er} . Hémorrhagies pulmonaires. Ch. 2. Hémorrhagies pleu- rales.	Ch. 5. Epistaxis.	Ch. 4. Hémorrhagies de l'estomac et des intes- tins. Ch. 5. Hémorrhagies ré- nales.	Ch. 6. Hémorrhagies cé- phaliques. Ch. 7. Hémorrhagies ra- chidiennes.	Ch. 8. Purpura.
4 ^e Classe. GANGRÈNES. PRÉLIMINAIRES.	CHAP. 1 ^{er} . Gangrène des bronches. Ch. 2. Gangrène du pou- mon. Ch. 5. Gangrène de la plè- vre.	Ch. 4. Gangrène de la bou- che. Ch. 5. Gangrène du pha- rynx.			Ch. 6. Gangrène de la peau et des parties génitales externes.
5 ^e Classe. NÉVROSES. PRÉLIMINAIRES.	CHAP. 1 ^{er} . Coqueluche.	Ch. 2. Spasme de la glotte.		Ch. 5. Convulsions. Ch. 4. Chorée. Ch. 5. Contracture. Ch. 6. Paralyse.	
6 ^e Classe. FIÈVRES CONTINUES. PRÉLIMINAIRES.			CHAP. 1 ^{er} . Fièvre typhoïde.		Ch. 2. Variole. Ch. 3. Scarlatine. Ch. 4. Rougeole.
7 ^e Classe. TUBERCULISATIONS. PRÉLIMINAIRES.	Ch. 2. Tuberculisation des ganglions bronchiques. Ch. 3. Tuberculisation du poumon et lésions secon- daires. Ch. 4. Tuberculisation de la plèvre et lésions se- condaires. Ch. 5. Tuberculisation du péricarde et lésions se- condaires.	Ch. 6. Tubercules et ulcé- rations du larynx.	Ch. 7. Tuberculisation du péritoine et lésions se- condaires. Ch. 8. Tuberculisation des ganglions mésentéri- ques. Ch. 9. Tuberculisation de l'estomac et des intes- tins, et lésions secon- daires. Ch. 10. Tuberculisation du foie et lésions secon- daires. Ch. 11. Tuberculisation des reins et lésions se- condaires. Ch. 12. Tuberculisation de la rate.	Ch. 13. Tuberculisation des centres nerveux et lésions secondaires.	
8 ^e Classe. ENTOZOAIRES. PRÉLIMINAIRES.			Vers intestinaux.		

Fig 8.

Classement des Maladies Gastro-Intestinales, from Rilliet & Barthez's *Traité Clinique et Pratique de Maladies des Enfants* (1853) (19).

Fig 9.

The 'new' instruments of clinical medicine – the stethoscope, thermometer, weighing scales and microscope.

Fig 10.
Ice calorimeter used by Lavoisier and Laplace to measure ‘animal heat’ (1783).

Fig 11.
 Histological sections of the intestinal mucosa.

Fig 12.

Maps showing locations of children's hospitals in Europe, 1802 to 1847 (37).

Fig 13.

The mortality of breast-fed and artificially fed infants in Paris during an epidemic of summer diarrhoea (cholera infantum) in 1898 (38).

Fig 14.
Soxhlet's Milk Steriliser (1891).

Fig 15.
L'Oeuvre de la Goutte de Lait showing Gaston Variot in the Bellville Dispensary, Paris.
Print after Jean Geoffroy 1901.

Fig 16.

Cover of *Jahrbuch für Kinderheilkunde* (1909) showing international European editors, including Biedert, Escherich, Finkelstein, Jacobi, Henoch, Hirschsprung, and von Pirquet.

Fig 17.
Theodore Escherich with his colleagues and students in Graz in 1902.

Fig 18.
Radiogram of barium meal in three-week old infant with congenital stenosis of the duodenum (39).

Fig 19.
Method of palpating the projection of the liver below the ribs (27).

Fig 20.
Children with rickets outside the Royal Hospital for Sick Children, Glasgow.

Table 1

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

Annual Meetings of ESPGHAN				Significant People, Scientific or Medical Events, Discoveries or Inventions of that Country
Year	Meeting	Venue	Country	
2018	51st	Geneva	Switzerland	Charles Chossat (1796-1875). Experimental researches into starvation, 1843.
2017	50th	Prague	Czech Republic	Jan Purkinje (1787-1869). Anatomist who discovered Purkinje cells and fibres, 1839.
2016	49th	Athens	Greece	Soranus (c. 1st/2nd C AD). Advice on infant feeding and quality of breast milk.
2015	48th	Amsterdam	Holland	Herman Boerhaave (1668-1738). Aphorisms on child health and treatment of disease, 1709.
2014	47th	Jerusalem	Israel	Ada Yonath (b. 1939). Crystallographer who elucidated the structure of the ribosome, 2000.
2013	46th	London	England	Samuel Gee (1839-1911). Physician who described clinical features of coeliac disease, 1888.
2012	45th	Stockholm	Sweden	Nils Rosen von Rosenstein (1706-1773). Author of Diseases of Children and their Remedies, 1764.
2011	44th	Sorrento	Italy	Giovanni Morgagni (1682-1771). Author of Seats and Causes of Disease Investigated by Anatomy, 1761.
2010	43rd	Istanbul	Turkey	Mary Wortley Montagu (1689-1762). Introduction of smallpox inoculation to England, 1717.
2009	42nd	Budapest	Hungary	Ignaz Semmelweis (1818-1865). Prevention of puerperal fever by hand-washing, 1847.
2008	41st	Iguassu	Brazil	Henrique Pinotti (1929-2010). Described oesophageal stenosis in Chagas Disease, 1988.
2007	40th	Barcelona	Spain	Santiago Ramon y Cajal (1852-1934). Pathologist who identified nerve fibres in gut, 1890s.
2006	39th	Dresden	Germany	Justus von Liebig (1803-1873). Chemist who pioneered analysis of composition of milks, 1830s-40s.
2005	38th	Porto	Portugal	Garcia de Orta (1501-1568). First European physician to describe symptoms of cholera, 1563.
2004	37th	Paris	France	Claude Bernard (1813-1878). Experimental physiologist of digestion and sugar metabolism, 1860s.
2003	36th	Prague	Czech Republic	Joseph Škoda (1805-1881). Promoter and populariser of clinical percussion, 1839.
2002	35th	Taormina	Italy	Santorio Santorio (1561-1636). Physiologist and pioneer of energy balance studies, 1614.
2001	34th	Geneva	Switzerland	Paracelsus, aka Theophrastus von Hohenheim (1493-1541). Pioneering chemist and toxicologist.
2000	33rd	Boston	USA	Thomas Rotch (1849-1914). Inventor of the percentage infant feeding method, 1910s.
1999	32nd	Warsaw	Poland	Walery Jaworski (1849-1924). Gastroenterologist who described gastric bacteria <i>Vibrio rugula</i> , 1899.
1998	31st	Toulouse	France	Louis Pasteur (1822-1895). Pasteurisation of milk, immunisation, and germ theory.
1997	30th	Thessalonika	Greece	Hippocrates (c. 460-370 BC). Composed practical aphorisms for infant feeding and care.

Annual Meetings of ESPGHAN				Significant People, Scientific or Medical Events, Discoveries or Inventions of that Country
Year	Meeting	Venue	Country	
1996	29th	Munich	Germany	Robert Koch (1843-1910). Identified bacterial causes of tuberculosis and cholera, 1880s onwards.
1995	28th	Jerusalem	Israel	Jesus of Nazareth (c. 0-32). Healer and inspiration for foundation of many charitable hospitals.
1994	27th	Houston	USA	William Beaumont (1785-1853). Human experimentation on gastric physiology, 1822.
1993	26th	Göteborg	Sweden	Olaus Rudbeck (1630-1702). Physician and anatomist who discovered the lymphatic system, 1652.
1992	25th	Brussels	Belgium	Jules Bordet (1870-1961). Microbiologist and immunologist who discovered <i>Bordetella pertussis</i> , 1906
1991	24th	London	England	Francis Glisson (1597-1677). Described the capsule of the liver, and childhood rickets, 1651
1990	23rd	Amsterdam	Holland	Antoine van Leeuwenhoek (1632-1723). Microscopist and observer of micro-organisms, 1670s.
1989	22nd	Budapest	Hungary	Béla Schick (1877-1967). Paediatrician who invented test for diphtheria, 1910.
1988	21st	Copenhagen	Denmark	Harald Hirschsprung (1830-1916). Paediatrician who described Hirschsprung's Disease, 1886.
1987	20th	Lisbon	Portugal	Portuguese traders responsible for the adoption of cinchona bark for the treatment of malaria, 16thC.
1986	19th	Edinburgh	Scotland	Thomas Dalziel (1861-1924). Surgeon who first described chronic interstitial enteritis in children, 1913.
1985	18th	New York	USA	William Crosby (1914-2005). Inventor of suction biopsy capsule of small intestinal mucosa, 1957
1984	17th	Tampere	Finland	Arvo Ylppö (1887-1992). Paediatrician who elucidated biochemistry of neonatal jaundice, 1913.
1983	16th	Graz	Austria	Theodore Escherich (1857-1911). Paediatrician who discovered <i>B. coli</i> , 1885 (<i>E. coli</i> , 1919).
1982	15th	Madrid	Spain	Severo Ochoa (1905-1993). Physician, biochemist and Nobel Prize winner for research in RNA, 1959.
1981	14th	Berne	Switzerland	Guido Fanconi (1892-1979). Paediatrician responsible for characterisation of cystic fibrosis, 1934.
1980	13th	Capri	Italy	Scuola Medica Salernitana. First late medieval European medical school, 12th century.
1979	12th	London	England	Thomas Barlow (1845-1945). Paediatrician who distinguished infantile scurvy from rickets, 1883.
1978	11th	Paris	France	Charles Billard (1800-1832). Pioneering paediatrician, author of treatise on diseases of infancy, 1828
1977	10th	Utrecht	Holland	Willem-Karol Dicke (1905-1962). Paediatrician who developed gluten-free diet for coeliac disease, 1953.
1976	9th	Weimar	Germany	Eduard Henoch (1820-1910). Described syndrome of purpura, bloody diarrhoea and arthralgia, 1868.
1975	8th	Leuven-Brussels	Belgium	Andreas Vesalius (1515-1564). Anatomist and author of <i>De Humani Corporis Fabrica</i> , 1543.
1974	7th	Verona	Italy	Giovanni Santorini (1681-1737). Described the accessory duct of the pancreas, 1724.
1973	6th	Helsinki	Finland	Carl Ehrstrom (1803-1881). Pioneer of microbiological causes of infectious diseases, 1850s.

Annual Meetings of ESPGHAN				Significant People, Scientific or Medical Events, Discoveries or Inventions of that Country
Year	Meeting	Venue	Country	
1972	5th	Hamburg	Germany	Heinrich Finkelstein (1865-1942). Invented eiweissmilch (buttermilk) for 'alimentary intoxication', 1910.
1971	4th	Birmingham	England	Harriette Chick (1875-1977). Showed roles of codliver oil and sunlight in preventing rickets, 1920s.
1970	3rd	Lund	Sweden	Carl Linnaeus (1707-1778). Physician and botanist who invented binomial taxonomy, 1735.
1969	2nd	Interlaken	Switzerland	Alexandre Yersin (1863-1943). Microbiologist who discovered plague bacillus <i>Yersinia pestis</i> , 1894.
1968	1st	Paris	France	Antoine Lavoissier (1743-1794). Demonstrated role of oxygen in respiration and combustion, 1778.