Paediatric gastroenterology 1966–2000

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ABSTRACT – Between 1966 and 2000 the pattern of gastroenterological disease in children in developed communities changed. Clinically severe infective gastroenteritis has declined in incidence. Infection of children with the conventional serotypes of *Escherichia coli* dramatically declined. During this period many new infective agents notably rota virus were recognised. By contrast, more children with chronic inflammatory bowel disease (IBD), especially Crohn's disease, have been diagnosed than ever before. Gastrointestinal allergy is increasingly recognised but the pattern of disease has changed. Technological advance in accurate diagnosis occurred with an emphasis upon tissue diagnosis. Introduction to clinical practice of ileocolonoscopy in the late 1970s immensely increased the ability to make the diagnosis of chronic IBD in children. Therapeutic advance has seen development of parenteral nutrition and enteral feeding as major therapies for children. In the UK there has been a rise and fall in university departments of paediatric gastroenterology.

KEY WORDS: paediatric gastroenterology

Personal background

I started training in general medicine with a view to a future in adult gastroenterology and moved from Sydney to London to start training in 1962, and was house physician to Professor CC Booth at the Hammersmith Hospital a year later. As a research fellow in gastroenterology at the Royal Prince Alfred Hospital in Sydney, between 1964 and 1966, I decided to specialise in paediatric gastroenterology. At an international meeting, held at the Royal Children's Hospital in Melbourne, I was fascinated by the application of small intestinal biopsy to the investigation of children with gastroenterological problems and heard an inspirational lecture by Professor Andrea Prader of Zurich on disaccharidase deficiency, based on small intestinal biopsy studies. In 1962, as part of earlier training for general medicine, I had already completed six months basic training in clinical paediatrics at the Royal Alexandra Hospital for Children (RAHC) and returned in 1967 as professorial registrar where I was given the task of developing a small intestinal biopsy service and a clinical research programme for gastroenterology in children. My training in clinical paediatrics went hand in glove with developing gastroenterology in children, at a time when the discipline of paediatric gastroenterology did not exist.

The experience of suction small intestinal biopsy in children at the hospital had been disastrous before I arrived with three perforations and one death in children who had been biopsied with the inappropriate use of the adult Crosby capsule. I used the paediatric modification, which had a significantly smaller porthole size (2.5–3 mm) compared to the adult capsule (5 mm). Porthole size proved the key determinant for safety in children.[1] Subsequent studies involving large numbers of paediatric biopsies showed that the procedure was safe with a very low risk of any complication, when used appropriately in experienced hands. The role of small intestinal biopsy in children was to provide tissue for histological analysis to demonstrate an abnormal mucosa for the diagnosis of coeliac disease. Its use for secondary disaccharidase deficiency declined when replaced by stool testing for excess reducing substances and pH.[2,3]

Although my experience of paediatric gastroenterology is based on clinical experience gained in Australia and the UK, reflecting the pattern of disease in those two developed communities, I also experienced paediatrics in the Third World from seeing large numbers of immigrant children and my many visits to developing communities, especially in the Commonwealth.

Changing pattern of disease

Infectious disease

The most dramatic change in my clinical practice has been the decline in the number of children, with clinically severe infective gastroenteritis, complicated by dehydration of such severity that death was sometimes the outcome. I experienced deaths in hospital from gastroenteritis, mostly related to hypernatraemia, every year until 1979.[4] Simultaneously there has been a great expansion in knowledge of the infectious agents now known to cause infective diarrhoea. Initially only *Shigella*, *Salmonella* and conventional serotypes of enteropathogenic *Escherichia coli* (EPEC) were recognised.[5] The most notable discovery was rotavirus and later other stool viruses such as astroviruses.[6,7] Bacterial pathogens such as *Campylobacter* and *Yersinia* were recognised. There was a concomitant

increase in the understanding of pathogenesis. Infections with EPEC of the conventional serotype were recognised as a significant cause of chronic diarrhoea and severe enteropathy. Such infections disappeared as a clinical problem in the UK in the late 1990s but continue to be a major problem in developing communities.[8] Infections with entero-haemorrhagic *E coli* are now a major problem.

In the developing world, the use of oral rehydration therapy (ORT) using a glucose-electrolyte solution for rehydration has dramatically reduced the risk of death from dehydrating diarrhoea in infancy. This was a remarkable example of theoretical scientific knowledge being directly applied to a clinical problem. The application of ORT to children in the UK was also important, but a reformulated solution with a lower sodium and osmolality was required.[9,10] This revised formulation was later recommended by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) as appropriate for the European children.[11]

In the developing world the most dramatic event has been the appearance of AIDS in children. With a former postgraduate student Dr Beatrice Amadi we completed a study of the gastrointestinal (GI) and nutritional aspects of children in Zambia.[12]

Rise of chronic inflammatory bowel disease in children

While in Sydney and later in London in the early 1970s, I encountered very few children with inflammatory bowel disease (IBD); there were some cases of ulcerative colitis but Crohn's disease was a rarity. By the late seventies, however, because of clinical demand Dr Christopher Williams was called upon to establish the first diagnostic paediatric colonoscopy service in the UK at St Bartholomew's Hospital.[13] These children often had clinical features which were not regarded as typical, for example delayed growth in 43% and constipation in 20%.[14] When I visited Sydney again in the late 1970s a similar change had occurred. By the end of my career at the Royal Free Hospital in 2000, chronic IBD was probably the most important component of my clinical work in a tertiary clinic. Management of growth failure was a particularly important issue involving close collaboration with a paediatric endocrinologist and a surgeon.[15]

Gastrointestinal food allergy

Initially, GI food allergy was under-diagnosed in children. Only a few enthusiasts regarded it as a common and important paediatric problem. This related in part to diagnostic difficulties with a lack of consensus for diagnostic criteria. At QEHC the existence of cow's milk sensitive enteropathy as a form of temporary food allergy in infancy could be post-enteritic in nature.[16,17,18] The most dramatic cases illustrating the severe consequences of GI infection on the small intestinal mucosa in children in the developing world, were seen at QEHC, where children born in the UK, were taken to their ancestral homeland and returned gravely ill with very severe small intestinal mucosal damage.[19] With the decline of clinically severe gastroenteritis in the UK, however, as well as changes in the cow's milk protein content of infant feeds this type of food allergy, ie cow's milk sensitive enteropathy, became less common. At the Royal Free in the early 1990s, cow's milk allergy, as seen in a tertiary clinic, had changed its clinical presentation. It became more frequently associated with multiple food allergies and was often accompanied by gastro-oesophageal reflux.[20] There was indeed a new recognition of the importance of cow's milk sensitive oesophagitis.[21]

Technological advances in diagnosis

Stool electron microscopy transformed the accurate diagnosis of acute diarrhoea of viral aetiology and helped establish the importance of nosocomial infection in what appeared clinically to be the post-enteritis syndrome. Sadly this technique was not available universally, but at QEHC it was a vital diagnostic technique because of the clinical frequency of acute gastroenteritis in the local population of children from East London.[22]

The most dramatic advances for accurate diagnosis and clinical research concerning diseases of the small intestine, however, came from the widespread use of small intestinal suction biopsy using variations of the paediatric Crosby capsule. This transformed the accurate diagnosis and understanding of small intestinal diseases. The classical example of this transformation is coeliac disease. I attended the second meeting of the European Society for Paediatric Gastroenterology at Interlaken in 1969 when serial small intestinal biopsies following elimination and challenge with dietary gluten were recommended for the accurate diagnosis of coeliac disease.[23] Later I was associated with the revision of the ESPGHAN criteria, reserving serial biopsies for children under two years of age at onset of symptoms.[24] It was apparent that there were immunological abnormalities in children with coeliac disease.[25] Later research concerning the immunopathology of the small intestinal mucosa in coeliac disease became central in diagnostic precision and knowledge of pathogenesis.[26]

A similar approach to dietary protein elimination and challenge, was applied to young children with cow's milk allergy characterised by chronic diarrhoea and failure to thrive and showed that milk elimination until the disease resolved was effective. Once the entity had been recognised serial small intestinal biopsy was unnecessary for routine management, but the initial biopsy in a child with chronic diarrhoea and failure to thrive remained essential. Further research increased our understanding of immunopathology.[27]

Small intestinal biopsy in infants with intractable diarrhoea led to the recognition of a number of new disease entities. One of these was autoimmune enteropathy.[28] This became a major interest and a subject of further research.[29] Another was microvillous atrophy.[30] It too was a subject of further therapeutic and pathogenetic research.[31,32] Unfortunately the only prospect for cure at present appears to be small intestinal transplantation. Research into autoimmune enteropathy led to important advances in therapy.[33] A new syndrome of congenital heparan sulphate deficiency was also described.[34]

The advent of parenteral nutrition was a vital preliminary for survival among these children with intractable diarrhoea after which small intestinal biopsy could be undertaken.[35] It was in

this field that electron microscopic assessment of mucosal pathology was especially important in children with chronic diarrhoea.[36] Examples were microvillous atrophy where the morphological diagnosis is only possible by means of electron microscopy and in children with intractable diarrhoea following infection with EPEC where biopsy afforded the ultrastructural demonstration of the attaching effacing lesion.[37]

The introduction to clinical practice of ileocolonoscopy with multiple biopsies in the late 1970s completely transformed the accurate diagnosis of children with suspected IBD and led to a dramatic improvement in their management.[38] Significant advances were made in pathogenesis and recognition of new disorders such as intractable ulcerating enterocolitis of infancy.[39,40] Clinical studies included the role of viral and mycoplasma infections in children with chronic IBD.[41]

Therapeutic advances

The development of parenteral nutrition and then enteral nutrition, has transformed the nutritional management of many children with chronic gastroenterological disease. Enteral feeding is an effective first line specific therapy in children with Crohn's disease.[42,43]

Elimination diets, such as gluten-free and cow's milk free, have been very important as part of therapy and as part of the diagnostic approach. The advent of new hydrolysate and amino acid-based therapeutic formulae has greatly improved management.[20] Dieticians are key members of a paediatric gastroenterology service. Professional links with the infant feeding industry have been important in clinical research programmes to achieve these advances.

Rise and fall of speciality academic units

During my career the first chairs in the UK for paediatric gastroenterology and also hepatology were appointed and two university or academic departments of paediatric gastroenterology within the University of London were created.

In Britain, much of the initial development of paediatric gastroenterology came from within academic departments of paediatrics. Following my retirement at the Royal Free Hospital, the University Department of Paediatric Gastroenterology was abolished and a centre for paediatric gastroenterology was created but remained part of the University Department of Paediatrics. Furthermore at Queen Mary College the academic department of paediatric gastroenterology has been integrated with adult gastroenterology, although led by Ian Sanderson, professor of paediatric gastroenterology.

In the UK there has been a retreat from children's hospitals contrasting with in Australia where in Sydney new state of the art children's hospitals have been built. Outstandingly, RAHC has been re-built on a new site at West Mead with high-quality architecture and facilities tailored to the need of children, through the inspiration of Dr John Yu. Sadly the great metropolis of London lacks a stand-alone comprehensive children's hospital with accident and emergency facilities, serving a local community. QEHC was such a hospital but it was closed in 1998.

Conclusions

Paediatric gastroenterology is still a young discipline. Considerable advances have been made over a relatively short period. The organs of the alimentary tract have become accessible in children, through technological advances. Tissue diagnosis is at the centre of modern practice. Research on these tissues has demonstrated the importance of immunopathology in diseases of the small and large intestine in childhood. This biopsy approach has become routine because it is safe and does not cause undue distress to the child. Children have as much a right as adults to an accurate diagnosis based on the latest technology. More recently endoscopic biopsy in a child who has had a general anaesthetic has replaced suction small intestinal biopsy in the sedated child.[44] The period of 1970s to 1990s was a golden age where new knowledge led rapidly to the recognition of new disease entities. This led to great improvements in effective management of these children. There have been few other examples where an

Table 1. Disease-related lifetime advances experienced between 1960 and 2006.

Gastrointestinal infections
- Recognition of aetiological agents
- Viruses – notably rotavirus
- Bacteria – notably *Campylobacter*
- End of hospital mortality from gastroenteritis
- Advent of oral rehydration therapy
- Decline in clinical severity of gastroenteritis
- Disappearance of conventional serotypes of enteropathogenic *Escherichia coli*
- Appearance of AIDS with gastrointestinal features in developing world

Coeliac disease
- Advent of precise diagnostic criteria (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) in 1969 with key role of small intestinal biopsy
- Evolution of the diagnostic criteria
- Expansion of knowledge of pathogenesis

Gastrointestinal food allergy
- Emergence of clinical diagnostic criteria, with initial importance of small intestinal biopsy
- Change in clinical pattern, moving from chronic diarrhoea and failure to thrive to quick and slow onset syndromes with multiple food allergy

Intractable diarrhoea
- Parenteral nutrition permits survival of infants
- New entities observed notably autoimmune enteropathy and microvillous atrophy

Chronic inflammatory bowel disease
- Increase of Crohn's disease in childhood
- Advent of diagnostic ileocolonoscopy with multiple biopsies from 1978
- Expansion of knowledge of pathogenesis
- Advent of enteral nutrition as primary therapy in children
- Recognition of new syndromes of bowel inflammation

international active clinical research programme has resulted in so much benefit for children so quickly. The rational clinical care of children with disorders of the alimentary tract has been transformed but much still remains to be done.

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