PAEDIATRIC GASTROENTEROLOGY: How it Started and Major Landmarks to Date

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By

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I have been asked to give the Key note address at this Third Annual General Meeting and Scientific Conference of the Nigerian Society of Paediatric Gastroenterology, Hepatology and Nutrition taking place in Benin City, Edo State, with the theme: **Advancing Learning and Practice of Paediatric Gastroenterology and Nutrition in Nigeria**.

For me this is an honour and I accept with pride having been privileged to witness the birth of this Society. I must however, confess I had great difficult time trying to choose a title from a wide range and formidable menu of topics competing for attempt to rhyme with the theme of the conference. The common denominator for this competition is Gastroenterology. I have therefore, settled on the title of: “PAEDIATRIC GASTROENTEROLOGY; how it started and major landmark achievements to date”.

The topic of nutrition as wide as it is had been quintessentially addressed by previous 2 distinguished scholars in this forum. Bear with me for my adventure into this journey into a far country.

My agenda will be in three parts. The first part will be in evolution of Paediatric Gastroenterology/Hepatology as an organ subspecialty in the discipline of Paediatrics and how it came to what it is today. Secondly, the important landmark achievements in diagnostic technology, molecular basis of gastrointestinal disorders, and therapeutic advances both medical and surgical. Finally, I will briefly mention in passing what I consider in my opinion future agenda for Nigerian society of Paediatric Gastroenterology, Hepatology and Nutrition.

PAEDIATRIC GASTROENTEROLOGY: How it started and major landmarks

HISTORICAL BACKGROUND

Interest in Paediatric Gastrointestinal disorders started more than 200 years ago. Dr. Samuel Gee a distinguished adult physician in London published two articles in 1882 and 1888 in the St Bartholomew's Hospital Reports with the following titles:

i. Gee S 1882 On Fitful or recurrent vomiting
ii. Gee S 1888 On Celiac affection.

He drew attention to celiac disease in children. He contributed to the rise of paediatrics and paediatric gastroenterology. However, Gee was not recognised as a pioneer paediatric gastroenterologist, ostensibly because of his attitude. He himself stated that there were two medical terms he abhorred; the terms specialist and consultant.

Similar reports on gastrointestinal tract disorders in children emanated from Dorothy Anderson and colleagues who described pathologic features of cystic fibrosis of the pancreas in children followed by that from Professor Dickes (1950) in his MD thesis of the University of Utrech, the Netherland. He reported on the relationship of wheat flour to the development of symptoms and signs of coeliac disease. These and many more similar reports on childhood gastrointestinal disorders stimulated great interests in paediatric gastroenterology as a subspecialty in the paediatric discipline in the developed nations.

Towards the mid-20th century interest in paediatric gastroenterology subspecialty has gained wide acceptance and began to expand to the Tropical and Subtropical countries. About that time also, a group of physicians working in the London Tropical Hospital commissioned a team of expert in gastroenterology to contribute review articles in various aspects of gastroenterology diseases related to the tropical exposure. The articles focused, understandably, on infectious conditions of the gut and liver namely viral, bacterial, mycotic, protozoan and helminthic injuries. The articles were not entirely restricted to adults but included certain aspects of childhood gastroenterologic conditions.

In the next few paragraphs I will examine how these processes evolved in Europe and North America in particular and other parts of the world.

Evolution of Paediatric Gastroenterology in Europe and North America

The emergence of paediatric discipline as a branch of medicine took over 150 years. It was intensely debated and was clouded with suspicion. Likewise, the development of paediatric gastroenterology as a subspecialty in paediatric which occurred simultaneously in Europe and North America were all linked to establishment of children's hospitals.

Major events and developments that catalysed the emergence of paediatric gastroenterology are summarised in table 1 below.

Table 1: Events that catalysed the emergence of Paediatric Gastroenterology

1. Development of percutaneous liver biopsy for diagnosis and monitoring
2. Development of peroral intestinal biopsy for diagnosis and monitoring therapy
3. Parenteral nutrition
4. Oral rehydration
5. Endoscopy
6. Improved and safe paediatric surgery e.g. Portoenterostomy (Kasai procedure) and ileocolonoscopy
7. Genetic bases of diseases e.g. coeliac disease, cystic fibrosis, alpha-1-antitrypsin deficiency
8. Gut immunology and its significance in food allergy
9. Discovery of H.Pylori

These developments created great awareness and acceptance that special skills are needed to perform these techniques as well as manage diseases peculiar to gastrointestinal tract of children. The concept and need for developing organ specific subspecialty were accepted thereby leading to evolution of Paediatric Gastroenterology Centres.

Gastroenterology Centres

One of the early Paediatric Gastroenterology Unit was established in the 1960's at the Royal Children's Hospital, Melbourne, Australia, by Professor Charlotte Anderson popularly referred to as THE MOTHER OF PAEDIATRIC GASTROENTEROLOGY. Between 1951 – 53 Anderson was a research fellow at the University of Birmingham at the Institute of Child Health. While there she identified gluten as a component protein of wheat responsible for the aetiology of coeliac disease. She separated maldigestion due to cystic fibrosis and mucosal injury due to coeliac disease.

Anderson returned to Australia after her brief period in the late 1950's. Her work was published in the Lancet in 1952. She returned back to Birmingham and finally retired as the Director of the Institute of Child Health, Birmingham from 1975 to early 1980. At Birmingham, Anderson and Valerie Burke co-edited the Pediatric Gastroenterology textbook published by Blackwell Publications. The third edition was edited by Michael Gracey and Valerie Burke as Pediatric Gastroenterology and Hepatology.

Much of Andersons work on Cystic fibrosis and coeliac disease has changed with characterisation of sweat test electrolytes and discovery of chloride channel and mutation in the CFTR gene. For most part cystic fibrosis patients are now cared for by respiratory physicians. Likewise, now with advances in molecular genetics and immunology today coeliac disease is known to be an autoimmune, genetically based gluten sensitive enteropathy with intestinal and extraintestinal manifestations.

The good news now based on this knowledge of autoimmune phenomenon and beneficial effect of exclusive breastfeeding on food hypersensitivities and allergic disorders the incidence of the disease in infancy has decreased. Age of diagnosis has shifted to older age and the clinical presentation has changed from malabsorption syndrome to abdominal pain and some extraintestinal manifestation such as anaemia.

It was in Melbarne that Ruth Bishop a virologist characterised rotavirus.

In France, Alagille and O'dievre pioneered development in hepatology. They published their book "Maladies du foie et voies billiare chez l'infant" in 1978. The English version of this book came out in 1979.

In the Netherland, Dolf Weijers et al 1959 established paediatric gastroenterology, hepatology and nutrition.

Many more centres were established in Europe.

North America

In North America, several centres of excellent in paediatric gastroenterology developed at the same time. Murray Davidson at Einstein Medical School and the Bronx Lebanon Hospital in New York established a paediatric gastroenterology program directed at inflammatory bowel disease, infectious diarrhoea and motility disorders associated with gastrointestinal problems such as constipation and gastroesophageal reflux in the 1950's.

In Boston, Harry Schwachman with interest in cystic fibrosis established a paediatric gastroenterology in late 1950's and early 1960's. This centre eventually became a major training area for pediatric gastroenterologists under Richard Grant (1972 – 1982) and Allan Walker (1982 – 2001).

Paediatric Hepatology Centres

Development of Paediatric Hepatology occurred independently of pediatric gastroenterology. The development of hepatology as an organ subspecialty was as a result of research findings which were unique to childhood as biliary atresia, Reyes Syndrome. It also transpired that events occurring during hepatobiliary development were critical to physiologic variables in hepatic maturation. These variables accounted for the differences in diseases of liver in children compared to adults. During the early evolution of hepatology investigation largely focused on cholestasis of infancy, choleduchal cysts, extrahepatic biliary atresia, neonatal hepatitis. Liver biopsy for obtaining tissue for diagnosis became a cornerstone for establishing diagnosis and monitoring effect of therapy.

Indications for liver biopsy were defined thus:

- Congenital cholestatic disease (Extrahepatic and Alagille syndrome)
- Liver cirrhosis due to hepatitis B
- Metabolic diseases

These developments heralded expansion of workforce demanding specialised skills and care hence the birth of **Hepatology Units**.

North America

Centres of excellence in Pediatric Hepatology developed in many North American Medical Centres. Thaler, established a training centre in pediatric gastroenterology and hepatology in the University of California in San Francisco. Harvey Sharp, established gastroenterology centre with emphasis on hepatology in Minnesota.

France

The first centre established in 1964 at the Bicetre Hospital in Paris under Professor Alagille.

Britain

The University of London offered academic recognition of Paediatric Gastroenterology and Hepatology by offering appointments from 1970 onwards. Professor Tam Macdonald was appointed Professor in GUT Immunology. Alex Mowat took the lead in Paediatric Hepatology in the University of London. Professor Mowat edited the book “Liver Disorders in Childhood” published in 1979, by Butterworths London - Boston.

Birmingham was the first centre in Britain to offer paediatric liver transplantation.

To date many centres of Paediatric Hepatology, have been established e.g Cincinati Children's Hospital Sao Paolo, Santiago, Sydney, Jerusalem, Tokyo, Chicago etc.

Paediatric Gastroenterology, Hepatology and Nutrition Societies/Associations

In Germany, Osmar Boas was the pioneer in the formation of paediatric gastroenterology society in 1895. Two years later, 1897, Dr. Steward in Philadelphia formed a similar society. Similar societies were simultaneously emerging in Europe and N. America independently.

In November, 1967, Dolf Weijers, initiated the formation of European Society of Paediatric Gastroenterology, Hepatology and Nutrition by inviting Litretch Bertil Lindguist from Sweeden and Jean Rey from France to a meeting to discuss the possibility of a society for Paediatricians with special interest in Paediatric gastroenterology. The group included Dr. Jan Von de Kamar, a biochemist. The group met in Paris and the European Society of Paediatric Gastroenterology Society, the first of its kind was formed. The meeting emphasised the importance of nutrition in child survival. Gradually other Paediatric Gastroenterology Societies emerged.

Further development in formation of Paediatric Gastroenterology Societies is summarised in the table 2 below.

Table 2: Important Milestone in Paediatric Gastroenterology Societies

Year	Events
1968	European Society for Paediatric Gastroenterology and Nutrition 1st Annual meeting in Paris
1969	Paediatric Gut Club formed
1973	North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGAN)
1978	Joint meeting of European Society of Paediatric Gastroenterology, Hepatology and Nutrition and North American Society of Paediatric Gastroenterology Hepatology and Nutrition was held in Paris

1984	NASPGAN Annual General meeting held in Chicago
1990	Journal of Paediatric Gastroenterology and Nutrition born
1994	Commonwealth Association of Paediatric Gastroenterology and Nutrition inaugurated in September in Hong Kong
1998	Commonwealth Association of Paediatric Gastroenterology and Nutrition (CAPGAN) granted observer status at Commonwealth Ministers Meeting in Barbados, November 15 – 19th, 1998.
2000	First World Congress of Pediatric Gastroenterology Hepatology and Nutrition was attended by NASPGAN, ESPGHAN, L'ASPGHAN, APPSGHAN

Abbreviations:

APPSGAN	-	Asian Pan Pacific Society of Gastroenterology and Nutrition
ESPGHAN	-	European Society of Paediatric Gastroenterology, Hepatology and Nutrition
LASPGHAN	-	Latin American Society of Pediatric Gastroenterology Hepatology and Nutrition

Journals and Textbooks

The importance of medical publications for dissemination of new discoveries and advance of knowledge was recognised as far back as 17th Century – Philosophical Transactions. By the mid-18th Century the concept of medical journal was widened from that of reporting empirical research to involve criticisms. From the 18th century onward there has been increase in the emergence of specialist journals including gastroenterology journal. The first Paediatric Gastroenterology Journal came out from Germany: “Archiv fur Verdaungs Krankeiten” in 1895.

In 1982, Lebenthal emerged as the editor-in-chief of Journal of Pediatric Gastroenterology and Nutrition, and Ettore Rossi emerged as associate editor. In 1991, the journal was adopted as the official journal of both European Society of Paediatric Gastroenterology Hepatology and Nutrition and North American Society of Pediatric Gastroenterology Hepatology and Nutrition. Later, APPSPGAN and LASPGAN became affiliated. There is no doubt this journal represent a worldwide field of gastroenterology.

Along with journals, textbooks in paediatric gastroenterology were being published. In 1971, Arnold Silverman, Claude Roy and Frank Cozzetto from Gastroenterology Center Denver published the first book in paediatric gastroenterology. Anderson and Burke, 1975 published a comprehensive textbook in Paediatric Gastroenterology, others were A. P. Mowat "Disorders of the Liver in Childhood" 1979. Gryboski J. 1975 – "Gastrointestinal Problems of Infancy etc".

Major Landmarks in Paediatric Gastroenterology and Hepatology and Nutrition

Progress in basic sciences i.e. Biochemistry, Immunology and deeper understanding of aetiopathogenesis of diseases were made possible through introduction of new diagnostic procedures, miniaturised diagnostic equipment, imaging techniques and organ biopsies. Therapeutic and surgical advances in the management of children included total parenteral nutrition, oral rehydration therapy. New surgical procedures resulted in specific organ transplantations. These are discussed under the following captions:

A. Diagnostic techniques (see table 3)
B. Therapeutic (surgical and medical) advances
C. Molecular basis of gastrointestinal disorders
D. Preventive interventions (vaccines)

Table 3: Landmarks in Diagnostic Techniques in Gastroenterology

i. Improved diagnostic techniques and knowledge
   a. Endoscopy
   b. Ultrasound
   c. Magnetic Resonance Image

ii. Organ biopsies
   a. Peroral Jejunal/duodenal
   b. Rectal
   c. Percutaneous liver biopsy
   d. Ultrasound guided biopsy

iii. Therapeutic (Surgical and Medical)
   a. Total Parenteral Nutrition (TPN)
   b. Organ transplantation (Small intestinal, Liver, Pancreas)

4. Preventive
   a. Rotavirus vaccine
   b. HBV vaccine

A. ADVANCES IN DIAGNOSTIC TECHNIQUES IN GASTROENTEROLOGY

Recent advances that have greatly improved better understandings and knowledge in Paediatric gastroenterology include endoscopy, organ biopsies, immunoassays and ultrasonography and magnetic resonance imaging.

Endoscopy:

This procedure is safe and more sensitive than radiology in detection of superficial mucosal lesions, gastric and duodenal ulcers. Complications usually minor bleeding occurs in less than 2%. Indications are haematemesis and melaena.

Uses:

(a) Endoscopy is useful in the diagnosis of peptic and duodenal ulcers and oesophageal varices.

(b) It offers a good opportunity: for biopsy of tissue for accurate histologic diagnosis.

Therapeutic Uses Are:

(a) Treating bleeding varices by sclerotherapy thereby, avoiding shunting procedures which are useless in children

(b) Dilating strictures with wire guide dilators

(c) Performing of antral mucosal diaphragm and percutaneous replacement of gastrotomy tube.

Ultrasound:

Ultrasound has gained wide acceptance in the diagnosis of gastrointestinal diseases in addition to endoscopy and x-ray. Ultrasound is useful in emergency diagnosis of acute disorders e.g. appendicitis, diverticulitis, ileus and perforation. In chronic inflammatory conditions ultrasound can give information on fistula, abscess, stenosis, changes in stomach wall, tumours and their complications (perforation, penetration).

Therapeutically it can give a far interventional therapies for abscesses (puncture and drainage under favourable conditions).

Magnetic Resonance Imaging:

Uses:

- Diagnosis and monitoring treatment e.g. liver cirrhosis
- Detection of abnormalities of bile ducts
- Detection of inflammatory bowel disease e.g. Chron's disease and ulcerative colitis.

ORGAN BIOPSIES

1. **Jejunal Biopsy**:

a. Peroral Biopsy: The development of the technique of peroral intestinal biopsy for obtaining mucosal tissues undoubtedly has been a great advance in rational diagnosis and management of many disorders of the gastrointestinal track. It provides information on both the morphology and functions of the small gut for example the morphologic appearances of the small bowel in conditions that give rise to flat or subtotal villous atrophy e.g.
Coeliac disease
Tropical sprue
Giardiasis
Zollinger – Ellison syndrome
Malnutrition (kwashiorkor)

Biopsy tissues can be used for biochemical assays. Assays of mucosal disaccharidase activities are useful in differentiating from secondary sugar intolerance.

The commonly used instrument in peroral jejunal biopsy is the Crosby capsule. This is useful in establishing the diagnosis of malabsorptions syndromes, coeliac disease and lymphomas.

(b) Rectal biopsy is useful in diagnosis of Chron's disease and helminthic fibrosis e.g. schistosomiasis; Entermoeba histolytica lesions.

Complications:

Complications arising from peroral jejunal biopsy are rare and include bleeding and perforation in severely morasmic children. Occasionally the capsule can become firmly attached to the mucosa and detached. Premature firing or failure to fire is related to poor maintenance of the capsule.

LIVER BIOPSY

Liver biopsy was introduce by Paul Ehlich, a German physician in 1883 by aspiration method. The technique of percutaneous liver biopsy for diagnosis was performed in 1920. The other route of liver biopsy is transjugular introduced in 1970 by Charles Dotter a radiologist. Other methods of liver biopsy are percutaneous, transvenous and or abdominal surgery where wedge biopsy is obtained at laparotomy. Percutaneous subcostal approach is the most preferred approach in Paediatrics.

In our attempt to establish the pattern of liver disease in the Paediatric gastroenterology unit of Ahmadu Bello University Teaching Hospital in 1985 in Zaria, 78 children with diagnosis of liver disorders were studied. The indications for liver biopsy were:

-	Persistent conjugated hyperbilirubinaemia (Biliary atresia)	-	27
-	Hepatomegaly		
	? a. Schistosomiasis	-	19
	? b. Unknown cause	-	16
-	Chronic hepatitis	-	8
-	Portal hypertension (cirrhosis)	-	4
-	Reye's Syndrome	-	4
			78

* Reye's syndrome biopsy at post mortem

Table 4: **Histopathologic Diagnosis in 78 Children who had Percutaneous Liver Biopsy**

Histologic Diagnosis		No of Cases
1.	**Hepatic Schistosomiasis**	**27**
2.	Biliary atresia	25 (12 with cirrhosis)
3.	Cirrhosis	9
4.	Chronic hepatitis	2
5.	Reye's syndrome	2
6.	Congenital hepatic fibrosis	2
7.	Neonatal giant cell hepatitis	2
8.	Portal Fibrosis	2
9.	Tropical splenomegaly syndrome (Hyper-reactive malaria splenomegaly syndrome)	1
10.	No pathologic diagnosis	6
	Total	78

Liver biopsy was useful in establishing definite pathologic diagnosis in 92% of the cases.

In the 6 cases where histology reports were inconclusive it was however, useful in exclusion diagnosis of diffuse lesions like hepatitis or cirrhosis. In some of these cases malarial pigments were demonstrated but these did not contribute to the diagnoses.

B. MOLECULAR BASIS OF GASTROENTEROLOGICAL DISORDERS

Knowledge from molecular biology techniques have greatly improved our understanding of pathophysiologic changes that occur in gastrointestinal tract disorders. For example mitochondrial ATP production normally takes place through oxidative phosphorylation pathway. Oxydative phosphorylation biogenesis depends on both nuclear and mitochondrial encoded gene products and or mutations in both genomes. This process if disrupted it affects electron transport which in turn disrupts ATP synthesis. This ultimately leads to dysfunction of organ and disease subsequently developed.

Molecular mutations have been unravelled as genetic origins of gastroenterologic disorders. The following conditions will be discussed as illustrations of molecular basis of disease.

1. **H. Pylori**:

The discovery of Helicobacter Pylori in 1982 not only changed the treatment of peptic ulcer from surgery to medical treatment with antimicrobial agents but also, provided further knowledge in gastrointestinal disease. It is now clear that infection with H. Pylori predominantly occurs in childhood and is strongly associated with duodenal ulcer in 33 – 100% later in adulthood. The risk of peptic ulcer is between 10 – 20% in life time and gastic cancer 1 – 2%. H. Pylori has also been implicated in aetiology of colorectal polyp and colorectal cancer.

Mechanisms of Cancer Development in H. Pylori:

Two mechanisms are being proposed for the development of cancer:

a. There is enhanced production of free radicals and increased cell mutation

b. **Perigenetic pathway**: This involves alteration in epithelial cell protein. H. Pylori induces inflammation associated with signalling TNF-alpha and interleuking 6 which cause alteration in gastric epithelial cell adhesion leading to dispersion and migration of mutated epithelial cells. Strains of H. Pylori associated with gastric cancer produce two toxic proteins – vacuolating toxin A and cytotoxin A genes. The effect of these proteins are to act as tumour suppressors.

2. Functional Disorders of Gastrointestinal Tract

Definition: "Symptoms from an organ without overt pathology"

The absence of overt disease or pathology is only apparent than real because it has been established that inflammatory insult in the gut leaves changes in the nerves supplying the gut and mucosal functions which are only detectable by special techniques. Approximately 10% of irritable bowel syndrome have post infectious origin.

Polymorphism of genes specifically G-Protein B_3 (GNB3) subunit, polymorphism 5-HT transporter genes C825T have immunomodulatory and neuromodulatory effects in events producing symptomatology of functional disorders of the gastrointestinal tracts.

Functional Disorders of the GIT are:

- Irritable bowel syndrome
- Infantile regurtitation
- Infant dyschezia
- Functional dyspepsia
- Functional constipation
- Toddlers diarrhoea

3. **Pancreatic Disorders**

(i)
a. Juvenile Tropical Pancreatitis Syndrome
b. Tropical chronic pancreatitis
c. Tropical calcific pancreatitis
d. Afro-Asian pancreatitis
e. Fibrocalculous pancreatitis

a – e refer to the same disorder.

Definition: This is “A juvenile form of chronic calcific non-alcohol pancreatitis prevalent exclusively in the developing countries of the tropical world. Some of its distinctive features are younger age at onset, presence of large intraductal calculi, and accelerated course of the disease leading to end points of diabetes and or steatorrhoea and a high susceptibility to pancreatic cancer”. WHO International Study Group on diagnosis of diabetes mellitus.

Tropical Chronic Pancreatitis is a consequence of dysfunctional mutation in cationic trypsinogen PRSSI, RIZZH and SPINK 1 genes (serine protease inhibitor Kazal type 1). This mutation alters the target amino acid within the trypsin position under condition of low calcium concentrations in the pancreatic acinar cells where trypsin is synthesised and stored. Chronic inflammation of Tropical chronic pancreatitis leads to increase genomic damage and increase cellular proliferations which favours malignant transformation of the pancreatic cells. SPINK 1 gene mutation is a precursor for fibrocalculous diabetes mellitus. SPINK 1 is always seen in pancreatic cancer preceded by tropical chronic pancreatitis. Therefore, SPINK 1 mutation appears to be a strong link to tropical pancreatitis and pancreatic cancer.

(ii) **Pancreatic Cancer**:

Three protein genetic mutations identified in pathogenesis of pancreatic cancer are:

H-ras
N-ras
K-ras

These proteins exist as either active or inactive. Mutation point in K-ras is located at codon 12, 13 or 16. K-ras mutation at codon 12 has frequency of 85 – 95% of pancreatic cancer with amino acid substitution being G to A transition. K-ras mutation activates proteins which signal ras/raf/mitogen activated protein Kinase cascade enhancing cell proliferation.

P_3 is another gene associated with pancreatic cancer. P_3 is a suppressor gene located in the short arm of chromosome 17. It encodes a 53-kd nuclear phosphorylation which function as a transcription factor that triggers cell cycle arrest and or apoptosis in response to DNA injury from whatever cause including hypoxia. Over expression of P_{53} is caused by high stability of mutated proteins.

Other molecular gene mutations linked to pancreatic cancer include growth factors and growth factor receptors. These are all involved in carcinogenesis where they influence cell proliferation, invasion and metastasis.

4. **Molecular Basis of Hepatocellular Carcinoma**: (HB and C) Virus Induced.

Infection with hepatitis B and C virus had been linked with development of hepatocellular cancer in more than 90% of cases. Although, the mechanism of pathogenesis of HBV/C induced hepatocellular cancer is still not clear the accepted hypotheses to date are based on two template, direct and indirect. Summarized in table 5 below.

Table 5: Mechanisms of HCC in HB and C

Direct:

Integration of HBV DNA into hepatocytes. Integration within a near functional cellular gene.

HBX Protein:

- HBX protein is a transcriptional activator
- Activates the Ras – RafMAPK pathway
- Interacts with P_{53}
- Truncated HBsAg gene product acts as transactivator which leads to release of Kinase associated with cell proliferation.

Indirect:

Inflammation and regeneration with chronic HBV infection through cirrhosis associated with chronic infection.

Hepatitis C act through similar mechanisms above by genetic alterations in the hepatocytes.

THERAPEUTIC ADVANCES

TOTAL PARENTERAL NUTRITION (TPN)

The idea of temporary partial or total exclusion of gastrointestinal tract through intravenous infusion to maintain nutritional states in severely ill children with medical disorders has revolutionised the clinical course of many conditions hitherto lethal to both medical and surgical interventions.

The technique of TPN was developed by Dr. Stanley Dudrick a resident surgeon in 1968 in Pennsylvania and perfected by Dr. Wilmore. This has become widely accepted as an alternative mode of feeding patients who cannot take orally Essentially the solution contains water, electrolytes, glucose, amino acids, lipids, essential vitamins, (minerals and trace elements) are added based on need. Lipid, glucose and protein can be combined in one solution. Emulsifier commonly used is lecithin because it has the advantage of being biodegraded without toxicity.

Total parenteral nutrition involves provision of macronutrients (amino acids, lipids and carbohydrates) in a single delivery system. Newer substrates are also being made available. Deficiencies of essential fatty acids, trace elements can be replaced intravenously. The solutions can be customised for any patient.

Table 6: Indications for TPN

- Intestinal fistula
- Short bowel syndrome
- Chronic pancreatitis
- Advance inflammatory bowel disease
- Delayed postoperative gastrointestinal function
- Extensive small bowel resection
- Protracted diarrhoea of infancy
- Hypermetabolic states
- Extensive burns
- Severe malnutrition

Table 7 (i): **Complications**

(a) Catheter related
Pneumothorax
Accidental arterial puncture
Catheter related sepsis

(b) Metabolic Complications
Feeding syndrome:
1. Hypokalaemia
2. Hypophosphataemia
3. Hypomagnesaemia

Hyperglycaemia may occur at the start of therapy

Hypoglycaemia occur with sudden stoppage of therapy

Table 7 (ii):

Bone diseases

Osteoporosis

Osteomalacia

Table 7 (iii):

Others
Steatosis
Biliary sludge
Fatty liver disease and liver failure
Cholestasis
Micronutrient deficiency
Renal dysfunction
HUNGER – The patient may feel hungry because of stoppage of oral feeding

ORGAN TRANSPLANTATION

Transplantation of organs is now an accepted therapy for end-stage organ failure in Paediatric practice. In many centres the results are quite good. Progress has been made in intestinal and liver transplantations with improving survivals. However, these progress are marred by rejection complications.

(a) **Intestinal Transplantation**:

Small Intestinal transplantation is indicated in children with permanent intestinal failure with life threatening complications of parenteral nutrition.

Intestinal failure is defined as:

“REDUCTION IN FUNCTIONING GUT MASS BELOW MINIMAL AMOUNT NECESSARY FOR DIGESTION AND ABSORPTION OF THE NUTRIENTS AND FLUID REQUIREMENT FOR THE MAINTENANCE IN ADULTS OR GROWTH IN CHILDREN”

This is a functional definition. Anatomically – this is defined as: "HAVING LESS THAN 75CM OF RESIDUAL SMALL INTESTINE AFTER RESECTION" in postnatal life.

Small intestinal lengths in various stages of development are shown in the table 8 below.

Table 8: Small Intestinal Lengths in Perinatal, Infancy through Adults

Age	Mean Bowel Length (cm)
24 – 26 wks post conception	70 ± 6.3
30 – 32 wks post conception	117 ± 6.9
36 – 38 wks post conception	143 ± 12.0
39 – 40 wks post conception	157 ± 11.2
0 – 6 months	239 ± 8.3
7 – 12 months	284 ± 20.9
1 – 2yrs	272 ± 25.1 – 364 ± 18.2
2 – 4yrs	240 ± 16.9 – 367 ± 37
Adults 33 – 100yrs	796 ± 129

Table 9: <u>Causes of Intestinal Failure Classified According to Age</u>

1. **Prenatal and Neonatal**:
   - Short bowel syndrome
   - Gastroschisis
   - Atresia
   - Volvulus
   - Long segment Hirschprangs disease
   - Necrotising enterocolitis
   - Vascular thrombosis

2. **Childhood**:

- Short bowel syndrome
- Volvulus
- Intussusception
- Trauma
- Tumour
- Neurovascular disorders
- Chronic inflammatory bowel disease

The North American Paediatric Gastroenterology Society gave the following 3 groups of indications for small bowel transplantation:

Group 1: Patients with intestinal failure who have high risk of mortality despite optimal parenteral nutrition

Group 2: Patients with intestinal failure and total parenteral nutrition failure caused by major complications of TPN.

Risk Factors for TPN Dependency include:

- Atresia
- Bacterial overgrowth
- Liver failure
- Septic complications of TPN and loss of central venous line

Group 3: Patients with locally invasive tumours of the abdomen intra-abdominal tumours such as familial adenomatous polyposis.

Table 10: **Causes of Failure of Small Intestinal Transplantation**

- High risk of rejection despite use of tacrolinus (a monochlonal aimed at T-lymphocyte depletion)

Infectious agents such as:

- Adenovirus
- Cytomegalovirus and
- Cryptosporidium pose great challenge.

5. Liver Transplantation:

Liver transplantation for children with life threatening acute or chronic liver disease has proven within the last two decades or so to have high success rates. The first attempt at liver transplantation with one year survival was in 1967. Between 1967 and 1979, there was a 30% 2 year survival rate in few centres in Europe and the USA. After 1980, several centres in the USA were carrying liver transplantations. Major complications recorded included graft rejection, portal hypertension, severe septicaemia and high mortality rates.

By 1990, refined surgical techniques and improved immunosuppressive management led to high success rate. This period coincided with two landmarks development in progress in Hepatology namely the characterisation of hepatitis C virus infection and the awareness that infection with hepatitis C virus causes end-stage liver disease. Infection with hepatitis C is linked to hepatocellular cancer.

The second was the realisation that liver transplantation in patients with hepatocellular carcinoma was successful.

The success story of liver transplantation was challenged by complications such as hepatic artery thrombosis, bile perforation, biliary stricture, bowel perforation and graft rejection.

Table 11: Indications for Liver Transplantations are:

i. Cirrhosis mainly due to extrahepatic biliary atresia and primary biliary cirrhosis, hepatitis B and C infections.

ii. Acute hepatic failure

iii. Cholestatic disease

iv. Primary tumours of the liver

v. Secondary liver tumours (carcinoid)

vi. Congenital biliary disease (Alagille syndrome, choleduchal cysts)

vii. Metabolic disease (alpha-1-antitrypsin deficiency)

viii. Non-Alcoholic fatty liver disease

Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease is an emerging chronic liver disease related to excessive accumulation of hepatic fat. It is now considered as an hepatic component of metabolic syndrome occurring in both children and adult. The spectrum of the disease range from fat accumulation alone (Steatosis) to significant histologic steatohepatitis. It is progressive ultimately leading to end stage disease requiring transplantation. It has a high prevalence among the obsessed children. The liver acts as an ectopic site for fat deposition.

The exact pathophysiology of NAFLD is unclear at the moment but inter play of insulin resistance, glucose intolerance, dyslipidaemia, oxidative stress and release of proinflammatory cytokines appear critical. Many genes are implicated but PNPLA 3 gene appear to have a strong association with development of NAFLD which runs in families. There is high risk of cirrhosis and cancer.

NAFLD is an indication for 10 – 16% liver transplantation in North America.

Survival: Following Liver Transplantation

Five to seven years success rate of liver transplantation is reported to be as high as 90% in excellent centres.

The issue of survival is a twofold phenomenon. One is the survival of donor liver and the other that of the recipient. Patients and grafts survival rate for cadaveric recipient do not appear to be different from those recipients of living donors. However, biliary complications appear more common among cadaveric liver recipients than living donors recipients.

Other Challenges Associated with Liver Transplantation are:

(i) Long term complications of immunosuppression therapy e.g. growth retardation neurotoxivity.

(ii) Risk of malignancy

PANCREAS TRANSPLANTATION

The first recorded pancreas transplantation was carried by Dr. Kelly and his team in 1966 in a 28 year old lady. Real progress occurred between 1993 and 1997 when 1 year and above survival rate reached 100%.

Indications for Pancreas Transplantations are:

- Diabetes mellitus particularly in patients with renal failure who require kidney transplantation
- Those patients with life threatening hypoglycaemia.

More than 90% of pancreas transplantation are simultaneous pancreas – kidney transplantations.

Table 12: Types of Pancreas Transplants

1. Pancreas alone for patients with type 1 diabetes who frequently suffer severe hypoglycaemia but have adequate renal functions
2. Simultaneous pancreas – kidney transplant from same donor to recipient
3. Pancreas – after kidney transplant when a cadaveric donor pancreas after previous and different living or deceased donor kidney transplant
4. Simultaneous deceased donor pancreas and live donor kidney.

therapy. Allograft acceptance or tolerance is an active process. The major advance which allows for prolonged graft survival is the use of immunosuppressive drugs. The immunosuppressive drugs used vary from centre to centre. Basically 3 categories are:

1. Early immunosuppressors
   E.g. Calcineurin inhibitors – Tacrolimus, cyclosporine

2. Late immunosuppressors
   E.g. Antimetabolites – Azathioprine
   Purine synthesis inhibitors – mycopheno
   Late mofetil

3. Pan immunosuppressor – Corticosteroid

Current Practice in Immunosuppressive Therapy involve:

(a) Use of calcineurin inhibitor with low dose of steroid
(b) Tacrolimus + steroid + azathioprine
(c) Tacrolimus + steroid + mycophenolate mofelil

Prognosis after pancreas transplantation is very good. One year after transplantation more than 95% are alive, and 80 – 85% of all pancreas are still functional.

DIARRHOEAL DISEASE AND ORAL REHYDRATION THERAPY

Until the mid-1960s, the scientific, aetiologic and pathophysiologic bases of childhood diarrhoeal disease remained largely unknown. Different cultural beliefs such as infidelity, evil spirit, teething among some Africans, Indians Brazilian and European societies respectively were accepted as the aetiologies of childhood diarrhoea. This lack of understanding of the aetiology and pathophysiologic bases of childhood diarrhoeal disease no doubt contributed to irrational drug use in diarrhoeal case management. In the health facilities health professional use intravenous fluid therapy as the cornerstone mode of treatment and fluid replacement and maintenance of electrolytes in all cases of diarrhoea. This mode of therapy required hospitalisation and skilled medical supervision.

Early attempt at the use of oral rehydration was carried out with success by Darrow and Harrison in 1955. For many years trials in the use of oral fluid therapy in childhood diarrhoea were carried out in many countries e.g. Bangledesh, the West Indies, Phillipines and London under widely varying conditions. These trials demonstrated that oral rehydration was effective in hydrating over 80% of children with moderate to severe dehydration.

ORAL REHYDRATION THERAPY – A MIRACLE CURE

The impact of oral rehydration therapy in the Bangladesh study is illustrated in the table below.

Table 13: Impact of ORT in 2 Rural Areas in Bangladesh

Age in Yrs	Diarrhoea Case Fatality/1000		Diarrhoea Mortality/1000	
	Samlapur	Dordil	Samlapur	Bordil
< 1	0.5	6.3	1.0	11
1 – 4	0.0	23	10	17
5 – 9	0.2	13	0.2	14

(1) In Samlapur ORS was given to 80% of children with diarrhoeal disease compared to Bordil where ORS was used for only 38% of diarrhoeal cases.

(2) Another study in Philippines and Turkey showed that children with diarrhoea who were given ORS, and mothers that received dietary education about continuing breast feeding and other foods gained more weight than children with diarrhoea who were not given ORS and whose mothers had not received dietary education.

(3) When ORT was used on hospital ward and in OPD it reduces diarrhoeal case – fatality rates, diarrhoeal disease admission rates fall by 61%, frequency and duration of IV therapy and thus cost of diarrhoeal treatment were drastically reduced.

(4) ORT was successful in 95% of rotavirus patients

These and many more gave wider support of the use of ORT.

The Scientific Basis for the Sources of ORT are based on Pathophysiology of the Gastrointestinal Tracts that:

(1) The absorptive mechanism of the gut remains intact in diarrhoeal disease of diverse aetiology even in the presence of inflammation in the small intestine.

(2) Sodium absorption is enhanced by the presence of the glucose. Sodium absorption in the gut is by coupling with small organic molecules such as D-hexoses, neutral amino acids, dipeptides particularly glucose. The presence of glucose at the brush border enhances sodium and chloride uptake thereby allowing flow of water passively.

Lancet in its editorial 1983 summarised the benefits of Oral Rehydration Therapy as follows:

- ORT is effective
- Inexpensive
- Easy to use
- Safer than IVF
- Involves the mother in her child’s case.

In Nigeria the history of salt sugar solution dates back to the early 1950s and 1970. David Morley in Ile-Ife and Richard Dobbs in Zaria were among the early advocates of the use of salt-sugar solution. Various formula were advocated in different parts of Nigeria, thus creating so much confusion.

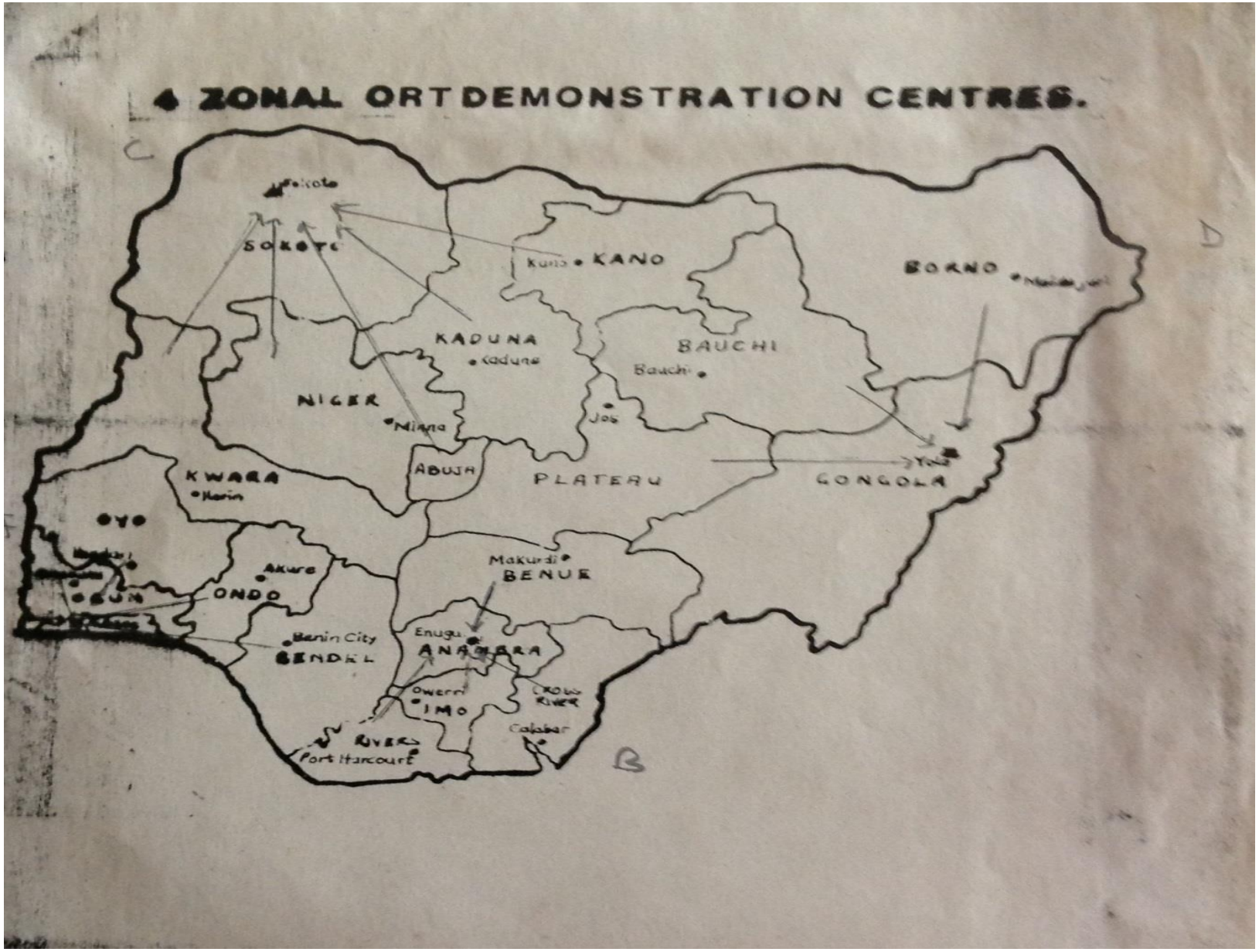
Real progress on the use of standard ORS started when in 1982, the Federal Ministry of Health and the World Health Organisation collaborating with each other commissioned multicentred studies in Eastern Nigeria, Western and Northern Nigeria with Okeahialam (Enugu) Sarki (Ibadan) and Abdurrhaman (Zaria) respectively to find the acceptability, efficacy or otherwise of the WHO standard ORS. The study reported wide acceptability among mothers and efficacy of ORS.

Having adopted the Primary Health Care as the cornerstone of health care delivery in Nigeria, ORT as a technology in the control of diarrhoeal disease became an essential entry point in the Primary Health Care, consequently, the Federal Ministry of Health /UNICEF in 1985 commissioned 4 consultants namely: Professor Okeahialam (Enugu), Professor Grange (Lagos), Professor Yakubu (Zaria) and Abiodun (Benin) to assist in planning and implementing ORT Program in Nigeria.

The implementation of the program involved:

- Touring the entire country
- Establishment of ORT units in health facilities
- Establishment of ORT/Diarrhoea Training Centres
- Organising seminar for doctors and other health professionals
- Demonstration of ORT use
- Production of jingles to disseminate messages to the public

[See Map]


4 ZONAL ORT DEMONSTRATION CENTRES.
SOKOTO
KANO
BORNO
KADUNA
Kaduna
BAUCHI
Bauchi
NIGER
Minna
Jos
ABUJA
PLATEAU
GONGOLA
KWARA
Ilorin
OYO
Akure
ONDO
OGUN
Makurdi
BENUE
Benin City
BENDEL
Enugu
ANAMBRA
Owerri
IMO
CROSS RIVER
Calabar
RIVERS
Port Harcourt

The country was divided into 4 zones with consultants as follows:

SW Zone - Professor Grange
Midwest Zone - Professor Abiodun
SE - Professor Okeahialam
Northern Zone - Professor Yakubu – assisted by:
Professors Grange and Okeahialam because of massive landmass area.

The Team's Achievement Included but not Exhaustive:

(1) Standardisation of home-made solution for use at home to prevent development of dehydration i.e.

1 teaspoon level of salt
+
10 teaspoon level of granulated sugar or 5 cubes
+
1 beer bottle of water or 2 soft drinks of water (650mls)

Composition of this solution yielded:
80 – 90 millimoles/litre of sodium
83 – 111 millimoles/litre of glucose

Very close to WHO ORS composition

(2) In-service training of doctors
(3) Wide awareness and acceptance of SSS/ORS by different health professionals and others
(4) Introduction of diarrhoeal care management in undergraduate curriculum
(5) Production of training materials
(6) Impact assessment of ORT Program

For example, in 1995 in a rural community household survey in Ikara, Kaduna State it was found that regardless of educational level of mothers 82% of mothers were aware of ORS and SSS use in treatment of diarrhoeal although only 60% knew how to use the mixtures correctly few years after the ORT campaign.

The use of IV fluid and hospitalisation of diarrhoeal cases has dropped by 70%. It is a statement of fact that cases of severe dehydration coming to children's emergency has nearly vanished.

HEPATITIS VIRUS VACCINE – PREVENTIVE MEASURES

Hepatitis A vaccine was introduced in 2001 by GlaxoSmithKline. It is currently available in combination with hepatitis B virus vaccine. Hepatitis A vaccine is recommended to be given at 1 month and 6 months later and to all those who are at risk.

Hepatitis B Vaccine:

This is the first anti-cancer vaccine. It is effective against hepatitis B virus infection. The first generation vaccine (Heptavac) was manufactured by Merk Pharmaceuticals and came into use 1982. The current second generation vaccine came into use in 1986.

Efficacy:

- It is 95% effective
- Evidence from Taiwan
  - i. Prevalence of HBsAg in children 6 – 14 years was 10% in 1980 prior to introduction of universal vaccination programme of hepatitis B vaccine
  - ii. In 1994, fourteen years after introduction of hepatitis B vaccine prevalence of HBsAg in the same age group dropped to 1.3%
  - iii. Incidence of hepatocellular carcinoma in children same age group 0.70/100,000 in 1980 dropped to 0.19/100,000 in 1999.

Evidence Linking HBV to Hepatocellular Carcinoma (HCC)

Epidemiologically chronic infection with HBV has been linked to the development of hepatocellular carcinoma for over three decades. This is based on the following evidence:

a. More than 80% of patients with HCC are found in high incidence areas of HBV infection e.g. east Asia and Sub-Saharan Africa.

b. 90% of HCC cases have antibody to hepatitis B core antigen detected in the serum.

c. Beasley in Taiwan in a study of over 22,000 male municipal workers who were HBsAg positive had significantly higher rates of HCC than controls. The relative risk for HCC among those HBV infected was 63 compared to uninfected.

d. Universal infant vaccination with HBV vaccine programme in several countries effectively reduced the rate of hepatocellular carcinoma in children.

e. Antiviral therapy against hepatitis B virus is effective in causing prolonged lowering of serum levels of HBV DNA. Evidence reveal that prolonged antiviral therapy reduce the risk of hepatocellular carcinoma among patients with chronic hepatitis B virus infection.

Prevention:

Many countries have introduced universal infant vaccination programme. WHO have adopted the following measures for the control and prevention of HBV infection:

i. Raising awareness, promoting partnership
ii. Formulating evidence-based policy data for action
iii. Promoting prevention of transmission through vaccination, safe injection practices and blood safety.

In March 2015, WHO launched its guidelines for the prevention, care and treatment of persons living with chronic hepatitis B virus infection. WHO further recommends:

(a) Promote the use of simple, non-invasive diagnostic tests to assess the stage of liver disease and eligibility for treatment.

(b) Prioritize treatment for those with most advanced liver disease and at greatest risk of mortality.

(c) Recommend the preferred use of the nucleoside analogues with a high barrier to drug resistance (tenoforvir, entecavir) and entecavir in children aged 2 – 11 years for 1st and second line treatment.

(c) Recommend guidelines for life long treatment in those with cirrhosis and regular monitoring for disease progression toxicity and early detection of liver cancer.

(e) WHO organised and adopts World Hepatitis Day, July every year.

ROTAVIRUS

In 1943, Jacob Light and Horace Hoodes, discovered a filterable agent in the faeces of children with infectious diarrhoea. The same agent was proved to cause diarrhoea in livestock. Three decades later, preserved sample of the agent proved to be rotavirus.

In 1960, Ruth Bishop and colleague in Melbourne described this virus in stools of children with gastroenteritis.

In 1974, Thomas Flewett, suggest the name rotavirus based on the observation that under electron microscope these viruses look like wheel.

Rotavirus a double stranded RNA virus is responsible for majority of severe diarrhoea in infancy and children under 5 years causing million death annually.

However, good news came in 1998 with the development of Rothshield vaccine by Wyeth which was licenced in the USA. The vaccine was acclaimed effective with efficacy ranging from 80% to 100% in USA, Venezuala and Findland.

Rothshield was withdrawn in 1999 by the manufacturer following heated debate based on the report that the vaccine contributed high to risk of intussusception in children who were given the rotavirus vaccine.

These was followed by new rotavirus vaccines:

- Rotarix by GlaxoSmithKline
- Rotaleq by Merk
- New product by Sonafi affiliate of Shantha Biotech 2015
- Rotavac by Bharat Biotech (2013) India

Rotarix is a monovalent human, live attenuated vaccine containing one rotavirus strain of GIP. Effective in preventing diarrhoea caused by G1, G3, G4, and G9 strains.

Rota Teq is live attenuated pentavalent containing 5 strains.

Rotavirus is effective as evidence by many clinical trials. On 5th June, 2005 WHO recommended the inclusion of rotavirus in all national immunisation programs. The rotavirus vaccine program and the accelerated vaccine introduction initiative have worked well in studying the efficacy of rotavirus. This is spear headed by international non-government organisations, PATH, WHO, CDD Atlanta, and Global Alliance for Vaccines and Immunisation.

Efficacy:

In 2009, review in Mexico, Nicaragna examples of countries that introduced rotavirus vaccines in 2006 it was found that:
In Mexico, death from diarrhoeal illness due to rotavirus dropped by more than 65% while in Nicaragna this was 60%. Globally it was estimated that rotavirus vaccination will prevent 45% (228,000) annual death due to rotavirus.

Future Agenda:

Paediatric Gastroenterology, Hepatology and Nutrition

1. There is need to develop post fellowship training program. This will serve as a source of producing future clinicians and basic clinical science researchers to provide opportunity for young paediatric gastroenterology investigators for mentoring.

2. Establishment of paediatric organ specific centres of excellence e.g. Hepatology and gastroenterology units with common git disorders to obtain, analyse and disseminate data for further research and training.

3. Improvement in diagnostic services.

4. Paediatric Gastroenterology, Hepatology and Nutrition pear reviewed Journal to serve as an outlet for Nigerian Society of Paediatric Gastroenterology

5. Sustenance of annual general meeting.

6. Documentation of NISPGAN history for future generations to build on.

Hamilton:

“A pediatric specialty as having professional status once it has a peer-review journal, professional associations, the task forces (in Europe working groups) and examinations to assess professional competence”.

Our Association is only 3 years a great deal of work remains to be done for children with gastrointestinal disease both in terms of treatment and prevention. It is our interactions locally and international that will offer greater opportunity for the future.

CONCLUSION

In conclusion I wish to admonish this young society to be more proactive in implementing the theme of this conference to purposefully move the society forward.

In my introduction I mentioned that this was a journey into a far country. By this I am reminding the audience of the quotation from the Physician Dr. Luke 15: 13 which reads:

“AND NOT MANY DAYS AFTER THE YOUNGER SON GATHERED ALL TOGETHER AND TOOK HIS JOURNEY INTO A FAR COUNTRY AND THERE WASTED HIS SUBSTANCE WITH RIOTOUS LIVING”

For the past close to one hour I have wasted your time with useless stuff.

I thank you for your endurance.

ACKNOWLEDGEMENT

I acknowledge immensely all the authors cited in the reference listed. Excellent secretarial work of Stella Onyejiuwa, is proudly appreciated.

THANK YOU