

## **THE STATUS OF PAEDIATRIC PRACTICE AND RESEARCH IN NIGERIA WITH REFERENCE TO GENETICS: A PLEA FOR ESTABLISHMENT OF MEDICAL GENETICS RESEARCH CENTRE**

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### **Abstract**

*Background:* There is a general agreement that one way to assess medical scientific progress in different countries is to analyse the publication rate in scientific journals and the nature of the limitations in facilities in such studies.

*Method:* The status of paediatric practice and research in Nigeria in the last one decade with particular reference to the country's progress in medical genetics was assessed, by auditing of published Nigerian studies in paediatrics between 1992 and 2001 based on articles published in 8 Nigerian medical journals and contributions made by Nigerian authors in two widely circulated international quarterly journals on tropical paediatrics.

*Results:* Of the 2497 articles published in 8 Nigerian medical journals, 873(35%) articles were devoted to paediatrics. Of these, 270(31%) papers were related to genetics, dysmorphology and congenital malformations. There were also 101(11.6%) of the 873 articles that were primarily on non-genetic disorders, but needing investigatory facilities based on cytogenetic analysis, special staining techniques, molecular testing, special biochemistry or electron microscopy. Thus, there were 371(42.5%) of 873 studies devoted to paediatrics in which such special investigatory facilities could have improved the quality of practice or research in Nigeria. Regrettably, in only 8(2.2%) of 371 studies were the appropriate investigations available, mostly done either abroad or in collaboration with workers abroad. Furthermore, of the 1040 articles published in the last one decade in two widely circulated international quarterly journals on tropical paediatrics, up to 281(27%) were contributed by Nigerian authors. Of these 35(12.5%) were devoted to genetics and congenital malformations on Nigerian children, but in only 7 of these studies were all the necessary investigations available, but done in developed nations.

*Conclusion:* This audit reveals that although Nigerian paediatricians have been very active in research, qualitative work on medical genetics is problematic and scientific progress in this very important field is very slow. It seems that in a developing nation like Nigeria collaboration with developed nations provides a strategy to address the problem. A plea is therefore made for the establishment of a reference medical genetics research center for Nigeria through such collaboration.

**Key words:** Paediatric, genetics, research, Nigeria

### **Introduction**

The disciplines of population genetics, biochemical (or molecular) genetics and cytogenetics have recently reached an advanced state and are used in combination in studying, defining, counseling and treating inherited pathological processes. Medical

genetics is currently regarded as an essential discipline for an understanding of human biology and has increasing relevance to clinical experience.<sup>1-10</sup>

A new era in cytogenetics began in 1956 with the discovery by Tjio and Levan<sup>1</sup> that the human chromosome number was 46. Since then, the field of cytogenetics has advanced with explosive rapidity.

Improved techniques using Giemsa banding and fluorescent staining became available in the 1970's and these made possible the identification of individual chromosomes and their subsets.<sup>1-3</sup> Abnormalities in chromosome number or structure associated with numerous clinical syndromes began to be diagnosed more than 40 years ago.<sup>4</sup> More sophisticated methods of detecting chromosomal aberrations became available in the late 1980's.<sup>5</sup> Detection of chromosomal aberrations in the human interphase nucleus by visualization of specific target DNA with radioactive and non-radioactive insitu techniques were developed in 1986 and were used to diagnose trisomy 18 with probe (L1.84).<sup>5</sup> Translocations, deletions and inversions of chromosomes can now be precisely confirmed and related to abnormal phenotypes.<sup>2</sup>

Applied research in paediatrics is now being organized in the light of new acquisitions of basic knowledge. Hereditary diseases are being precisely described with the localization and cloning of mutant genes and the identification of structural and functional proteins on which they depend.<sup>2,6</sup> This is complimented by chemistry of recombinant DNA. Recombinant DNA technology has since the 1980's<sup>7</sup> made possible the synthesis of protein products on mass scale-with production of safer vaccines,<sup>8</sup> safer and more culturally acceptable insulin, and antenatal diagnosis of a variety of conditions, including sickle cell disease.<sup>9</sup>

Recent advances in molecular genetics have made gene therapy possible.<sup>10,11</sup> Gene therapy – which is the transfer of recombinant DNA, transiently or permanently into human cells for correction of disease<sup>2</sup> began in September 1990.<sup>10</sup> A 4 years old girl with adenosine deaminase deficiency (ADA) was treated with autologous lymphocytes in which the normal ADA gene has been transfected.<sup>10</sup> Since, then, human gene therapy, as Miller<sup>11</sup> asserts, has come of age. Human gene therapy clinical trials in malignant and non-malignant diseases – using the strategy of retroviral-mediated gene transfer have reached an advanced stage for non-malignant diseases like severe combined immunodeficiency (SCID), familial hypercholesterolaemia, haemophilia B, and for malignant diseases such as melanoma.<sup>12</sup> Gene therapy is currently undergoing evaluation and monitoring in developed nations.<sup>12</sup>

Currently, there has been a growing recognition of the influence of genetic factors in human disease.<sup>2,12,13</sup> The appreciation of the importance of inherited components of common diseases, congenital malformations and cancer has increased substantially in recent years. In the last 10 years, revolutionary developments have occurred in the basic science of

genetics. Major efforts have focused on the application of molecular genetics to understanding heritable and acquired diseases.<sup>2,12,13</sup> Extraordinary progress has been made to use these advances in the practice of medicine.<sup>2,6-12</sup> It is well known that a collaborative international effort of unprecedented scope has been initiated, known as the Human Genome Project (HGP).<sup>2</sup> The spatial location of many human genes and DNA segments have been established. The rate of gene-disease associations has rapidly accelerated as consequences of 40, 000 partially sequenced genes, and the genetic maps of humans provided in 1996.<sup>14</sup> At the beginning of this millennium the human genome had been virtually completely mapped, and cloning of human embryos is a scientific reality.<sup>15</sup> Researchers can now identify and characterize new genes that are important in the pathogenesis of a vast number of inherited and acquired human disorders. The diagnostic, investigative and therapeutic potential of these efforts are reshaping entirely the way in which medicine is practiced, and research conducted in the new millennium.<sup>14,15</sup>

Regrettably, despite the tremendous progress made in medical genetics; the field seems to be the most neglected clinical discipline in our practice – particularly with regards to the availability of the most basic laboratory investigatory facility. Karyotyping – which was first developed in the 1950's<sup>1,2</sup> further refined in the 1970's,<sup>3</sup> and had reached advanced technological perfection in the 1980's<sup>5</sup> and 1990's<sup>2</sup> is still rarely available to Nigerian children in whom the test is required for proper diagnosis, management and genetic counseling.<sup>16-22</sup>

There is a general agreement that one way to assess medical scientific progress in different countries is to analyse the publication rate in scientific journals<sup>23</sup> and the nature of the limitations in facilities in such studies. The aim of this paper is to critically review the status of paediatric practice and research in Nigeria in the last one decade (1992 – 2001), with special reference to medical genetics. The paper aims at highlighting the importance of medical genetics in applied research in paediatrics in Nigeria, and drawing attention to the paucity of the investigatory facilities that could have improved the quality of practice and research in paediatrics in the country.

## Method

The study consists of two series. In the first series, an audit of all publications in the last one-decade (between 1992 and 2001), of published studies in 8 medical journals published in Nigeria was made.

The total number of articles was recorded. The proportion of the contribution made by Nigerian pediatricians was noted from enumeration of articles devoted to paediatrics. Out of these, studies devoted to genetics and congenital malformations were noted, enumerated, and the contents critically analyzed, with a view to determining the limitations of the studies, particularly with regards to investigatory facilities. Also, disorders that were primarily non-genetic, but in which investigatory facilities based on cytogenetic analysis, special staining techniques, molecular testing, special biochemistry or electron microscopy could be useful, were enumerated, and the availability or paucity of the relevant investigations was noted. For studies in which all the relevant investigations were available, the role of collaboration with researchers abroad was noted.

In the second series all articles published in the last 10 years (1992 – 2001) in two reputable international journals devoted to tropical paediatrics were enumerated, analyzed by topics, authors, and particular attention was paid to articles on genetics and congenital malformations, contributed by Nigerian authors. In such studies the availability or paucity of the relevant investigations as well as the collaboration with researchers abroad were noted.

## Results

The first series of published Nigerian studies revealed that of 2497 articles published in 8 Nigerian medical journals, 873 (35%) articles were devoted to paediatrics. Of these, 270 (31%) papers were related to genetics, dysmorphology and congenital malformations. There were also 101 (11.6%) of the 873 articles that, were primarily on non-genetic disorders, but needing investigatory facilities based on cytogenetic analysis, special staining techniques, molecular testing, special biochemistry or electron microscopy (Table 1). Thus, there were 371 (42.5%) of 873 studies devoted to paediatrics in which such special investigatory facilities could have improved the quality of practice or research in Nigeria. Only in 8(2.2%) of 371 studies were the appropriate investigations available, mostly done either abroad or in collaboration with workers abroad. In the second series in two widely circulated international, quarterly journals on tropical paediatrics 1040 were articles were published in the last one decade; 281(27%) of these were contributed by Nigerian authors. Of these, 35(12.5%) were devoted to genetics and congenital malformations on Nigerian children, but in only 7 of these were all the necessary investigations available, and they were done in developed nations (Table 1).

Table 1: Audit over ten years (1992 – 2001) of Nigerian studies in paediatrics related to medical genetics

### First Series: Articles published in Nigeria

No. of Nigerian medical journals reviewed	8
Total no. of articles reviewed	2497
No. of articles devoted to paediatrics	873 (35%)
No. of papers related to genetic and various congenital malformations	270 (31% of 873)
No. of non-genetic studies needing investigatory facilities based on cytogenetics, special staining techniques, electron microscopy	101 (11.6% of 873)
No. of studies in which appropriate investigations were available/done abroad or with collaboration abroad	8 (2.2% of 371)

### Second series: Articles published abroad in tropical paediatric journals

No. of foreign journals reviewed	2
Total no. of articles reviewed	1040
No. of articles contributed by Nigerian authors	281 (27%)
No. of papers devoted to genetics and congenital malformations	35 (12.5% of 281)
No. of Nigerian studies with adequate investigatory facilities (collaborative studies)	7 (20% OF 35)

Table 2: Published Nigerian studies in paediatrics in which there was paucity of relevant investigation facilities related to medical genetics

Author(s)	Centre	Abbreviated title of paper	Unavailable facilities
Asindi AA <sup>16</sup>	University of Calabar Teaching Hospital, Calabar	Neurologic disabilities in children	Karyotyping. 19 cases of Downs syndrome diagnosed on clinical grounds alone
Adeyemo et al <sup>17</sup>	University College Hospital, Ibadan	Major congenital malformations in paediatric admissions	Karyotyping. Out of 531 major congenital malformations 14 were diagnosed as Down's syndrome on clinical grounds alone
Oredugba & Stote <sup>19</sup>	Lagos University Teaching Hospital, Lagos	Dental abnormalities in handicapped children	Karyotyping. Cases of Down's syndrome diagnosed on clinical grounds
Okogbo & Amadin <sup>25</sup>	Aminu Kano Teaching Hospital, Kano	X-linked hydrocephalus: Bickers Adams syndrome	Ultrasound or brain CT to demonstrate stenosis of aqueduct of Sylvius, Karyotyping
Folade et al <sup>28</sup>	University College Hospital, Ibadan	Orbital rhabdomyosar – coma mimicking Burkitt's lymphoma	Immunohisto chemical stain, Electron microscopy. Histogenetic origin of tumor couldn't be identified
Olarenwaju & Renner <sup>18</sup>	Lagos University Teaching Hospital, Lagos	Infantile achalasia in Down syndrome	Karyotyping
Johnson & Mokuolu <sup>20</sup>	University of Ilorin Teaching Hospital, Ilorin	Russel-Silver syndrome	Karyotyping

Table 3: Published Nigerian studies in paediatrics in which the relevant investigations related to medical genetics had to be done abroad

Author(s)	Centre	Abbreviated title of paper	Unavailable facilities
Ahmed et al <sup>29</sup>	Usmanu Danfodiyo University Teaching Hospital, Sokoto	Kartagener's syndrome	Nasal brushing techniques, photometric method, EM for demonstration of ciliary dyskinesia
Ahmed. & Falope <sup>30</sup>	Usmanu Danfodiyo University Teaching Hospital, Sokoto	Hardings variant of Friedreich's ataxia and type-1 NF	Nerve growth factor assay; Mitochondrial malic acid emzyme, MRI
Ahmed & Hassan <sup>21</sup>	Usmanu Danfodiyo University Teaching Hospital, Sokoto	Laurence – Moon- Bardet S– Biedl – syndrome	Karyotyping. This is ideally indicated in any dysmorphic child
Ahmed et al <sup>34</sup>	Usmanu Danfodiyo University Teaching Hospital, Sokoto	Giant congenital pigmented naevus & early malignant transformation	Tissue culture of cells of the neoplastic growth to carry out genetic biologic & immunologic characterization of tumour
Ahmed H <sup>31</sup>	Usmanu Danfodiyo University Teaching Hospital, Sokoto	Childhood ataxic syndromes	Screening for relevant metabolic genetic disorders
Ahmed et al <sup>32</sup>	Usmanu Danfodiyo University Teaching Hospital, Sokoto	Xeroderma pigmentosum (XP)	XP Complementation grouping. DNA, studies and cell fusion techniques
Ahmed et al <sup>22</sup>	Usmanu Danfodiyo University Teaching Hospital, Sokoto	Pathological obesity syndromes	Karyotyping

EM = Electron microscopy, NF = Neurofibromatosis, MRI = Magnetic resonance imaging

Table 4: Published Nigerian studies in paediatrics in which the relevant investigations related to medical genetic or molecular biology, electron microscopy or special biochemistry had to be done with collaboration of scientists abroad

Author(s)	Centre	Abbreviated title of paper	Investigations done abroad
Eke & Simpson <sup>41</sup>	University of Port Harcourt Teaching Hospital, Port-Harcourt	Rotavirus gastroenteritis	Electron microscopy (EM) of stools, polyacrylamide gel electrophoresis (PAGE) of rotavirus done in Birmingham, UK
Omotade et al <sup>42</sup>	Lagos University Teaching Hospital, Lagos	Rotavirus Serotypes and subgroups	EM of stools, immunochemical staining, PAGE of rotavirus RNA, Rotavirus RNA genome done in Nottingham, UK
Adah & Olaleye <sup>43</sup>	Lagos University Teaching Hospital, Lagos	Serotypes and genotypes of rotavirus strains in Nigeria	ELISA, radioactive dot-blot hybridisation technique, polymerase chain reaction (PCR) done in Germany
Ighogboja & Angyo <sup>44</sup>	Jos University Teaching Hospital, Jos	Galactose-1-phosphate uridyl transferase defc. In a Nigerian infant	Erythrocyte galactose-1-uridyl transferase activity assay done in a London hospital
Ahmed et al <sup>45</sup>	Ahmadu Bello University Teaching Hospital, Zaria	G6PD and aflatoxins	Kit for UV quantitative method of G6PD assay obtained abroad. Also HPLC for quantifying aflatoxins levels in serum done in Liverpool, UK
Ahmed et al <sup>46</sup>	Ahmadu Bello University Teaching Hospital, Zaria	Aflatoxins & Neonatal jaundice	Same as above
Ahmed et al <sup>47</sup>	Usmanu Danfodiyo University Teaching Hospital, Sokoto	Portal vein thrombosis and sickle cell disease	Doppler US, hepatic angiography protein S levels, protein C levels, investigation of patient and family for inherited thrombophilia done in Royal Free Hospital, London, UK

G6PD = Glucose-6-phosphate dehydrogenase; HPLC = High performance liquid chromatography, US = Ultra sound, UV = Ultra violet, defc. = deficiency

Table 2 gives a summary of examples of published Nigerian studies in paediatrics in which there was paucity of relevant investigations related to medical genetics. This table summarises 7 articles based on experience of paediatric colleagues elsewhere in Nigeria. The facilities not available are indicated in the table. Table 3 also gives examples from 8 published Nigerian studies in paediatrics in which there was paucity of relevant investigations related to medical genetics. The facilities that were not available in Nigeria but which could have improved the quality of the work are indicated in tables 2 and 3.

Table 4 gives a summary of some studies related to medical genetics or needing investigations based on molecular genetics contributed by Nigerian authors, in

which investigatory facilities had to be obtained abroad in collaboration with foreign authors.

## Discussion

This audit reveals that Nigerian paediatricians have been very active in research, and have made significant contribution in reputable medical journals, locally and abroad. The papers published are of fairly high standard, but qualitative work on medical genetics is problematic and scientific progress in this very important and topical field is very slow, despite the fact that up to 30% of published studies, by Nigerian paediatricians, is related to genetics and

congenital malformations.

This slow progress is attributable to paucity of the necessary, basic investigatory facilities. Thus, in 1986 Asindi<sup>16</sup> reviewed the neurologic disabilities in children in Calabar, and diagnosed 19 cases of Down syndrome on clinical grounds alone. No karyotyping was done because facilities were not available. Similarly, Adeyemo et al,<sup>17</sup> eight years later, (in 1994) published their findings in a reputable international paediatric journal, on major congenital malformations in paediatric admissions, in UCH Ibadan, and claimed that out of 531 major congenital malformations 14 were diagnosed as Down syndrome, again on clinical grounds alone.<sup>17</sup> A year earlier (in 1993) Olarenwaju and Renner<sup>18</sup> in Lagos described in a female, the first case of infantile achalasia in Down's syndrome. Unfortunately, facilities for karyotype study were not available. Six years after the report of Olarenwaju and Renner,<sup>18</sup> Oredugba and Sote<sup>19</sup> (in 1999) in Lagos, analyzed the dental abnormalities in handicapped children and based their diagnosis of Down's syndrome also on clinical grounds alone. No Karyotyping was available. Thus, for the last 13 years publications on Down syndrome in Nigerian children have been based on clinical features alone.<sup>16-19</sup> Although the diagnosis of Down syndrome (DS) can be made on clinical grounds, the differential diagnosis include a variety of disorders-including other trisomies and triple X syndrome which share many features with DS.<sup>1,2</sup>

The chromosomal genetic defect in Down syndrome may be trisomy 21(in 95% of cases); various types of translocations ( 4%); the translocations include D/G translocations –t(14q21q), t(15q21q), t(13q21q) and G/G translocations consisting of t(21q21q) or t(22q21q); and mosaicism (46/47) (in 1%)<sup>2,24</sup>. Overall, translocations account for 9% of the children with Down syndrome born to mothers below 35 years.<sup>2</sup>

It is very important to identify the type of genetic defect in Down syndrome since this is very useful for diagnosis and proper genetic counseling.<sup>1,2,24</sup> The genetic defect can be easily identified by karyotyping. The karyotype in Down syndrome determines the recurrence risk. Thus for trisomy 21 the overall recurrence risk is 1% while for translocations of the D/G type t(14q21q) the risk is 5% for maternal translocations and 2% for paternal, and the rare G/G translocations t(21q21q) carries a recurrence risk of 100%.<sup>1, 2</sup> Therefore, without karyotyping, the diagnosis of Down syndrome can always be challenged and proper genetic counseling cannot be given. Unfortunately this basic genetic investigation is not readily available in Nigeria.

Prenatal diagnosis of Down syndrome is now available using amniocentesis, chorionic villus sampling, alpha-fetoprotein, human chorionic gonadotrophine (HCG) and estriol.<sup>24</sup> Prenatal diagnosis improves the quality of genetic counseling and offers the couple the information needed to make decisions on available options.<sup>1,2,24</sup>

In 1993 Okogbo and Amadin reported a case of X-linked hydrocephalus-Bickers-Adams syndrome in a child in Kano.<sup>25</sup> The authors<sup>25</sup> could not do transfontanelle ultrasound or brain CT scan to demonstrate the stenosis of the aqueduct of Sylvius-the primary structural defect associated with the X-linked disorder.<sup>26</sup> An improvement in research on this condition in Nigeria was made in the work of Iroha and Egri-Okwaji<sup>27</sup> who recently (in 2001) reported cases of Bickers-Adams syndrome in a Nigerian family based on the typical clinical presentation, genetic pedigree analysis and demonstration of the stenosis of the aqueduct of Sylvius.<sup>27</sup> Johnson et al<sup>20</sup> recently described a case of Russel-Silver syndrome in a Nigerian child in Ilorin, and lamented that they could not perform karyotyping in the dysmorphic child.

With regards to non-genetic disorders in which investigations related to cytogenetics are useful in arriving at the correct diagnosis, a recent examples is the work of Falade et al.<sup>28</sup> These workers reported (in 1998) a case of bilateral orbital rhabdomyosarcoma that was initially diagnosed as a case of Burkitts lymphoma. The authors highlighted the difficulties which because of lack of differentiation are associated with the diagnosis of small round cell tumours of childhood.<sup>28</sup>

Concerning examples of published Nigerian studies in paediatrics in which there was paucity of relevant investigatory facilities for medical genetics, from the personal experience of the author, eight selected studies are hereby discussed to illustrate the problem.<sup>21, 22, 29-34</sup>

In 1997 Ahmed et al<sup>29</sup> described a 4-year old male child with Kartagener's syndrome (KS)-being the first case to be documented in Nigeria<sup>29</sup> and followed up the case for 6 years. The diagnosis of KS depends on the combination of clinical features (mirror image dextrocardia –ie dextrocardia and situs inversus, associated with bronchiectasis and sinusitis, the so called Kartegener triad<sup>35</sup>) plus demonstration of abnormalities in the ultrastructure and function of the cilia.<sup>29</sup> With regards to the demonstration of ciliary dyskinesia and poor mucociliary clearance, only the saccharin test was available to Ahmed et al.<sup>29</sup> The saccharin test is a simple screening test of mucociliary clearance and involves the movement of particle of saccharin posteriorly through the nose.<sup>35</sup>

An abnormal test (as obtained in the patient described by Ahmed et al<sup>29</sup>) is usually highly suggestive of ciliary dyskinesia and would indicate a need for more sophisticated studies such as nasal brushing technique and examination by photometric method<sup>35</sup> for ciliary motility and electron microscopy to examine for a variety of structural defects. Unfortunately, in Nigeria, such tests are still not available, although they have been well established in clinical practice for more than 20 years.<sup>36</sup> Thus, Rutland and Cole,<sup>36</sup> in 1980, described non-invasive sampling of nasal cilia for measurement of beat frequency and study of ultrastructure in a variety of respiratory disorders.

In 1999 Ahmed and Falope<sup>30</sup> described an unusual association of a rare variant of Friedreich's ataxia with type-1 neurofibromatosis (NF1) in a Nigerian Fulani family (in a 39-year old mother and her 12-year old) and followed up the cases for 5 years. The authors concluded that they were dealing with a combination of Harding's spastic ataxia of childhood<sup>37</sup> and NF1, which formed an interesting but puzzling phenomenon.<sup>30</sup> Cranial and spinal computerized tomography (CT) scans in both mother and child showed no signs of tumours.<sup>30</sup> The authors wished they could do magnetic resonance imaging (MRI) on the patients, since CT scan is not as good as magnetic resonance at demonstrating posterior fossa abnormalities, spinal tumours and spinocerebellar degenerative processes,<sup>38</sup> but this was not possible then due to lack of facilities. Karyotyping, DNA probe on chromosome 17, assay of nerve growth factor and the levels of mitochondrial malic acid enzymes might have contributed to better understanding of the complex association.<sup>30</sup>

Ahmed and Hassan<sup>21</sup> described Laurence-Moon-Bardet-Biedl syndrome (LMBBS) in siblings of a Nigerian family in 1999-the first of such description in Nigeria.<sup>21</sup> LMBBS is an autosomal recessive disorder characterized by the pentad of obesity, mental retardation, digital anomalies (postaxial polydactyly, syndactyly or both), retinal dystrophy (retinitis pigmentosa) and hypogonadism.<sup>39</sup> Brain CT scan, which was indicated in the proband because of the associated ataxic gait, was normal. Karyotyping could not be done. Although the karyotype in LMBBS is normal and doesn't assist in the diagnosis of LMBBS,<sup>39</sup> it could have been informative to do it, since karyotyping is indicated in any child with dysmorphic features,<sup>24</sup>

Again, Ahmed<sup>31</sup> in 1999 described his experience of childhood ataxic syndromes in Sokoto.<sup>31</sup> The author noted that metabolic genetic disorders did not seem to play a significant role in his series. Facilities for screening for the relevant metabolic genetic disorders were not available.

In 2001 Ahmed et al<sup>32</sup> described the first series on xeroderma pigmentosum syndrome in black children in the West African sub region and noted the phenotypic variations among the three consecutive siblings of a Nigerian family. We confessed that we had no facilities in Nigeria to determine the complementation groups of our patients and the individual gene mutations of these children.<sup>32</sup>

Furthermore, in 2001 Ahmed<sup>33</sup> and Ahmed et al<sup>22</sup> described their experience of neurocutaneous syndromes in Nigerian children<sup>33</sup> and of pathological obesity syndromes in Nigerian children,<sup>22</sup> with special emphasis on practical management problems.<sup>22, 33</sup> In these studies<sup>22, 33</sup> the limitation in diagnostic facilities particularly chromosomal studies, were some of the major practical management problems.

With regards to non-genetic disorders in which cytogenetic and molecular genetic investigations are needed, Ahmed et al<sup>34</sup> in 2001 described a case of giant congenital pigmented naevus (GCPN) with unusual presentation and early malignant transformation in a Nigerian infant,<sup>34</sup> and concluded that the 6-month old infant had clinical and histological features of malignant melanoma, in association with the GCPN. Yet it has been shown that cells from neoplasms arising from GCPN, despite the clinical and histologic picture of malignant melanoma, could be phenotypically benign.<sup>40</sup> We lamented that we had no facilities to carry out genetic, biologic and immunologic characterization of the tumour to prove its malignant or benign nature.<sup>34</sup>

With regards to illustrative, published Nigerian studies in paediatrics, in which the relevant investigations related to medical genetics, molecular biology, special biochemistry or electron microscopy had to be done abroad, the following is a brief review of selected studies.<sup>41-47.</sup>

In 1991 Eke and Simpson<sup>41</sup> studied rota virus gastroenteritis at the University of Port-Harcourt Teaching Hospital (UPHTH). Stool samples had to be sent by courier mail to Birmingham, England for rota virus page typing using polyacrylamide gel electrophoresis, and electron microscopy. Sera were also posted to England for ELISA.<sup>41</sup>

In 1995 Omotade et al<sup>42</sup> looked into rota virus serotypes and genotypes in children with diarrhoea in Lagos. The electron microscopy of stools, immunochemical staining, polyacryl gel electrophoresis (PAGE) of rotavirus RNA genome were done abroad.<sup>42</sup> Similarly, Adah and Olaleye<sup>43</sup> studied the serotypes and genotypes of rota virus strains also in Lagos and the ELISA, radioactive dot-blot hybridization technique and polymerase chain reaction (PCR) were all done in Germany. In 1995 Ighogboja and Angy in Jos described a child with

galactose-1-phosphate uridyl transferase deficiency and the assay of the enzyme had to be done abroad (in a London hospital).<sup>44</sup> The authors suggested that there is no doubt that cases of galactosaemia in our community remain largely undiagnosed; and that there is the need to establish regional centers for metabolic screening in our country.<sup>44</sup>

In 1995 Ahmed et al<sup>45</sup> looked into glucose-6-phosphate dehydrogenase (G6PD) status of neonates in Zaria with special reference to aflatoxins. The kit for UV quantitative method of G6PD assay had to be obtained from Liverpool, UK. Also, the high performance liquid chromatography (HPLC) for quantifying the aflatoxin levels in serum had to be done abroad.<sup>45, 46</sup>

In 1997 Ahmed et al<sup>47</sup> described a child with sickle cell anemia, oesophageal varices and recurrent haematemesis that turned out to be due to portal vein thrombosis. Portal vein thrombosis is exceedingly rare in sickle cell anemia. Doppler ultrasonography and hepatic angiography done in Royal Free Hospital, London (RFH) confirmed the portal vein thrombosis. The child was also investigated at RFH for inherited thrombophilia, and these investigations showed that the child might have a genetic predisposition to prothrombotic tendency.<sup>47</sup>

It is obvious that our experience<sup>21, 22, 29 - 33</sup> is similar to the experience of our paediatric colleagues elsewhere in Nigeria,<sup>16 - 20</sup> with regards to paucity of special investigatory facilities for medical genetics. It has been recognized that as a group, genetic disorders represent a sizeable problem in developed countries, where environmental causes of ill health have become far less important due to improved nutrition, living standards and better medical care.<sup>13</sup> It has also been recognized that, currently, environmental problems (e.g. diarrhoea, malnutrition and infections,) in developing nations greatly overshadow those of genetic origin.<sup>13</sup> There is a general agreement, however, that as funding and facilities improve, and environmental causes of ill health are controlled, genetic disorders will become increasingly important in the developing world, as they have been in the developed nations.<sup>13</sup> Furthermore, our present audit has demonstrated, to some extent, that progress in applied research in paediatrics is enhanced by application of molecular genetics even in a common tropical paediatric problem such as diarrhea,<sup>41 - 43</sup> which is regarded as primarily environmental and acquired disorder. Similarly, we have also given examples of environmental, non-genetic disorders such as tumours<sup>28, 34</sup> which may need investigatory facilities based on cytogenetics, molecular genetics, special biochemistry, special staining techniques, cell cultures or electron microscopy for proper diagnosis

and for improvement of quality of care and research even in a developing nation, like Nigeria.<sup>28, 34.</sup>

A recent Spanish study<sup>23</sup> that surveyed journals listed by the Science Citation Index of 160 nations for the period from 1991 until 1998 has shown that 85% of all scientific papers during this period, originated from three regions: Western Europe, North America and Asia (Japan, Hong Kong, Indonesia, Malaysia, China Singapore, South Korea, Taiwan and Vietnam in that order). Up to 70% were attributable to just Western Europe and North America. In contrast the African continent as a whole produced only 1% of worldwide scientific publications during this period. The study also showed that papers from Latin America, Eastern Europe and the Middle East had a foreign co-author on at least 50% of the publications. The authors<sup>23</sup> suggested that in developing world collaboration with developed nations provides a strategy to address these disparities; and that for small economies; this collaboration with developed nations may be the best approach to increased scientific progress.<sup>23</sup>

Examples of this type of collaboration at the individual researcher level in Nigeria have been discussed in this review.<sup>44 - 47</sup> Nigerian paediatricians continue to maintain such collaboration as evidenced by more recent publications.<sup>48</sup> For example, in 2002, Ikpat et al<sup>48</sup> in their study of seroprevalence of human herpes virus-8 (HHV-8) among children in Calabar, South-eastern Nigeria collaborated with the Oncology Unit of the University of Padua, Italy where sera were screened for antibodies for the small capsid related protein encoded by ORF65 using ELISA technique, with purified recombinant dehydrofolate reductase (DHFR) as control antigen<sup>48</sup>. Although such collaboration, at the individual levels,<sup>41 - 48</sup> is commendable and can enhance progress in research in our country, it will not address our research needs to an appreciable extent. It seems that collaboration at a higher level - at governmental level is also urgently needed.

The establishment of a medical genetics research and referral centre for the country is urgently needed. Such a centre can be set up in collaboration with international scientific organizations on terms that are most acceptable and beneficial to Nigerians. The centre should have facilities for basic genetic investigations such as cell culture, karyotyping, other cytogenetic analysis, molecular testing, special staining techniques for modern immunodiagnostic and immunopathological tests, screening for metabolic disorders, polymerase chain reaction (PCR) - based investigations for diagnosis of a variety of infections, and special biochemistry.

The establishment of this centre will curtail the



costly and cumbersome practice of posting specimen (stool, urine, blood, other body fluids, and tissues) abroad by individual Nigerian researchers<sup>41 - 48</sup> and will minimize the costly, often risky, referral of patients abroad.<sup>49</sup> The centre will also enhance progress in applied research in paediatrics and other medical and surgical specialties, and will improve the quality of health care in the country. This is because the centre will be relevant not only to the patients with genetic disorders, congenital malformations and tumours, but also to those with the common non-genetic problems such as malaria<sup>50 - 52</sup> and tuberculosis.<sup>53</sup> Thus, recent molecular genetic studies on HLA genes and malaria have shown that the possession of HLA-B-53 allele in Gambian children reduces the risk of death from severe malaria by up to 40%<sup>50</sup>. It has also been demonstrated that natural immunity to malaria may be conferred by complex genetic factors governing nitric oxide synthase activity.<sup>51</sup> Furthermore, remarkable progress has been made in the production of safe and effective malaria vaccines based on recombinant DNA technology.<sup>52</sup> Therefore, modern research on malaria needs the application of molecular genetics. With regards to tuberculosis, various polymerase chain reaction (PCR) assays have been developed for faster identification of mycobacteria.<sup>53</sup> The value of such investigations in routine laboratory work was first assessed more than a decade ago (in 1991), and it was concluded that DNA amplification is a reliable method for early detection of mycobacterial infections.<sup>53</sup> Again, this shows that progress in the field of tuberculosis can be enhanced by application of molecular biology.

I do not recommend the establishment of costly, sophisticated genetic laboratories for every teaching hospital. This is not feasible, not affordable and is inappropriate<sup>49</sup> for a developing nation like Nigeria. It is obvious that at least one medical genetics research and referral centre is needed for a country of more than one hundred million people.

Sawyer<sup>54</sup> has identified four principal kinds of organizations, which may support medical education, research and care in developing countries. These are philanthropic foundations, governmental agencies, non-governmental organizations - such as professional scientific and technical societies, and industrial concerns. Various nations provide support to developing countries through governmental agencies. Sawyer<sup>54</sup> observes that there is likely to be considerable bureaucracy in the pursuit and use of such funds, but they may be the most likely source of support for big projects<sup>54</sup> (like the proposed medical genetics research centre).

A plea is, therefore made to the Federal Government of Nigeria to urgently set up the

machinery for the establishment of a Medical Genetics Research Centre for the country.

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