UNIVERSITY OF LAGOS
Inaugural Lecture Series 2014

TOPIC:

ORDER AND DISORDER: EXPLORING THE LOGIC OF LIFE

By
PROFESSOR SMITH I. JAJA

ORDER AND DISORDER: EXPLORING THE LOGIC OF LIFE

An Inaugural Lecture Delivered at the University of Lagos Main Auditorium on Wednesday, 19th November, 2014

BY

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UNIVERSITY OF LAGOS

University of Lagos Press and Bookshop Ltd

Published

By

University of Lagos Press and Bookshop Ltd
Unilag P.O. Box 132
University of Lagos
Akoka – Yaba, Lagos
Nigeria.

ISSN 1119-4456

PREAMBLE

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Members of Senate of the University of Lagos;
My Lords, Spiritual and Temporal;
Members of the Fourth Estate of the Realm;
Distinguished Ladies and Gentlemen.

INTRODUCTION

Historically, this is the third Inaugural lecture from the Department of Physiology, College of Medicine of the University of Lagos. The first was given by Late Professor Felix Oladejo Dosekun, First Emeritus Professor of the University of Lagos, Former vice Dean of the University of Lagos Medical School (now CMUL) and Former Provost, College of Medicine of the University of Lagos. That lecture, with the title "THE PLACE OF PHYSIOLOGICAL SCIENCES IN MEDICINE" was delivered on 3rd October, 1962.

The second was delivered by Professor Olusoga Adegoke Sofola, former Head, Department of Physiology, Former Deputy Provost and later Provost, College of Medicine of the University of Lagos, former Deputy Vice Chancellor, (Academic and Research), University of Lagos and former Ag vice Chancellor, Ogun State University, Ago Iwoye. Prof. Sofola delivered his lecture on 27th August, 1997 with the title "FROM ANIMAL TO MAN, PHYSIOLOGY IN THE SERVICE OF MEDICINE."

This lecture is also the second Inaugural lecture in this university from the historic King JAJA House of OPOBO. The first was given by Late Prof. Millar O.A. Jaja, a distinguished orthopedic surgeon, in this very auditorium on 10th June, 1987. The title of his lecture was "THE HALT IN SOCIETY."

WHAT IS PHYSIOLOGY?

Chambers Students' Dictionary defines Physiology as "The study of the way in which living bodies work." It is defined as "The science that treats the functions of living organisms or their parts" by Blakiston's Illustrated Pocket Medical Dictionary. Physiology has also been defined as the science of biological function and adaptation (Diamond, 1993).

However, the Chinese define Physiology as "THE STUDY OF THE LOGIC OF LIFE" (Boyd and Noble, 1993).

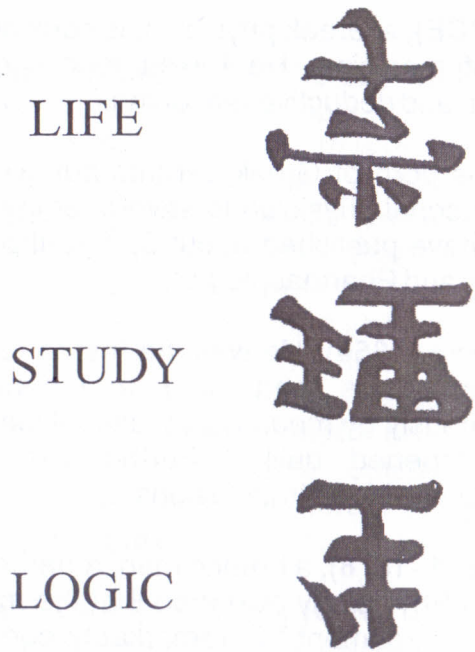


Fig.1 The word 'PHYSIOLOGY' is written in Chinese characters. (From 'The Logic of Life: The challenge of integrative physiology.' Eds. C.A.R. Boyd and D. Noble, Oxford University Press, 1993).

It had been argued that "if physiology is a search for order, for the logic of life, the subject cannot be defined by methodology. **What characterises the physiologist is therefore not the apparatus but rather the way in which he/she thinks."** If it is about logic of life then it is not about specific experimental methodology but a way of thinking.

PHYSIOLOGY IN HISTORY

Let us consider some of the people who have contributed to the study of Physiology or the Logic of life.

Hippocrates (460 BCE), a Greek physician, is considered to be the father of medicine. He based medicine on objective observation and deductive reasoning.

Galen (130 CE) was born of Greek parents but lived in Rome. He was a personal physician to several emperors. He was reputed to have published about 500 treatises in Anatomy, Physiology and Pharmacology.

Sir Christopher Wren (1656): He was the first to record experimentation on dogs and also administered medications intravenously by means of an animal bladder attached to a sharpened quill. Further, he also experimented with canine blood transfusions.

Claude Bernard (1831–1878), a French man, regarded as the father of modern Physiology observed that the ***milieu interieur,*** "internal environment," is remarkably constant despite changing conditions in the external environment.

Walter Cannon (1871–1945), an American, coined the term ***homeostasis*** in 1926 to describe the constancy of the internal environment. He suggested that many mechanisms of physiological regulation have one purpose; maintenance of internal constancy. (Homeostasis (Greek); ***homoios*** like; ***stasis*** = standing still).

Alfred Nobel (1833–1896): Alfred Nobel was born on 21 October, 1833 in Stockholm, Sweden. He was the inventor of the dynamite and holder of 355 patents. At the age of 17, he could speak fluently, five different languages. He was a

Chemist, Inventor, Engineer, Entrepreneur, Business man, Author and Pacifist. By the time he died in 1896, he left about $265m in his will to fund the Nobel Prizes which he established in 1895.

ESTABLISHMENT OF NOBEL PRIZES

In 1888, a French newspaper published Noble's obituary, titled *'The Merchant of Death is dead.'* But, it was a case of mistaken identity because it was Nobel's brother, Ludvig, who had died. Surprised and unhappy with the content of the obituary and concerned that his legacy would reflect poorly on him, Nobel wrote his final will. The last will was written a little over a year before he died at the age of 63, on 10th December, 1896. In his final will, Nobel requested that his money be used to create a series of prizes for those who confer the **"greatest benefit on mankind."** Thus, five Nobel Prizes awarded for outstanding contributions in Chemistry, Physics, Literature, Peace and ***Physiology or Medicine*** were established.

NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

This prize awarded for discoveries in Physiology or Medicine has been of benefit to mankind. It has been awarded 105 times to 207 Nobel Laureates between 1901 and 2014. However, the prize was not awarded between 1915 and 1918 (period of the First World War), 1921, 1925 and 1940-1942 (period of the Second World War).

CERTAIN CHARACTERISTICS OF THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

1. Because of the length of time that may pass before the significance of a discovery becomes apparent, some prizes are awarded many years after the initial discovery.

   In 1916, Peyton Rous discovered the role of tumour viruses in chickens, but was not awarded the prize

until 1966 (50 years later).

2. The 2009 award was the first time two women have been awarded the Physiology or Medicine prize at the same time. It is also the first time in the Nobel Prize's history that more than one woman has been the recipient of the Nobel Prize in a single year.

3. The Nobel Prize in Physiology or Medicine has been awarded to only living people, not dead individuals. However, in 2011, the prize was awarded to a dead person, Ralph M. Steinman, the Canadian immunologist who died three days before the announcement, unknown to the committee. The committee however, allowed the prize to stand since it was awarded "in good faith." Nobel Prize has been awarded posthumously to Dag Hammarskjold (Nobel Peace prize, 1961) and Grik Azel Karlfeldt (Nobel prize in Literature, 1931).

4. The Committee selects researchers working in the basic sciences over those who have made applied contributions.

   Ordinarily, Jonas Salk or Albert Sabin was expected to receive the prize for their development of the polio vaccines. The award rather went to John Enders, Thomas Weller, and Frederick Robbins who discovered that the polio virus could reproduce in monkey cells in laboratory preparations. This was considered a very fundamental finding that led to the elimination of the polio disease.

   Furthermore, Harvey Cushing, an American neurosurgeon who identified Cushing's syndrome was never awarded the prize. Also, Sigmund Freud

was also not awarded the prize as his psychoanalysis lacks hypotheses that can be tested experimentally.

5. Through the 1930s, prizes were awarded in classical Physiology, but after that the field began dissolving into specialties.

   The last classical Physiology laureates were John Eccles, Alan Hodgkin and Andrew Huxley in 1963, for their findings regarding "unitary electrical events in the central and peripheral nervous system."

IN THE BEGINNING

After my NYSC at Bida, Niger State, I went back to Port Harcourt. I sought employment at the University of Port Harcourt, School of Nursing, Port Harcourt and School of Basic Studies, also in Port Harcourt. I could only get a job at the School of Basic Studies because my Chemistry teacher in secondary school had become the Principal. After about two months, I became dissatisfied with the job. But during the NYSC period, I had sat for the qualifying M.Sc. examination and did not get any result. That was why I went back to Port Harcourt in the first place.

I then travelled back to Lagos to ask for the result of the examination. I met my teacher and then Head of the Department, Prof. (Mrs.) Oyinade Elebute, who gave me my letter of admission into the M.Sc. course and employment as a Graduate Assistant. They admitted and employed three of us: Mr. Chikodi N Anigbogu (now Prof), Mr. Philip Egbengu Egbe, a Cameroonian, (now Prof.) and myself.

MODUS OPERANDI

In all our studies, attempt had been made to establish what is normal (logic or order) and then relate the normal

to the diseased (disorder) state. Finally, an intervention was made in an attempt to revert to normal physiology (logic of life). Hence, the title of this inaugural lecture, "ORDER AND DISORDER: EXPLORING THE LOGIC OF LIFE." We had used this principle to study:

(1) Lung function in Nigerians
(2) Salt-sensitivity in Nigerians
(3) Exercise as an adjunct intervention/treatment in the rehabilitation of stroke patients and in the management of patients with bi-ventricular heart failure
(4) Supplementation with antioxidants in the management of sickle cell disease.

LUNG FUNCTION IN NIGERIANS

Prof G.O. Ojo supervised my study of "Lung Function in Nigerians." We measured static and dynamic lung volumes in apparently healthy, sedentary Nigerian males and females and also athletes of different sports. We then established prediction equations for the estimation of forced vital capacity (FVC), forced expired volume in the first second (FEV_1), FEV_1 as a percentage of forced vital capacity (FEV_1%) and peak expiratory flow rate (PEFR). Our studies covered Nigerians between ages 6 years and 80 years. The results of these studies were published in the 80s and 90s which followed the elegant and trail-blazing studies of Femi-Pearse and Elebute in the 1970's. Prior to these studies, prediction of the lung function of Nigerians with prediction equations derived from Caucasian subjects over-estimated such parameters **suggesting that such Nigerians were suffering from respiratory ailments when in actual fact they were not.** Our studies, coming about a decade after those of Femi-Pearse and Elebute, updated their prediction equations as we found that our subjects were taller than those used by the earlier workers. It would be quite interesting to see new studies that would still update the

earlier values as it is suspected that our children will grow even taller than us.

SALT AND HYPERTENSION IN NIGERIANS

Hypertension is a major risk factor for stroke (Lisk, 1993) and heart failure (Amoah et al, 2000). Elevated salt ingestion has been linked to the development of hypertension (Sofola, 2004). It is common knowledge that there is a link between salt and hypertension, hypertension and stroke and heart failure.

The prevalence of hypertension in Nigeria has been increasing over the years. It was reported to be 14.5% by Cooper in 1997 and 32.8% by Ulasi and his co-workers in 2010 (Cooper et al, 1997; Ulasi et al, 2010). There is some controversy on the role of salt in the pathogenesis of hypertension. A relationship between salt intake and blood pressure was first reported in 1904 (Dahl et al, 1962). Since then, studies have shown that hypertension was common in societies with more than an average salt intake of about 3g/day. The increase in blood pressure also increases with age (Dahl et al, 1962). In Northern Japan, salt intake has been reported as 13.8g/day and in most industrialised societies; salt intake is about 3.5g/day. Yanomamo Indians of Brazil consume about 0.47g/day. The average allowable salt intake is 1.52g/day (Panel on Dietary Reference Intakes for Electrolytes and Water, 2004). Dahl et al (1962), has also observed that in every population that ingested high salt diet, there were individuals in that population that did not develop hypertension. This has led to the suggestion that hypertension is a consequence of environmental factors (e.g. salt) and genetic background of the individual (Basyam, 2007).

Dr Simiat Olanike Elias, currently Senior Lecturer in the Department of Physiology, Lagos State University, Ikeja, investigated this problem for which she earned a Ph.D.

from this University. Professor O.A. Sofola and I supervised the work. An abridgement of some of the findings of that study is presented below:

(1) Salt sensitivity is present among hypertensive and non-hypertensive Nigerians being more prevalent among hypertensive subjects (55%) than normotensive (34%) subjects (Elias et al. 2011).

(2) Potentiation of sympathetic nervous regulation of cardiovascular function plays a significant role in hypertension among Nigerians (Elias et al, 2013).

(3) An enhanced epithelium sodium channel (ENaC) activity is an important determinant of hypertension among Nigerian subjects. Although, the β-T594M mutation was seen in some of the subjects, four previously unreported mutations of the β-subunit of the channel were also seen in other subjects (Elias et al, 2014).

The study of previously unreported β-T594M mutations of the β-subunit of the epithelium sodium channel (ENaC) is engaging our attention in the department.

EXERCISE TRAINING IN STROKE SURVIVORS

Hypertension is a major risk factor for stroke in Africa. Among Nigerians, hypertension had been found to consistently predominate as the most frequently encountered modifiable risk factor for stroke (Danesi et al, 1983). The economic burden of stroke is enormous. In the USA, about 750,000 people experience new and recurrent strokes each year. About $30b is expended each year on these patients (National Stroke Association, 2005). Levels of functional recovery are related to the economic burden. Although, intervention is effective in reducing the disability associated with stroke, limited resources can affect the type and duration of rehabilitation services received by stroke survivors. Recovery of walking is therefore an important component

of functional recovery of patients with stroke (Olawale et al, 2011).

We evaluated the effects of treadmill walking and over-ground walking exercise training on recovery of walking function in an African (Nigeria and Ghana) group of stroke survivors. Sixty patients with chronic stroke (≤ 3 months) were selected. All subjects received individual outpatient conventional physiotherapy rehabilitation for 12 weeks. In addition, subjects in Group A (n=20) received treadmill walking exercise training (TWET) while those in Group B (n=20) received over-ground walking exercise training (OWET). Those in Group C (control) (n=20) received conventional physiotherapy rehabilitation only.

Outcome measures were: (I) 10-metre walk time (10MWT) test and (ii) six-minute walk distance (6MWD) test. These were evaluated at the entry into the study and at the end of every four weeks. Subjects in the TWET group recorded 22.6±1.5% decrease in 10MWT and 31.0±4.3% increase in 6MWD; those in the OWET group made 26.8±1.3% and 45.2±4.6% improvement in 10MWT and 6MWD respectively. Subjects in the control group made 2.2±0.7% and 2.9±0.8% improvement in the two functions. These changes were significant for the TWET and OWET groups (P≤0.05) Olawale et al, 2011).

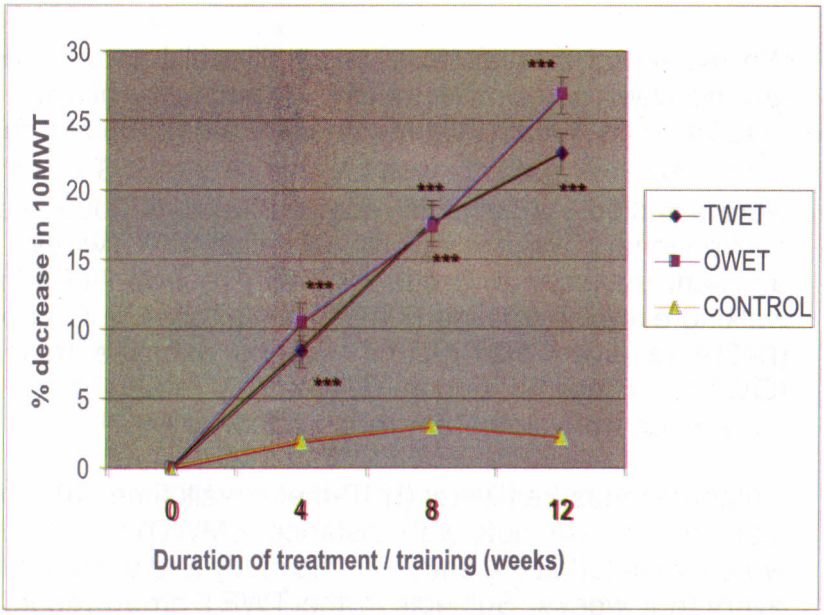


Fig 2: Changes in walk time function with exercise training (Olawale et al, 2011)

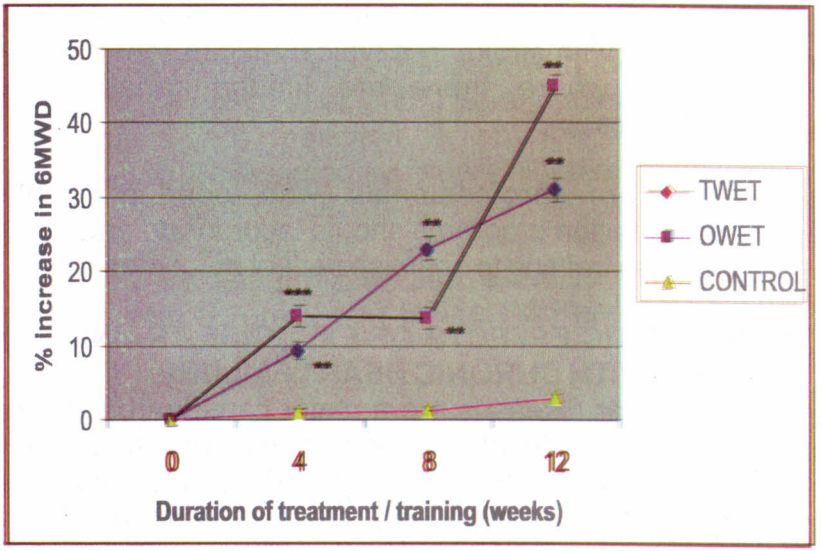


Fig 3: Changes in walk distance function with exercise training (Olawale et al. 2011)

This study indicated that treadmill and over-ground walking exercise-training programs, combined with conventional rehabilitation, improved walking function in an African group of adult stroke survivors. This study thus has the following clinical messages:

- Treadmill and over-ground walking exercise training produced significant improvements in walking function in an African group of stroke survivors.
- Treadmill training is a safe, feasible and effective intervention for stroke survivors.
- Over-ground walking exercise could be more effective than treadmill walking exercise training for improving walking function in patients with stroke.
- Over-ground walking exercise training is a simple, safe and inexpensive rehabilitation modality which

could be widely employed in the management of patients with stroke in a typical African rehabilitation setting where there are limited rehabilitation resources.

Therefore, professionals who conduct stroke rehabilitation programs should incorporate and utilise exercise training to optimise patient outcomes.

THERAPEUTIC EFFECTS OF EXERCISE TRAINING IN PATIENTS WITH CHRONIC HEART FAILURE

Cardiovascular diseases are a major cause of death and suffering in both developed and developing parts of the world (Stewart et al, 2002). In 2010, cardiovascular diseases accounted for 31.9% of all deaths in the United States of America (AHA, 2014).

Heart failure (HF) is characterised by the inability of the heart muscle to pump out adequate amount of blood to meet tissue energy demands. This results in fatigue initially on exertion and progresses to fatigue even at rest (Elahi et al, 2010; Conrads et al, 2013). It is the most prevalent cardiovascular disease and the leading cause of sudden cardiac death in Nigeria (Adedoyin and Adesoye, 2005).

Systemic hypertension is the most common cause of heart failure in the black race (Isezue et al, 2000). In Nigeria, hypertension and rheumatic fever are major causes of heart failure (Amoah and Kallen, 2000). Despite major advances in pharmacological treatment of heart failure, the number of people afflicted with the ailment continues to rise resulting in poor quality of life (Benno et al, 2006). However, structured exercise training had been shown in Caucasians to improve oxygen consumption, muscle strength and mass and quality of life (Meyer et al, 1996; Giannuzzi et al, 2003). Other

studies had also suggested that exercise training could remedy the abnormal autonomic, neuro-humoral and hemo-dynamic functions associated with the heart failure syndrome (Westhof et al, 2007; Karapolat et al, 2009). On the other hand, reduction in physical activity either produced by the symptoms of heart failure or prescribed by physicians treating heart failure may result in a state of physical de-conditioning that may excercebate the symptoms of heart failure and exercise intolerance in patients with chronic heart failure (McKelvie et al, 2002; Fulster et al, 2013).

In developed countries, exercise training is being recommended as a useful intervention for patients with stable chronic heart failure (Hunt et al, 2009). Even in developed countries, the acceptance of exercise training by the medical community as a part of patient management has not been enthusiastically received (Tabeta et al, 2009).

One of our Ph.D. students, Dr. Olufunke Adewumi Ajiboye, evaluated the role of therapeutic exercise on selected cardio-respiratory functions, exercise walking capacity, activity level, quality of life, muscle strength and body composition in Nigerians with stable bi-ventricular heart failure. She also investigated whether these patients were able to maintain the improvement in quality of life after supervised exercise training with home-based aerobic exercise and to establish gender specific prediction equations for sub-maximal exercise capacity of apparently healthy Nigerians. Supervision of this Ph.D. was done in conjunction with Prof C.N. Anigbogu and Prof. J.N. Ajuluchukwu.

Her study established that in patients with bi-ventricular heart failure, therapeutic exercise:

(1) Enhanced cardio-respiratory functions.

(2) Improved functional capacity, muscle strength and quality of life (Ajiboye et al, 2013).

Thirdly, she showed that structured home-based aerobic exercise programme is safe and effective for bi-ventricular heart failure patients after hospital-based exercise training (Ajiboye, 2013). Fourthly, she established gender specific regression equations for predicting 6-minute work distance (6-MWD) in apparently healthy Nigerian adults (Ajiboye et al, 2014). **Through these studies, our group (Dr. Ajiboye, Prof. Anigbogu, Prof. Ajuluchukwu and I) won the Faculty Best Researcher Award (Clinical Sciences) of the UNILAG Golden Jubilee Research Conference and Fair 2012 and also in 2014.**

THE SICKLED CELL: OUR CROSS

Since 1998, I have been studying the use of anti-oxidants in the management of sickle cell disease. I have found willing collaborators in Professor M.O. Kehinde (Department of Medicine) and Professor E.O. Temiye (Department of Paediatrics). This is therefore my major contribution to knowledge.

Sickle cell disease is a hemoglobinopathy characterised by intermittent vaso-occlusive events and increased susceptibility to infections (Onwubalili, 1983; Sergeant, 2001). It is caused by a replacement on the β chain of Hb of glutamic acid by valine in the 6th position (Ingram, 1956). Point mutation in the β chain structurally changes the normal hemoglobin molecule giving rise to the sickle cell disorder. It has been **identified as the first known human molecular disease** (Sergeant, 2001).

The first publication of sickle cell disease was in 1910 by Dr Herrick in the USA. The disease was identified by Dr. Earnest E. Irons (an intern) in 1904, in Walter Clement Noel, a dental student from Granada (Sergeant, 2001). In

Africa, SCD had been known and given different names. The names include: *ogbanje and abiku* (Nzewi, 2001).

INCIDENCE

Incidence of SCD in West, Central and East Africa is between 5-20%. It is less common in Northern and Southern Africa. Gene frequency is higher in low-lying, wet regions with a high prevalence of malaria. (Diallo and Tchemia, 2001). In Africa, 120,000-200,000 babies are born each year with the gene, (WHO, 1994). In Nigeria, 45,000-90,000 new babies are born each year with the gene. (Shenoy, 2007).

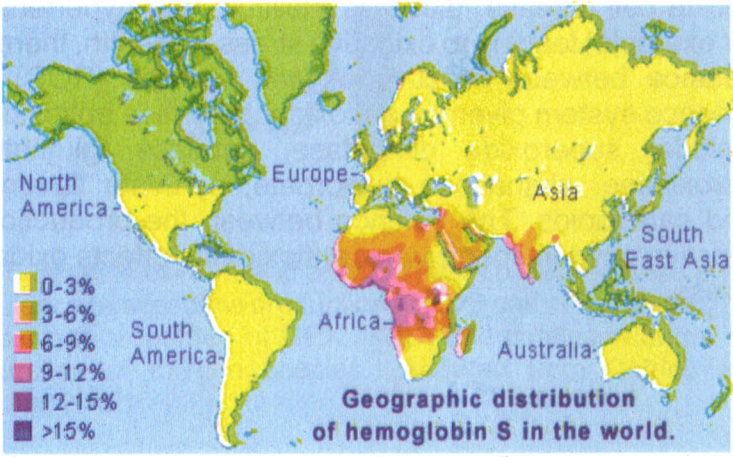


Fig. 4 Map Showing Distribution of Hemoglobin S world-wide

With an incidence of about 5-20% in Africa, it is therefore clear that the sickle cell gene is our cross. With an estimated population of over 120 million people, the number of people carrying the sickle cell gene must be staggering. The economic burden to the nation and cost of caring for these patients has not been computed in Nigeria. The economic burden includes hospitalisation time and costs, loss of school time and therefore loss to the country and unquantifiable agony, stress and anxiety

of parents. In a study done in the United States, average cost per month- patient was $1,389 (Kauf et al, 2009).

OXIDATIVE STRESS

There is oxidative stress during normal life, during disease states and even during exercise. Oxidative stress exists when there is an imbalance between the systemic manifestation of reactive oxygen species and the biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Thus, reactive oxygen species (ROS) are produced in the course of normal living. The levels are higher in disease states (sickle cell disease, diabetes mellitus, and hypertension, for example) leading to oxidative stress. In health, there is a balance between reactive oxygen species (ROS) and defence system given by antioxidants. These antioxidants include: superoxide dismutase, catalase, gluthatione peroxidase, gluthatione, ascorbate, pyruvate flavonoids and carotinoids. The balance between the production of reactive oxygen species and antioxidants affects oxidative stress.

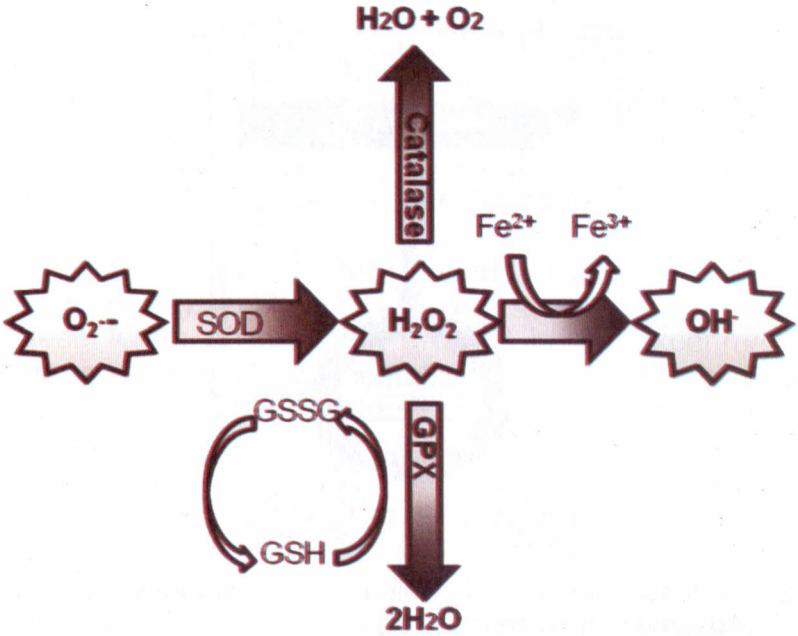


Fig. 5 Balance of ROS and antioxidants. Oxidative stress is the imbalance between the production of ROS and antioxidants. The antioxidant properties of GPX, SOD, and catalase control the production of oxygen species. (Adapted from Chirico and Pialoux, 2012)

Increased production of oxidants or decreased availability of antioxidants causes oxidative reactions damaging lipids, proteins and DNA and ultimately leading to death (Droge, 2002).

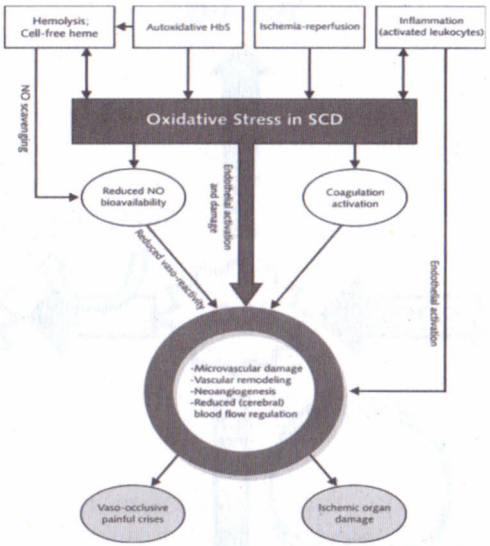


Fig. 6: Causes and pathophysiologic role of oxidative stress in SCD (Adapted from Nur et al, 2011)

SOURCES OF OXIDATIVE STRESS IN SICKLE CELL DISEASE

The sources or causes of oxidative stress in SCD are shown in Figure 6. They can be summarised into the following categories:

- Excessive levels of cell-free Hb with its catalytic action on oxidative reactions
- Recurrent ischemia-reperfusion injury
- Chronic pro-inflammatory state
- Higher autoxidation of sickle cells.

SOME INTERVENTIONS

Hydroxyurea (Kato, 2008: Raghupathy & Billet, 2009). The use of hydroxyurea in the management of sickle cell disease has become very popular. One of its advantages is that it decreases the polymerisation rate of Hb S by increasing hemoglobin F (Hb F) concentration. Also, it is safe in the short term but has myelosuppresive effects on

WBC and platelets. In addition, hydroxyurea does not prevent stroke even with elevation of Hb F levels (Atweh & Schechter, 2001). Hydroxyurea sells for about N60-N70 per capsule in Nigeria and about $54-$142.00 for 100 capsules in the USA. It may therefore not be affordable for the average Nigerian sickle cell patient.

Stem Cell Transplantation/Gene Therapy (Townes, 2008; Shenoy, 2007)
These forms of treatment are still in the experimental stages in the USA. Its current cost in the US is between $250, 000. 00 to $500,000. 00. The procedure had been carried out once at the University of Benin Teaching Hospital, Benin City in 2011. The cost of the procedure remains unknown to the public. However, a non-governmental organisation (NGO) had placed a price of N17m for treatment to take place in Italy, (Adekunbi Aro, *Tell Magazine*, Wednesday, July 6th, 2011).

Nitric Oxide inhalation (Gladwin and Schechter, 2001; Raghupathy and Billet, 2009)
Nitric oxide (NO) inhalation had been employed in the management of persistent pulmonary hypertension of the infant in the United States of America. Its use had been suggested for the treatment of SCD especially for those that had developed pulmonary hypertension (Gladwin and Schechter, 2001; Raghupathy and Billet, 2009). However, the cost of installing infrastructure for production and delivery of NO could be very high. In the United States of America, it costs about $41,609.00 per treatment (Lorch et al, 2004). It is therefore clear that the cost of offering these types of treatment to Nigerian patients could be prohibitive and unacceptable.

ANTI-OXIDANTS TO THE RESCUE

Since 1998, we have been studying the effect of supplementation with low dose antioxidants, namely:
1. Vitamin C (300mg/day for 6 weeks for adults)

2. Vitamin C (100mg/day for 6 weeks for children)
3. Vitamin E (100IU/day for 6 weeks for adults)
4. L-Arginine (1g/day for 6 weeks for adults)

These medications are cheap and affordable especially in economically disadvantaged populations like ours. Vitamin C costs about N30 for 100 tablets while L-Arginine costs about N1, 200.00 for 60 capsules.

Our studies have confirmed that when compared with normal subjects, sickle cell anemia subjects (SCAS) had:

(a) Lower arterial blood pressure (BP), but a higher pulse pressure (PP) (Jaja et al, 2003; 2008; Ogungbemi et al, 2013);
(b) Reduced haematological indices (Hb, PCV, RBC count, etc) (Jaja et al, 2008);
(c) Decreased antioxidant enzymes (catalase, glutathione peroxidase, superoxide dismuthase) levels (Ogungbemi et al, 2013);
(d) Reduced Nitric oxide metabolites (NO_x) activity (Ogungbemi et al, 2013);
(e) Liver enzymes (Aspartate aminotransaminase, alaninie aminotransaminase and alkaline phosphatase) and trace metals (Zn^{++}, Mn^{++} and Cu^{++}) were higher during painful crises than in steady state sickle cell anemia subjects (SCAS) or non sickle cell anemia subjects (NSCAS) (Kehinde et al, 2010).

TABLE 1: SUMMARY OF LEVELS OF ENZYME MARKERS AND TRACE ELEMENTS

Parameter	NSCD (a)	SCD-SS (b)	SCD-Cr (c)	(a) Vs (b)*	(a) Vs) c)*	(b) Vs (c)*
AST	36.4 ± 4.1	31.8 ± 5.2	60.0 ± 8.1	NS	< 0.01	< 0.01
ALT	14.2 ± 0.8	13.3 ± 1.3	22.1 ± 3.7	NS	0.05	< 0.05
ALP	9.3 ± 2.1	1.8 ± 3.0	32.3 ± 2.5	< 0.01	< 0.01	NS
Cu^{++}	0.07 ± 0.03	0.06 ± 0.02	0.17 ± 0.03	NS	<0.	< 0.01
Fe^{++}	0.70 ± 0.04	0.80 ± 0.10	1.0 ± 0.20	NS	NS	NS
Zn^{++}	0.70 ± 0.07	0.70 ± 0.06	3.4 ± 0.70	NS	< 0.001	< 0.001
Mn^{++}	0.10 ± 0.04	0.07 ± 0.005	0.20 ± 0.07	NS	< 0.05	< 0.01

*ANOVA from Kehinde et al, 2010

Further, our studies have shown that low dose vitamin C (300mg/day in adults or 100mg/day in children) or vitamin E (200 IU/day in adults) or L-Arginine (1g/day in adults) supplementation for 6 weeks caused:

(i) Reduction in:

(a) Arterial blood pressure (BP), Irreversibly sickle cell count (ISCC), Forearm vascular resistance (FVR) and liver enzymes, (Jaja et al, 2000; 2001; 2002; 2003, 2013; Gbenebitse et al, 2005).

(b) Malondialdehyde (MDA) level (index of lipid peroxidation), (Gbenebitse et al, 2005).

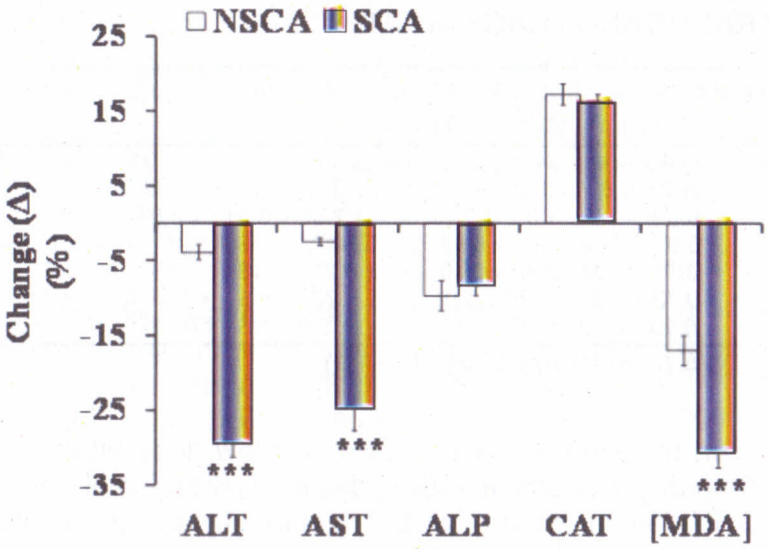


Fig. 7: Changes in plasma levels of liver enzymes, malondialdehyde and catalase in SCA and NSCA subjects following vitamin C supplementation (***p<0.001). (Jaja et al, 2013)

(ii) Increased:

(a) Antioxidant enzymes (catalase, superoxide dismuthase and glutathione peroxidase), (Jaja et al, 2013).

(b) Trace metals (Cu^{++}, Mn^{++} and Zn^{++}) (Ogungbemi et al, 2014, in press).

(C) Nitric oxide metabolites concentration (Kehinde et al, 2014, in press).

(d) Forearm blood flow (Jaja et al, 2002; 2003; Gbenebitse et al, 2005).

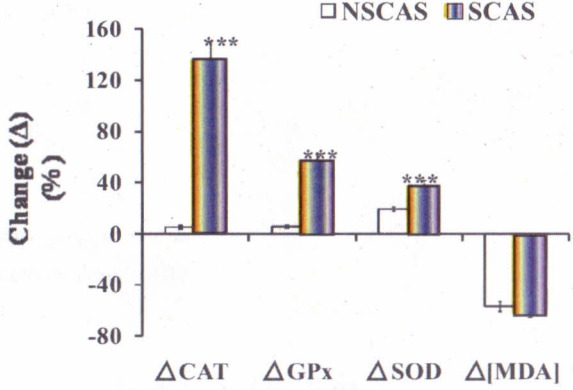


Fig 8: Changes in antioxidant enzymes and malodialdehyde concentrations following L-Arginine supplementation. (Ogungbemi et al, 2014, in Press)

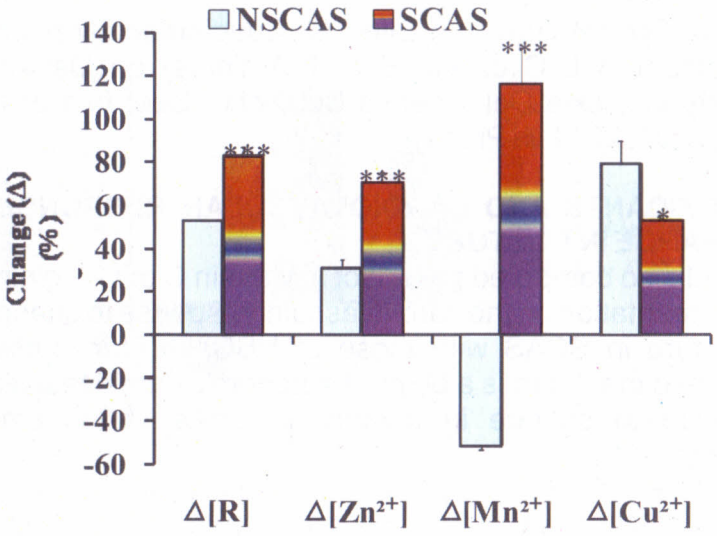


Fig 9: Changes in L-Arginine (R), and trace metals concentrations following L-Arginine supplementation (Ogungbemi et al, 2014, in Press)

(iii) Shifted the Osmotic Fragility Curve to the left

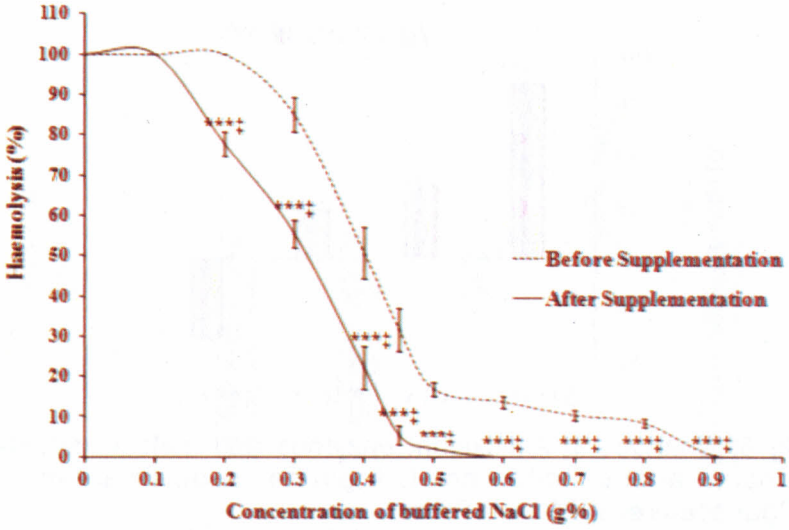
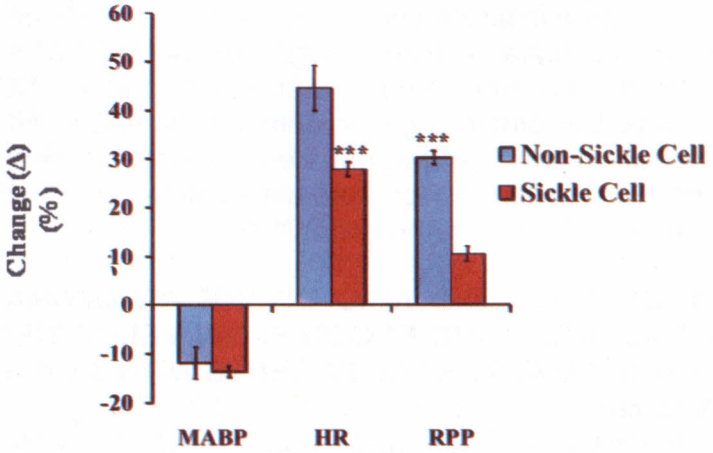


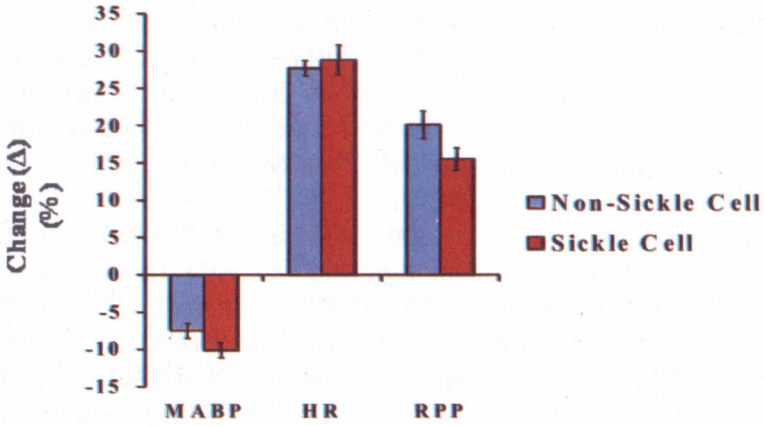
Fig. 10: Typical Graph of Effect of Supplementation with Antioxidant (Vit. C or Vit. E or L-Arginine) on Osmotic Fragility in Sickle Cell Anemia Subjects. (See Jaja et al, 2000; 2001, 2014, in Press)

ANTIOXIDANTS AND CARDIOVASCULAR RESPONSES TO CHANGE IN POSTURE

We had also compared the effect of vitamin C or L-Arginine supplementation on the cardiovascular response to change in posture in SCAS with those of NSCAS. Our studies confirmed that there is a blunted autonomic cardiovascular response to change in posture in sickle cell anemia subjects.



Effect of change in posture from supine laying to standing on mean arterial blood pressure (MABP), heart rate (HR) and rate-pressure product (RPP) in non-sickle cell and sickle cell anaemia subjects. *** = p <0.001 = significant



Effect of change in posture from supine laying to standing after vitamin C supplementation on mean arterial blood pressure (MABP), heart rate (HR) and rate-pressure product (RPP) in non-sickle cell and sickle cell anaemia subjects

However, vitamin C or L-Arginine supplementation equilibrated the cardiac and autonomic responses to

change in posture in sickle cell anemia and non-sickle cell anemia subjects (Jaja et al, 2008; Ogungbemi et al, 2013). These effects may have been mediated in part by NO because oral L-Arginine supplementation increased NO availability and activity and attenuated pressor and heart rate responses to change in posture especially in sickle cell anemia subjects (Ogungbemi et al, 2013).

EFFECT OF ASCORBIC ACID INTAKE ON INTIMA-MEDIA THICKNESS AND BLOOD FLOW VELOCITIES IN THE CAROTID ARTERY OF PATIENTS WITH SICKLE CELL ANEMIA

Various studies have been carried out on the interaction between sickle red cells and vascular endothelium, with researchers demonstrating that almost all major adhesion pathways are involved in this interaction. Carotid endothelial damage results in plaque formation, which, when detected sub-clinically, enables early intervention, thereby preventing stenosis, infarction, and stroke. On average, 11% of patients with sickle cell anemia (SCA) will develop a clinically apparent stroke by age 20 years and 24% by age 45 years. The first episode usually occurs between ages 2 and 15 years (Huttenlochereral, 1984).

We carried out a study to compare the effects of vitamin C supplementation on peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistivity index (RI), intima-media thickness (IMT), and cross-sectional diameter (CSD) of the common carotid arteries of SCA patients with those of non–sickle cell anemia (NSCA) subjects. Measurements were made using a duplex sonographic scanner (Aloka ProSound SSD-3500; Aloka, Wallingford, Connecticut) with a high-frequency (5–10 MHz), linear-array transducer.

Twenty (20) NSCA (HbAA) students of the College of Medicine, University of Lagos, with genotype HbAA, were

recruited as controls for this study. Also, 10 HbSS patients registered with the adult Sickle Cell Clinic of the Lagos University Teaching Hospital were recruited for the study. Both groups comprised young adults aged 16 to 25 years. Informed consent was obtained from every volunteer used. Blood pressure and pulse rate were measured and recorded with a digital blood pressure monitor (model 6016, American Diagnostic Corporation [ADC], Hauppauge, New York). Height and weights were measured with appropriate equipment.

We found that the cross sectional diameter (CSD) and end-diastolic volume (EDV) were significantly higher in SCA than in NSCA subjects. After vitamin C supplementation, we found significant differences in changes (Δ), in the measured parameters when the two groups of subjects were compared (Olowoyeye et al, 2011).

Our studies using these antioxidants suggest that routine prescription of an antioxidant (Vitamin C or L-Arginine) to patients with sickle cell disease as prophylaxis may protect against oxidant damage thus preventing vaso-occlusive crises and its associated morbidity. Dr. Stephen Ogungbemi has obtained his PhD working in this area.

We are therefore planning a clinical study, results of which, we hope will permit the clinical use of any of these antioxidants in the management of sickle cell disease.

NIGERIAN FOODS AS SOURCES OF ANTIOXIDANTS

Several foods consumed by Nigerians have antioxidant properties. We have studied a fruit and a leafy green vegetable to determine their antioxidant status.

(a) *Persea americana:* Avocado pea, *ewe pia* (Yoruba), *eben mbakara* (Efik), *ube oyibo* (Ibo), *ganyen pia* (Hausa).
We showed that the aqueous extracts of the leaves of *P. americana* have vaso-relaxant properties on isolated rat aorta (Owolabi et al, 2005).

After feeding the aqueous extract to Sprague-Dawley rats for 5 days, we found in the urine of the rats:

- The metabolites of the aqueous extract were polyphenolic in nature.
- Extensive degradation of the flavonoid of *P. americana* (Owolabi et al, 2005).
  Polyphenols may be the vaso-relaxant agent in *P. Americana,* which may act via endothelium –dependent mechanisms or increased nitric oxide bioavailability (Owolabi et al, 2005).

We isolated the following flavonoids from the leaves of *P. americana:*

- Isorhamnetin
- Luteolin
- Rutin
- Quercetin
- Apigenin (Owolabi et al, 2010)

(b) Vernonia amygdalina: Bitter leaf, *etidot* (Efik), *onugbu* (Ibo), *chusar duki* (Hausa)

We found that extracts of *V. amygdalina:*

- Contain natural antioxidants against aqueous radicals and reactive species
- Total phenolic content of the extracts is related to its total flavonoid
- This may be responsible for its total antioxidant activity (Owolabi et al, 2008).

Our research group (Dr M. A. Owolabi, Prof. H. A. B. Coker and I) won the UNILAG Best Researcher award in 2006, 2007 and 2012, in the College of Medicine/Faculty of Pharmacy category.

CONCLUSION AND RECOMMENDATION

Our studies have been collaborative between researchers based within the same department or in different departments. Our studies have been based on individual initiative and not on any identified national need. When available, research grants have been mainly from the Central Research Committee (CRC) of the University of Lagos. The grants cover mainly consumables and do not substantially improve laboratory capacity. I have been a recipient of one of such grants. **This amount needs to be increased substantially to enable researchers improve laboratory capacity and thus train more Ph.D.**

- There is also a need for a central body **(a National Bio-Medical Research Institute)** to be set up to direct and co-ordinate biomedical research in Nigeria. **This body must be independent of the NUC or TETFUND or Nigerian Institute of Medical Research (NIMR) or other such bodies.** Such a body must borrow ideas from organisations like the National Institutes of Health of the USA.

When set up, such a body should:

- Have powers to determine the direction of biomedical research in Nigeria from time to time.
- Have authority to receive grants from government and other donor agencies or philanthropic organisations world-wide.
- Award research grants to individuals or groups of researchers for the purpose of carrying out biomedical research in Nigeria.

- Monitor the progress of such research and ensure that research grants are put to proper use.

If this is done, Nigeria will have a reservoir of information to tackle some of her biomedical challenges during emergency or not.

ACKNOWLEDGMENTS

First, thanks be to God for His mercies and **AMAZING GRACE;** for allowing us to see this day and for making this lecture possible; for ordering my footsteps and for His promises.

I pay special respect to my parents, Late Mr. Ishmael Adagogo (1921–2000; 79 years.) and Late Mrs. Abigail Iminabo (1928–2009; 81 years), Patesi Oko-Jaja. They were parents per excellence, teachers per excellence, strict but loving, always sacrificing for their children. As teachers, they brought up several children put in their care, directly or indirectly. **I pray that light perpetual will continue to shine on their souls.**

My utmost appreciation goes to those who intervened at critical times of my life. They include but are not limited to Late Prof. M.O.A. Jaja, Mr E. Adagogo Jaja, former Managing Director of Daily Times of Nigeria and Late Chief (Dr.) Solomon Jaja.

Members of the King Jaja Family Union in Lagos; members of Opobo Progressive Association, (OPA), Lagos; members of Lagos University Medical Society; members of the Fellowship of Faith and the Good Shepherd, Chapel of the Healing Cross Idi-Araba and the Physiological Society of Nigeria allowed me to serve them in different capacities. I thank you all.

I must appreciate the effort of my primary, secondary and tertiary level teachers. Examples at the university level are: Late Prof. F.O. Dosekun, Prof. (Mrs.) Oyinade Elebute, Prof. G.O. Ojo, Prof. O.A. Sofola and Late Prof. S.A. Adigun. These are just a few.

To my colleagues: Prof. (Mrs.) O.A. Adegoke, Prof. C.N. Anigbogu, Prof. (Mrs.) Ibiyemi I. Olatunji-Bello (former Ag. VC, LASU, Ojo), Dr. (Mrs.) Bola Iranloye, Dr. Ahmed

Oloyo, Dr. A.O. Morakinyo, Dr. F.O. Awobajo, Dr. A.P. Arikawe and all other lecturers, Technologists and Administrative Staff of the department, I thank you all.
I also pay special respect to Prof. Jim McNamee and Prof. Philip D. Watson (University of South Carolina, Columbia, USA), Prof. A.L. Lawson and Prof. Festus Adzaku (University of Ghana, Accra, Ghana) for making my stay in their respective departments of physiology at different times of my career worth the while.

I do not forget the support I received from my research collaborators from other departments: Prof. M.O. Kehinde (Medicine), Prof. E.O. Temiye (Pediatrics), Prof. Jane Ajuluchukwu (Medicine), Prof. J.K. Renner (Pediatrics), Prof. H.A.B. Coker (Pharmaceutical Chemistry) and all my Ph.D, M.Sc. and B.Sc. (Physiology) students.

I also drew strength from over 7,000 undergraduate medical, dental, physiology, pharmacology, pharmacy, physiotherapy, nursing and medical laboratory science students that I had come across during my over 30 years of service to this University.

At this point, I must acknowledge the untiring effort of the Vice Chancellor, Prof. Rahamon Ade Bello, assisted by the Deputy Vice Chancellors, Registrar and other members of the University Management team, in giving the University focus and direction. I also acknowledge the efforts of previous Vice Chancellors especially Prof. Oye Ibidapo-Obe, Prof. Tolu Odugbemi and Late Prof. Adetokunbo Sofoluwe.

I am grateful to all the Provosts, past and present, of the College of Medicine, University of Lagos who have given unqualified leadership to the College. Under some of them I climbed the rungs of the academic ladder. I specially congratulate all the past Deans, Faculty of Basic Medical Sciences, especially past Dean Prof. Sunday

Omilabu, the Current Dean, Faculty of Basic Medical Sciences, Prof. Olufumilayo O. Adeyemi, for their milestone achievements in the Faculty.

I also acknowledge all the Resident Ministers (past and present) of Chapel of the Healing Cross, Idi-Araba, (The Protestant Chapel of CMUL and LUTH) – for spiritual direction. These include Rt. Rev. George Bako, (retired Bishop of Lokoja Diocese of the Anglican Communion), Late Professor & Ven. Sam Ade Olaitan, The Very Rev. M. E. Euler-Ajayi, The Ven. (Arc) Olusegun Kuti, Ven. & Arc. Tunde Osho (Chief Resident Minister), The Ven. (Dr.) Dade Sadare, The Very Rev. Oluwatoyin Olumo, The Very Rev. Ayo J. Richards, The Very Rev. William Allotey-Pappoe, The Rev. Ebenezer Green and The Rev. Anthony Ajero.

I salute His Majesty, King Dandeson Jaja, Jeki V, Amanyanabo of Opobo and members of the King Jaja Executive Authority. I also pay my special respect to members of the Chief Patesi Oko-Jaja War Canoe House led by Alabo (Chief) Emmanuel Patesi Oko-Jaja and the Seniapu (elders).

To FRIENDS Club, F-R-I-E-N-D-S F-O-R-E-V-E-R.
To the Residents of D6–D9 (Christmas) Close, Eni Njoku Road, UNILAG. Thanks for the warmth and love. To my wonderful parents-in-law: Opu Senibo Nylander Jim-Wariso (91 years) and Mrs. Ethel Amiepiri Jim-Wariso (83 years,) for donating their daughter to me.

To my Siblings: Ms Rosalyn Oko-Jaja (NLNG, Bonny), Dr. Richard I. Oko-Jaja (Physician and Lecturer, University of PH), Rev Adagogo I. Oko-Jaja (District Overseer, Apapa/Ajegunle District, Four-Square Gospel Church, Lagos), Mr. Adango I. Oko-Jaja (Deputy Comptroller of Immigrations, Abuja). I thank you all for your love and support.

I pay special respect to my late sister, Mrs. Stella Adadiepiri Obiako, who died in the United States of America in 2011. MAY LIGHT PERPETUAL CONTINUE TO SHINE ON HER SOUL.

To my wonderful children: Soprinye (Soso), Biegbana (Bie), Tamunotonye (Tonye), Tamunonengiofori (Nengi). **I could not have asked God for anything better.**

To my lovely wife, Mrs. Ibiene Christiana Jaja (nee Wariso), Assistant Director, Ministry of Defence, Lagos – My (Chief) Counselor, (Chief) Confidant, (Chief) Manager, mother of all my children. Thank you for sticking it out.

Mr. Vice Chancellor, Sir, distinguished ladies and gentlemen, thank you all for your attention.

God Bless you all!

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