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**“...To Judge the Living and the Dead...”**  
**The Pathologist, the Misery, the Mystery**  
**and the Final Diagnosis:**  
**An Interminable Quest for Excellence**

By

**Olusegun Sylvester Ojo**  
*Professor of Anatomical Pathology*



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Mr. Vice Chancellor, sir, distinguished ladies and gentlemen, I consider it a great privilege to stand before you today to give this lecture, marking my inauguration as a Professor of Morbid Anatomy in the College of Health Sciences of this University. This event is a culmination of a most fortuitous coming together of occurrences strewn over a period of about four and a half decades. I marvel at how all these were made into a jigsaw that fit nicely into a story being told this day. It's only God, the father of our Christ, who deserves all the accolades for this marvelous brew.

Christians in this audience will easily recognise that the title of this lecture came from a segment of one of the stanzas of the Apostles Creed. Indeed, as affirmed in the creed, God judges and He it is who will ultimately judge all. But, while the earth and time exist, He has kindly given us the privilege to think His thoughts after Him. Mr. Vice Chancellor, sir, this is why I feel that doctoring involves, of necessity, an act of 'playing God' i.e. thinking like him. It involves delving into, inquiring and evaluating all issues that surround life and the existence of man, in order to have a comprehensive view and a holistic approach to duty. Doctoring is supposed to be always associated with the preservation of life. To be able to adequately fill that role, doctoring must also include a detailed study of death and its associated circumstances and consequences. But we need to start from the beginning.

#### **In the beginning.....**

In my opinion, a doctor cannot but ask fundamental questions about the origins of man and ponder the prevailing human condition. Obviously there are many accounts of how it all began and how we got to where we are today. Let us consider one of such accounts:

"In the beginning God created the heaven and the earth ....and God saw everything that he had made, and behold, it was very good. And the Lord God formed man of the dust of the ground, and breathed into his nostrils .....and man became a living soul. ....and the Lord

God planted a garden eastward in Eden; and there put the man he had formed. And out of the land made the Lord God to grow every tree that is pleasant to the sight, and good for food ..... and they were both naked, the man and his wife, and were not ashamed<sup>22</sup>) Genesis Chapter 1: 1-

*The Holy Bible*

Oxford University Press, London. 1984.

This account of the beginning of time, also known as the creationist theory, Mr. Vice Chancellor, appeals to my simple mind. Human experience so far would tend to suggest that we started from the serene, rather than with a 'big bang', and have since marched inexorably into states of ever increasing entropy. Indeed, I observe that the ideal to which all our noble and positive human efforts are geared to restoring is the harmony, peace and comfort reminiscent of the beginning as depicted in this account.

As a medical man, I find an enduring interest in the characteristics of the state described in the creationist account. In Eden, man was in his 'heavenly' state. In that state, it can be inferred, all his body systems must have functioned perfectly in a state of physiological harmony. In that state, there could not have been any diseases and therefore, medicines would not have been needed and the practitioners of the health sciences would have had no place. Obviously, Pathologists were not needed and I would think that they did not exist.

This state, alas, we are told, was to be short-lived, and soon dis-harmony, pain and chaos came and the human condition changed ever since. In the circumstance, we must hold that disease is perhaps one of the features of loss of the edenic bliss. With the advent of disease, the need was at once created for a specialised group of workers to study the disordered physiology of the post-edenic man, devise remedies and ways of coping with the misery of man's difficult existence that eventuated.

## The misery

The term 'disease' is a rather broad one. However, it connotes a state of poor health or the absence of health. Disease may simply be regarded as a state in which there is a malfunction of man's body or mind or both.

Among all human societies, disease exists as a source of misery, pain and death - an antithesis to all healthful and comfortable living. To this extent, disease may be seen as a source of opposition to survival and perpetuation of the human species. The evolutionists may prefer to see disease rather as constituting a 'selection pressure' for the refining of species *Homo sapiens*. Whichever way it is perceived, the existence of disease has elicited remedial efforts that have been fuelled by the fundamental instincts of self preservation and survival from antiquity. This instinctive response to the existence of disease is embodied in folk-medicine.

Instinct, being a self-preservation response, is hardly ever given to intellectual makeover, at least in its initial phases. This would explain why primitive medicine, in all ancient cultures, was an affair of plant-lore, as well as the use of psychotherapy, charms and spells, to stave off the effects of supernatural agencies thought to be harbingers of ill-health.

## Understanding the mystery of disease

Fundamental to understanding disease should be a concrete idea of its antecedents. The concepts of the origin and causes of disease are as many as there are cultures and religions in the various parts of the world. In most primitive and ancient cultures, it was widely held that the cause of disease was essentially spiritual. While some regarded disease as punishment handed down by the gods as retribution for personal or collective mis-deeds or sins, some others believed that diseases was the handiwork or influences of evil spirits and demons. This spiritual

explanation for the cause of disease is still highly prevalent in our country today. However, the current status worldwide is that the understanding and treatment of disease has developed into a major science. Thus to the rational modern man, throwing light on the causes, nature, and extent as well as predicting the possible end-points of a disease ought to be a fundamental requirement in designing an effectual remedy for it.

### The Origins of Western Medical Thought

As we can see from the foregoing, Medicine started as an art long before the understanding of disease itself commenced. Available written records<sup>3</sup> show that Hippocrates (460 – 370 BC), was perhaps the first to offer a materialistic or non-spiritual explanation for understanding the basis of disease. He proposed that man was made up of four 'humours' - air, blood, bile and fire and that these existed in equal proportions. He propounded that a disease was caused when the equilibrium between these humours was disturbed, with one or more of the humours existing in a greater proportion relative to the others. This principle later became known as **Humoral Medicine**. By this rather sharp departure from the conventional wisdom of his day, Hippocrates provided the impetus for the search for scientific explanation for the cause of disease and hence the birth of Western Medical thought. This feat deservedly earned Hippocrates a historical place as the 'Father of Medicine'.

Owing to its tenacity, disease continuously calls for a deeper examination of its origins. Thus according to Osler, "from Hippocrates to Hunter, the treatment of disease was one long traffic in hypotheses"<sup>3</sup>. We are now given to know that in health, the body's organ systems function in such a way as to maintain an internal 'steady state' or **homeostasis**, where fluctuations are kept to a minimum. Environmental factors impinge on this internal environment in a variety of ways, often serving as 'stress factors'. The human physiology is equipped to respond

appropriately to environmental influences while still maintaining a stable homeostasis. Most of the homeostatic mechanisms that make this possible are automatic and depend on complex enzymatic and hormonal pathways. Severe stress such as may accompany invasion by microbes or starvation may also be contained to a certain extent and within certain limits. Under such circumstances, the functional reserves of the organ-systems are called into play. In these extreme situations, the need to maintain life may dictate that a new functional internal environment be set up.

The process of setting up of this 'altered' or 'adapted' steady state is known as **adaptation**. In order to protect the internal environment from such severe stress and extreme situations, a variety of defence mechanisms also exist. Disease results when the defence systems falter, overwhelmed or they get out-foxed by the adverse influences. In such an event, the adaptive homeostatic mechanisms become inadequate and the physiological reserves of the organ-systems get exhausted.

### The Philosophy of Medicine

Medicine, as a profession, is almost as old as the human race, as old as the necessity for the removal of disease. It has since grown into a holistic study of humanity, his biology, his health, his sociology, his technology, his physical environment, his medicaments, his education and mis-education, his past, his present and his future. In short, Medicine is the Science of Life as much as it is a Life Science. It is also the forebear of scientific enquiry. For I concur with Hippocrates, the father of Medicine, when he said "I also maintain that clear knowledge of Natural Science must be acquired, in the first instance, through mastery of Medicine alone" Aristotle also said "Conscientious and careful physicians allocate causes of disease to natural laws, while the ablest men of science go back to Medicine for their first principles"<sup>3</sup> and Helmholtz confessed "I look back upon my medical studies as the school which taught me, in a more penetrating and convincing way than any other, the eternal principles of scientific work, principles so

simple yet continually forgotten, so clear and yet ever shrouded by a deceptive veil<sup>3</sup>. Ladies and gentlemen, Pathology, my specialty, is an important branch of the profession of Medicine. I crave your indulgence to introduce it to you.

### What is Pathology?

Pathology may be broadly defined as the study of disease processes. It developed as the science of the understanding of the mechanisms of disease and seeks to throw light on the **mystery** of disease. The origins of the subject of Pathology can be traced to the Renaissance period in Europe when questions about the cause of death in suspicious circumstances led to the practice of holding public **post-mortem** examinations. The publication of the first treatise on **post-mortem** appearances in certain diseases is often attributed to a Florentine surgeon, Antonie Benivieni ( ? - 1502). His book – ‘*De Abditis Causis Morborum*’ (‘On the Seat and Causes of Disease’) was published in 1507 AD. This, arguably, marked the beginnings of Morbid Anatomy. However, Rudolf Virchow (1821-1905) is widely regarded as the father of modern pathology. He brought the discovery of the light microscope, made earlier on by Anthony van Leeuwenhoek in his studies on **cork** in the late seventeenth century, to bear on the study of the fine structure of human tissues. He discovered that the cell **was the unit** of all living tissue and put forward the view that that the gross anatomical changes seen in disease were the expression of the changes that had occurred earlier at the cellular level. This later evolved into the concept and science of **cellular pathology**.

From its beginnings, the practitioners of this science, Pathologists, have always been called upon to evaluate every context of disease. Among the **living**, this is done by examining specimens from disease-bearing persons. When **death** has occurred, especially in situations where the cause is either unclear or is required to be legally defined, pathologists

are called upon to explain why and how death is caused. In short, Pathologists, in the course of duty, have always had to **judge the living and the dead**.

### Judging the Living

A major role of modern science is to throw light on natural **mysteries**. Basic Medical Sciences such as physiology and biochemistry have solved many a **mystery** about the **functioning** of the human body in health. Pathology **seeks** to do the **same** when disease becomes established. As a biological system, the human body responds to the onset of disease with a fresh set of physiological responses. The principal aims of these responses are to attempt a ‘repair’ and restoration of normal physiology while attempting to **eliminate** the cause of the disease.

However, some of these responses to disease are in themselves abnormal and may further aggravate the situation. Thus, they paradoxically contribute to the setting-up of the ‘disease physiology’ and, together with the factors arising from the agent of the disease, are known as **pathogenetic mechanisms**. These mechanisms subsist for the duration of the disease and often account for some of the clinical symptoms and signs associated with the disease. If the disease-state lasts for long enough, these pathological mechanisms usually lead to alterations in tissue structure and architecture. As a medical science, pathology seeks to explain the intricate pathogenetic mechanisms associated with disease and the consequences of the operation of these mechanisms.

In evaluating the context of disease, the pathologist is called upon to determine what might have gone wrong, how severe the disorder is and what the outlook of the disease process is likely to be, with, or without treatment.

## The lesional basis of disease

Over the millennia, Medical Science has shown that most diseases have an identifiable cause or **aetiology**. Advances in medical science have made it possible to precisely pinpoint the basis of disease i.e. what had gone wrong in the body systems in most disease situations. This is often referred to as the **lesion**. A lesion may be a purely functional or physiological disorder or it may be a change in tissue architecture or structure. However, it is more often a combination of these changes in varying degrees, either occurring simultaneously or sequentially. The lesion may be innate or directly induced by a noxious agent in the environment or caused by an inter-play of host factors and environmental influences. Such environmental influences may be microorganisms, extremes of temperature, ionising radiation or a nutritional lack.

Mr. Vice Chancellor, ladies and gentlemen, in summary, identifying the lesion in every instance of disease is the clinical role and burden of the Pathologist.

## The Pathologist as a diagnostician

A very important reason for studying diseases is to make accurate diagnoses. Put simply, pathology is the science of making clinical diagnoses. An accurate diagnosis makes it possible to make informed forecast of the likely course of events during an affliction. It also makes it possible to rationally formulate and empirically apply treatment. Accurate and definitive diagnoses can only be made if the causes of diseases are known and the characteristic pathogenetic mechanisms responsible for the associated physiological disorders are understood in each case. ∴

## Judging the Dead

At death, all life processes cease. Death is never anyone's favourite subject because it evokes a feeling of trepidation in most people. However, death, being the ultimate end of all, needs to be engaged intellectually. In any case, in various parts of the human body, are always observing a cycle of being born and dying, even in healthy persons. Thus death, although an unexciting aspect of life, is indeed an integral part of it.

In another breath, death may be seen as the ultimate biological purpose of all disease processes. Death, like disease, occurs first at the cellular level and, death of the whole organism occurs only when a set of cells, which serve a critical function, e.g. heart muscle cells, dies. In the clinical setting, it is the role of the pathologist to explain how death is caused when it occurs. This is done by carrying out autopsies or post-mortem examinations. Post-mortem examinations would appear to be the more popular aspect of the work of the pathologist among the lay public. It involves the dissection of bodies of the dead and the examination of the organs and tissues for the 'footprints' of disease.

While the determination of the cause of death, the so called **final diagnosis**, is a primary purpose of the autopsy, it may also be useful in resolving medico-legal issues when they arise. Post mortem examinations also provide opportunities for improving our understanding of the mechanisms of disease. This is because the post mortem examination affords a benefit of hindsight so as to be able to reconstruct the pathological events that led to the death of the patient. It may highlight errors, if any, in the diagnosis and treatment of the disease while it lasted. For this reason, well-conducted post-mortem examinations remain invaluable tools of both undergraduate and postgraduate clinical instruction. This is the origin of the aphorism: "the dead teach the living".

## My Academic Odyssey, a Widening Encounter with the Liver

Mr. Vice Chancellor, sir, I suppose that it is customary that a Professor being inaugurated should discuss the kernel of his academic interests. As a Medical Student, I developed an early interest in the liver. At first, I became entranced in awe of the great metabolic prowess of the human liver, as a freshman at the College Medicine of the University of Lagos. I recall the trouble that I had in understanding the metabolic pathways of deamination, of glycogenesis and gluconeogenesis in biochemistry tutorial classes in my early days in the medical school. Subsequently I developed a certain respect for the liver when I was taught the phenomenon of enzyme induction in pharmacology classes as a new clinical student. I learnt that the liver had the capacity to create entirely new enzymes or enzyme systems with which to break down and sort hitherto unknown substances should such get introduced into the body either as drugs or components of food. I simply marveled at such versatility.

In the early phase of my postgraduate education, I was became captivated by the magnificence of the fine structure of the liver. I remember that I often sat down and gazed in awe at histological sections of the liver that I obtained from my postmortem cases. I must be forthright, though, in admitting that I had a lot of difficulty in getting to grips with the microscopic anatomy of the liver. Indeed, I am yet to encounter any morphologist who did not have his own tough time understanding the finer structure of the liver. This area of Hepatology is still in continuous ferment as new concepts of the understanding of the liver's functional micro-anatomy are still being put out regularly in newer works on hepatic histomorphology<sup>1</sup>.

### A Peep into the Liver....

Indeed, the liver has elicited curiosity from antiquity. During the Babylonian times, the liver was considered as the seat of the soul and therefore important for foretelling events<sup>5</sup> "for the king of Babylon stood at the parting of the way, at the head of 2 ways, to use divination,

he made his arrows bright, he consulted with images, he looked in the liver"<sup>6</sup>. The Greek warrior, Adrastus is pictured on a Greek vase studying the liver before he left for the Theban war. Cahil<sup>7</sup>, in his recorded dialogue of Plato, gives an insight to the importance of the liver to the Greek physician.

The study of the liver also occupied the minds of early medical men. Galen, as well as the subsequent practitioners of galenic medicine, thought of the liver as the source of blood. This concept, as we have discovered in modern times, is not entirely wrong: the liver does, in fact, contain large amounts of the circulating blood at any one time. Moreover, the foetal liver is known as an important site for blood formation, a function which the post-natal liver may revert back to, should the bone marrow fail.

Ypers papyrus (1600 B. C. ) contains a reference to the therapeutic value of the liver taken by mouth. "Treat night blindness with the roasted liver of a black cock. If no response, the case is not genuine night blindness"<sup>8</sup>. Nearly 3600 years later, the discovery was made that if sufficient liver was fed to patients with pernicious anaemia, remissions were induced in this previously fatal disease<sup>8,9</sup>.

During the Renaissance, other functions of the liver started to become apparent, particularly with the discovery of blood circulation by William Harvey. In the mid 19<sup>th</sup> century, the great French physiologist, Claude Bernard opened up modern understanding of the liver function with his discovery of liver glycogen and the production from it of blood glucose.

Today, we know a lot more about the structure and function of the liver. It is the largest organ in the body accounting for up to one fiftieth of the adult body weight and an even greater proportion of the body weight in childhood. Apart from its role in replenishing plasma proteins, particularly albumin, it is a major center of metabolism of exogenous and endogenous substances, including drugs. It is also the clearance center for bilirubin, a bye-product of breakdown of red blood cells, as well as for toxins and toxic metabolic products.



## A Deeper Look into Hepatology

My early fancy for the liver soon grew into an academic curiosity. **Hepatology** is the modern name for the old, exciting and ever broadening field of the study of the liver, and within that, I got interested in the emerging body of knowledge on chronic hepatitis. The subject of chronic hepatitis was an enigma, engaging many minds in those days<sup>10 1111</sup>

Boyer J. L: Chronic hepatitis- a perspective on classification and determinants of prognosis.

*Gastroenterology*

70: 1161-1171, 1976.

. Not much was known about it then except that it was a cause of chronic ill-health, especially among the veterans of the 2<sup>nd</sup> World and the Korean Wars. Because it was poorly understood, its treatment was also uncharted, unclear and essentially ineffectual. There was also rapidly growing information about the medical importance of the A and B hepatitis viruses and, at the time, the shadowy non-A non-B hepatitis virus.

An unexplored world was opened to me when I looked up the local and African literature on chronic hepatitis. Although there were several reports of sero-epidemiological surveys<sup>12 13 14</sup> indicating a high prevalence of the hepatitis B virus among Nigerians, neither was the subject of chronic hepatitis much studied nor the clinical consequences and public health importance of this virus on Nigerians widely recognised. This obvious chasm led me to develop an intense academic and professional interest in the subject and I started off by making it the subject of my postgraduate dissertation work<sup>15</sup>.

### The Fascination with Chronic Viral Hepatitis

Inflammation is a major cause of liver disease worldwide. It is known as hepatitis. Two forms of hepatitis exist: acute and chronic hepatitis. Hepatitis may be caused by infective agents, parasites, metabolic

disorders as well as drugs and toxins. Among infective agents, viruses are the most important causes of hepatitis. In fact, owing to the frenetic pace research in this field in the last 2 decades of the 20<sup>th</sup> century, the study of viral hepatitis has grown into a major branch of Hepatology. Viral hepatitis is now recognised as a peculiar group of inflammatory diseases of the liver caused by the hepatotropic viruses - viruses that have special affinity for human liver cells. Today there are some 6 or 7 such well-known viruses, denoted by letters of the alphabet as A, B, C, D, E, and G hepatitis viruses, although newer ones are still being discovered.

As with generic hepatitis, two forms of viral hepatitis exist; acute and chronic. Acute viral hepatitis is usually dramatic, manifesting with such frightening symptoms as severe tiredness, and yellowness of the eyes, cloudy often cola-coloured urine. Its victims either go rapidly downhill, and are dead in days or a couple of weeks or, they make an equally dramatic recovery. Acute hepatitis may be caused by any of the hepatitis viruses but the major causes worldwide are the A, B and E hepatitis viruses. The overall mortality from acute viral hepatitis is low indeed, much lower than 5% overall. On the converse, chronic viral hepatitis has become recognised as a significant cause of economic drain - chronic ill-health, work absenteeism and high death rates in many parts of the world.

The clinical picture of chronic viral hepatitis is also peculiar. The onset of the disease is insidious rather than dramatic. As a result of this it is not easily discerned. Nonetheless, its course is unrelenting, its effect ravenous, destroying the liver cells, one after the other. So challenging has been the clinical delineation of chronic viral hepatitis from acute and subacute forms that it took an international panel of experts<sup>16</sup> to lay down the sole diagnostic criterion: an elevation of the blood level of liver enzymes, the hepatic transaminases, persistently for a period of at least 24 weeks or 6 months. The basis of this criterion is that liver enzymes are detectable in the blood only if and when liver cells die and that the amount of the enzymes detected is directly proportional to the liver cell mass that dies.

The most important causes of chronic viral hepatitis the world over are the B and C hepatitis viruses. Between them, these viruses infect a large segment of humanity – more than half a billion. The Hepatitis B virus infects about 350 million persons, mainly in sub-Saharan Africa, south-east Asia, Middle East and the North American Eskimos while approximately 170 million people worldwide, mainly in the United States, Europe and Japan are infected with the hepatitis C virus. These viruses share similar modes of transmission: through the transfusion of infected blood and blood products, the use of contaminated needles and surgical instruments and such non-sterile traditional birth practices.

As mentioned above, the ongoing destruction of liver cells is of a fundamental pathological significance in chronic viral hepatitis. This ongoing destruction of single and groups of liver cells evokes an increased laying-down of fibrous tissue - ostensibly an attempt at healing of the relentless destruction. With time, the balance of mass is tilted against liver cells but in favour of the fibrous tissue and the liver becomes nodular, fibrotic and tawny yellow. Such livers are known to be suffering from cirrhosis, an apt term that was first used by Renee Laennec, the great French Physician.

### **The Concept of Chronic Liver Disease**

In the current hepatological lexicon, the term '**chronic liver disease**' is applied to the chronic hepatitis–liver cirrhosis spectrum. To the morphologist, chronic liver disease is a continuous spectrum of varying degrees of liver structural damage and inflammation, ranging from a nearly normal liver histology to a fully developed cirrhotic re-modeling of the liver architecture. Clinically, a number of parameters can be identified which allow the precise localization of the pathological condition of each patient along the spectrum of chronic active liver disease. Such parameters include clinical, biochemical, serological, and histopathological data.

The overall clinical effect of the ongoing liver cell loss and progressive fibrosis in chronic liver disease is a gradual lowering of the functional reserve of the liver until such a time that a critical mass of liver cell loss is achieved and the features of liver failure become evident. Beyond liver cirrhosis and the imminent liver failure that it portends, chronic liver disease is associated with a substantial increase in the risk of the development of **liver cancer** among its sufferers. This association exemplifies the concept of double jeopardy: chronic liver disease and cirrhosis are in their individual rights independent risk factors for the development of liver cancer.

In Nigeria, a diagnosis of chronic liver disease has grave implications. Appropriate treatment is expensive, unaffordable to most and scarce to come by. Most unfortunately, Liver replacement therapy is virtually non-existent. We shall return to this shortly.

### **Chronic Liver Disease in Nigeria**

As I alluded to above, of the 2 most important causes of chronic viral hepatitis worldwide, the hepatitis B virus is much more prevalent in sub-Saharan Africa. We examined the individual roles attributable to each of the recognised viral agents of chronic hepatitis in a group of Nigerian patients that had histopathologically verified and classified chronic liver disease<sup>17 18</sup>. Our findings showed that the HBV alone was associated with over two-thirds of the cases. This finding elevated the HBV to an object of our research curiosity and I will crave your indulgence to allow me seize this opportunity to talk about the HBV in a little greater detail and mention some snippets of our rendezvous with the virus.

### **The Hepatitis B virus**

The Hepatitis B virus belongs to the group of Hepadna viruses that have a special affinity for human liver cells. Hepatitis B virus infection is acquired by the parenteral route i.e. via blood transfusion or by the

use of contaminated needles (as in drug abusers), or the use of unsterilized surgical materials for scarifications. It is now also considered a sexually transmitted infection because it can also be transmitted through seminal and vaginal fluids.

Structurally HBV contains two parts: The envelope or surface antigen (HbsAg) and the HBV core (HbcAg). The envelope is called the surface antigen and the core is called the core antigen. When assembled, the complete virion is called the DANE particle which is 42nm in length. The HBV has another antigen which is produced by the core gene (HbeAg or core associated antigen). The core antigen cannot be secreted by the infected cells. It is not usually found in blood, while the HbeAg is found in plasma because it can pass through the cell membrane. HbeAg is a soluble antigen. The core antigen is synthesized in the nucleus of the hepatocytes in association with a DNA polymerase enzyme. HbsAg is assembled in the hepatocellular cytoplasm and it tends to be produced in excess and can be released into the cytoplasm along a concentration gradient it is frequently seen in the peripheral blood either as tubules or spherules ranging from 22-27nm in size.

This surface antigen used to be called the Australian antigen because it was first detected in an Australian aborigine in 1973<sup>19</sup>. The surface antigen does not cause infection, but because of its ubiquity, it is used as a general diagnostic marker of HBV infection. Antibody to the HbsAg appears during the period of recovery. Antibody to HbeAg starts to be discovered shortly before the onset of recovery. Antibody to the core antigen can be found shortly after the onset of symptoms. The use of anti-HbcAg is to diagnose infection during the window period because not all patients would be able to produce HbeAg. It also tells us how many people in the population have had a contact with the virus.

HBV is a virulent agent because it is capable of causing both acute and chronic hepatitis. When an individual is infected, viraemia may precede the onset of symptoms by several weeks or months and the HBsAg

reaches a peak in the peripheral blood at about the time of onset of symptoms. At this time also, the HbeAg is abundant in peripheral blood and because it is a soluble product of viral replication, it is frequently used as an indicator of infectivity of a patient's blood, when present.

Acute HBV hepatitis may be massive or sub-massive in nature and survival depends on the dose of virus received at infection, and the state of the immunity of the host. In infected persons, the virus is removed from the body by the destruction of the infected liver cells by the person's immune system. Thus whereas those with a weak immune system are more likely to survive because few of their liver cells are killed, those with a very virile immune system will more likely suffer a severe or fulminant hepatitis and die or, alternatively, totally eliminate all the virus-infected cells and live. Among the survivors of acute HBV hepatitis, those with poor or weak immune systems are more likely to develop chronic hepatitis or become symptomless chronic carriers of the virus.

### **The Scourge of Chronic HBV-associated Chronic Liver Disease among Nigerians; what we now know.**

Sero-prevalence studies show that between 15 and 20%<sup>15,16,17</sup> or 18 to 24 million Nigerians are chronically infected with the HBV. As I mentioned above, we have been able to show that chronic HBV infection is the basis for at about 7 out of every 10 cases chronic liver disease in patients in our clinics at Ife<sup>20</sup>.

At this point, an anecdote will serve to illustrate the gravity of the burden of HBV among the Nigerian populace. We once encountered one instance where a 27-year old woman was able to carry a pregnancy to term only to die from antepartum haemorrhage caused by a rupture of a cancerous nodule in her liver<sup>21</sup>. When tested, both her blood and liver tissues were HBV-positive. She had obviously been infected by

the HBV, probably as a child, and had suffered from a sub-clinical chronic liver disease since then. Unknown to her gynaecologists, she, although pregnant, had a terminal HBV-associated liver disease. That experience, which has since also been seen repeatedly by us and others<sup>22, 23</sup>, has given a lie to the time-honoured teaching that the existence of chronic liver disease is incompatible with the achievement of a state of pregnancy because of the constitutional problems associated with the former.

Today, there is a proven link between chronic HBV-associated chronic hepatitis and liver cancer<sup>21</sup>. In Nigeria, HBV has been found in 70%, 49% and 80% of liver cancer patients at Ibadan<sup>25</sup>, Zaria<sup>26</sup> and Calabar<sup>27</sup> respectively. In fact, studies have shown that up to a quarter of patients with chronic HBV-associated hepatitis would develop liver cancer. Going by this estimate, up to between 4 and 6 million Nigerians would develop liver cancer and probably die from it. In consonance with this estimate, anecdotal data emanating from the few cancer registries in the country suggest that liver cancer is among the commonest causes of adult cancer deaths among Nigerians and is probably the third leading cause of death in adult male Nigerians.

### **Our Efforts in Confronting the HBV Challenge**

Our clinical work and early research findings and those of others highlighted the need to syndicate efforts and collaborate in further studying the nature of the HBV problem in Nigeria as a necessary prerequisite to combating the scourge of chronic HBV-associated liver disease among our compatriots. We initiated a local research group, The Ife Liver Disease Study Group (IFLDSG), and then a national one, the Association for the Study of the Liver in Nigeria (ASLIN). ASLIN, of which I have the privilege to be the current national leader, celebrated her 10<sup>th</sup> anniversary last year and has served well as a forum for national collaboration among Hepatologists on researchable issues and the education of specialists in liver disease. With the cooperation fostered by these bodies, we were able to carry out some further research work.

8We felt that there was a need to explore what might be responsible for the high prevalence of HBV in our population (and that of most parts of the tropics). We observed that the global epidemiological distribution of malaria was similar to that of the HBV. In addition, malaria is known to have a defining role of the potency of the immune system in childhood. We also know that the HBV needs a weakened immune system to perpetuate itself in individuals and, by extension, in the community. This made us to put forward a hypothesis that malaria, owing to these well-recognised immunological effects, might in some way contribute to the survival of the virus in populations of areas of high endemicity and that this perhaps would explain why the HBV was so highly prevalent in the tropics as much malaria is. This hypothesis caught the fancy of a journal editor that he published it with dispatch<sup>28</sup>. We sought to test this hypothesis experimentally. We needed an animal model that could be infected with both malaria and HBV. Only primates, especially chimpanzees could fill the role. We got German collaborators interested in the project but we could not proceed because of a worldwide restriction on primate research.

We also felt that the severe effects that HBV has on Nigerian patients deserved some further exploration. We searched for adjuvant factors. The hepatitis D virus (HDV), having similar epidemiological attributes as HBV, had to be eliminated as a culprit. HDV had been known to frequently co-infect patients together with hepatitis B and whenever that was the case, the course of the liver disease in such patients was much worse than a sole HBV infection. Now HDV Epidemiology was known to be highly variable in different parts of the world. Thus we explored the possible confounding role that a co-existing infection by the hepatitis D virus could play in hepatitis B-associated chronic liver disease in Nigerian patients<sup>29</sup>. We found that HDV did not have a uniform and predictable epidemiology nationally and that it was not common among Nigerian HBV-infected patients and as such could not be an important aggravating factor in HBV-associated chronic liver disease in this country.

We soon picked another trail of investigation. The advent of molecular biological techniques made a novel discovery about the mechanism of cancer development in the early nineties. The p53 gene was discovered as a tumour suppressor gene, a very important regulator of cell division. Its damage or mutation was found to underlie the development of many cancers. At the time, it was shown that mutations of the p53 gene, a tumour suppressor gene, were particularly common among liver cancers. More importantly, it was shown that a rather peculiar codon 249 hotspot mutation was strongly associated with Aflatoxin B1 toxicity. Now Aflatoxin is a chemical product of a fungus, *Apergillus flavus*, which grows on poorly-stored grains in the warm and humid environment of the tropics. This realization was exciting. Perhaps Aflatoxin was the real culprit behind the high rate of liver cancers in our country rather than HBV or perhaps both factors, Aflatoxin and HBV, worked in synergism. We investigated these hypotheses. Our study<sup>30</sup> showed that codon 249 hotspot mutation was not common among our liver cancers, leaving us with the conclusion that the HBV was the main agent responsible for malignant liver disease in this country.

The decade of the nineties further marked a significant advance in the treatment of chronic viral hepatitis. Interferons became commercially available. Interferons are naturally occurring substances whose immunomodulatory and antiviral properties had been recognised for several decades before then. We worked with a major marketer of the novel drug to carry out a national trial of the efficacy of this treatment of Nigerian patients<sup>31</sup>. We found that although interferons was of some value in the management of HBV-associated chronic liver disease in Nigerians, it perhaps would need some form of adjunct, say antiviral agent for better treatment outcomes. A study is being initiated, as I speak, to test the efficacy of one such agent, Lamivudine. It needs be said, however, that the cost of any of these treatments is beyond the means of Nigerians within the working class.

In addition to serving as a vehicle for research collaboration, ASLIN has also played advocacy roles to influence health policy and garner support from industry towards public awareness about viral hepatitis in this country. In 2004, we were able to form a National anti-HBV Initiative with GlaxoSmithKline Plc. That effort has built us an alliance with the popular press through which we have been able to raise public awareness about liver disease nationally. Internationally, ASLIN is now affiliated to the African Association for the Study of Liver Diseases (Afr. ASLD) and the International Association for the Study of the Liver (IASL). We have every hope that the opportunities for networking that these alliances afford would further strengthen our modest ongoing anti-HBV efforts.

### **The Goal of Controlling Viral Hepatitis and Liver Cancer in Nigeria**

To summarise the Nigerian HBV story, the virus doubtless remains a very great health challenge among us. Conservatively, we reckon that between 15 and 20% of Nigerians are HBV carriers. This is a large reservoir of infection indeed. Targeting the liver as it does, the virus causes chronic liver disease in up to 10% of those that get infected by it. It also significantly increases the chances of development of liver cancer in up to 25% of the chronic liver disease sufferers. The implications of these statistics is that between 4 and 6 million Nigerians who are alive at the moment face the scary prospect of developing liver cancer during their lifetimes and, since we are yet unable to transplant new livers into them, would most probably die from it.

Despite this frightening picture, we need to recognise the fact that we have a special advantage in controlling the prevalence of liver cancer in our country because it is mainly caused by an infectious agent – the hepatitis B virus. Therefore, efforts geared towards controlling HBV infection will ultimately lead to a reduction in the numbers of the sufferers of liver cancer and other severe diseases of the liver. We can approach this issue at three levels: health Education, vaccination and

improvements in the facilities for the treatment of diseases of the liver.

### *Health Education*

This is a most powerful tool that has been deployed in the successful control of many disease of man. We need to use the media to inform the public about practices that predispose to HBV infection. For example, we need to get people to desist from using non-sterile implements in traditional surgical and birth practices as well as also to stop the recycling of disposable needles. Blood transfusion practice should be strictly regulated. There ought to be a legal requirement for all health institutions to screen all blood and blood products meant for use in treatment of patients for HBV. Individually, every Nigerian is well advised to take a surface antigen (HbsAg) test and seek further specialist assistance if he/she discovers that he/she is positive for it.

### *Vaccination*

The invention of a safe HBV vaccine in the decade of the eighties has meant that liver cancer has become the first human cancer that is preventable by vaccination. Thus the World Health Organisation (WHO) has encouraged all nations to include the HBV vaccine into their basic programme of immunization. In Nigeria, whereas the HBV vaccine has been incorporated into the National Programme on Immunisation, implementation continues to pose great challenges to most of the health authorities. We may need to encourage individuals and corporate bodies to take steps to ensure we collectively improve the anti-HBV vaccination cover in the country

### *Liver Treatment Services*

Liver diseases, no doubt, deserve to be given a priority attention in the allocation of healthcare resources. Such resources must be used both in training more hepatologists and improving

diagnostic capacity and expertise among the generality of the healthcare personnel across the nation. We need to establish a clear and effective referral system for patients with severe liver disease so that they could receive the attention they need from the top experts. To be able to get the full benefits of a referral system, we need to set up at least one apical liver care centre in the country. The proposed centre should house up-to-date diagnostic and therapeutic equipment for liver diseases. Of course, the liver centre will have to be staffed by highly trained manpower so that it could also be a training centre for the liver care experts needed elsewhere in the country.

### **Future Research Demands**

The proposed apical liver care centre would also be eminently suited to be a place to foster further inquiry into chronic viral hepatitis in Nigeria. A number of studies are overdue. To begin with, there remains a need for a nationally applied and systematized reporting and gathering of clinical and laboratory data on chronic hepatitis B in Nigeria. Hopefully, this should lead to an ordering of research priorities in this field. For example, we do not know nearly enough about the other factors that aggravate the effects of the virus on the populace. What role might we reasonably attribute to childhood malaria in the HBV saga? How might we reduce the high rate of mother to child transmission? In addition, the dynamics of transmission, especially with regards to the molecular epidemiology of the various recently identified wild and mutant strains of the HBV, their reputedly different pathogenic potencies and immunopathology, still remain to be studied. The pathology of double (B and C) virus infections and the effects of other putatively harmful but popular Nigerian social practices, such as the use alcohol-containing medicaments for liver ailments, need to be explored. Finally, there is a yawning need for further epidemiological, clinical and experimental studies on liver cancer in Nigeria.

## Pathology in Basic and Continuing Medical Education

Mr. Vice Chancellor, sir, before I close, I feel a need to make some comments on the place of pathology in medical education in general and the state of affairs in our medical schools in Nigeria, in particular. Pathology is a fundamental component of the undergraduate medical curriculum because it integrates the knowledge gained in the pre-clinical school in the basic medical sciences with those of the main clinical sciences. For the new clinical student, the primary object of instruction in Pathology should be the inculcation of knowledge of the mechanisms of disease from first principles. This is crucial to enable the student not only to understand and interpret clinical symptoms and signs but also to learn to approach clinical problems rationally and scientifically.

### The Problems of Pathology Education in the Tropics

Although orthodox medical practice had its roots in Greco-Roman culture and its nurture to maturity in the Western civilization, Tropical Medicine, having its application geographically far removed from these two, has distilled out as a distinct major branch of the profession. This fact notwithstanding, most tropical medical schools still nurture Medical Students and Doctors on a diet of medical literature that is essentially foreign to the tropics. This is bound to produce professionals who are maladjusted and ill-equipped to combat the hordes of the peculiar and sometimes, extra-ordinary diseases that afflict the larger segment of global humanity residing within the tropics. There is doubtless a desperate shortage of appropriate books and teachers and other resources, especially for pathology education, in most medical schools in tropical countries.

As our modest contribution in this area, we syndicated efforts in writing a comprehensive pathology text for undergraduates: *Essential Pathology for Clinical Students in the Tropics*<sup>12</sup>. This book will be getting onto the sale shelves later this month.

## The Future of Pathology Education and Practice in Nigeria

There is little doubt that all is not well with pathology education in our country. Many medical schools do not have pathologists on their staff. This calls for an empowerment of the Faculty of Pathology of the National Postgraduate Medical College of Nigeria to train more pathologists. The training of pathologists, much like the other specialties of medicine, needs the updating, refreshing and grooming of an elite core of trainers in the profession. Being a science, the practice of modern medicine can only thrive when education continues throughout the life of the practitioner. This is also sadly missing in our country. The concept continuing education is yet to be fully implemented by the licensing bodies neither has it been consistently pursued by the postgraduate bodies.

For over several decades, there has been an incapacitating under-funding and lack of investment in higher education in our country. As expected, science-based education, being the more capital-intensive, has suffered the greatest dislocation. At the beginning of the eighties, the politicians came with the 'gospel' of 'looking inwards'. In retrospect, they probably meant that they were bent on seeing the bottom of the nation's coffers as, indeed, they did. By bringing this warped logic to bear on national planning, they have sequestered Nigeria from the rest of the global scientific community and made our intelligentsia strangers among their international peers. Both our science and our practices have been left behind those of the rest of the world. This unwholesome situation also continues to be an incubus on pathology education in our country.

The desperate need to reform, refine and refocus the undergraduate pathology curriculum to make it more appropriate for practitioners in the tropics stares us all in the face everyday. Most medical schools are facing a massive jump in the numbers of admissions. This otherwise good development is however also bedeviled by the hopelessly inadequate level of new investments in terms of manpower and facilities in the schools. All the foregoing failures and inadequacies have glaringly

dark implications for the quality of pathology education and the overall quality of the medical graduates that are being turned out. The challenge of updating, repairing and maintenance of laboratory equipment needs to be confronted by all, especially by the education authorities. We must all become advocates of the need to invest in our collective future by investing in science and medical education. In particular, special investment towards provision of modern scientific equipment to promote proper and adequate medical education in Pathology must be a *sine qua non*.

### **The Interminable Quest**

Mr. Vice Chancellor sir, ladies and gentlemen, as I bring this lecture to a close, we must return to the portals of 'medical justice' where, my lord the pathologist is presiding. It is often said that he that comes to equity must come with clean hands. But I have often asked "how must the judge himself sit? What must be his guiding principle"? I think that this judge must seek to make only just and scientifically sound pronouncements - to carefully evaluate every shred of evidence and the individual clinical context and so throw light onto the most unclear clinical situation. He must spare no effort in ensuring that he offers the best clinical counsel to the physician, surgeon, paediatrician and general practitioner, in their quest to heal or relieve the patient. His abiding maxim must be to reveal the 'clinical truth'.

And what is the nature of this truth? For the Anatomical Pathologist, I submit that all clinical truth is found in the tissues of man. It is his duty to find this truth using stains and different types of microscopes. In the modern age of molecular biology, to discover the truth, the pathologist may have to amplify nano-quantities of peptide sequences using the polymerase chain reaction and carry out *in situ* hybridization and other labeling techniques.

Esteemed listeners, it seems to me that the post of a clinical judge that a pathologist occupies carries a heavy weight of responsibility with it.

He must therefore pledge himself to an **interminable quest for excellence**. He must equip himself with information by searching all journals, annals, books, yea, all atlases, websites containing databases of microscopic pictures and recorded experiences of other pathologists. He must seek to maintain a rich mental library of countless images that he has encountered in his practice. He must also see every case as appertaining to the life and wellbeing of another and carefully look upon every specimen to read and interpret the information therein so that the truth is revealed and the path to healing and restoration to a semblance of Eden made a shining one.

The pathologist must be ready at all times to learn from his tissue specimens, colleagues and students. As an academic, he must be committed to teaching, to research and to the advancement of medicine. Beyond this he must see to it that he commits his thoughts and experiences to writing for those who shall come after him.

Mr. Vice Chancellor, sir, I gratefully cherish my inauguration and I hereby pledge myself and dedicate my tenure as a Professor of Anatomical Pathology at Obafemi Awolowo University to the pursuit of these tasks and ideals.

I thank you all for gracing this occasion and for your attention.

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