42nd Inaugural Lecture

EARLY CANCER DETECTION:
SAVING LIVES WITH TUMOUR OR CANCER MARKERS

by

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INTRODUCTION

An inaugural lecture is a statement of a **professor's scholarship** and **contributions** to **knowledge** in the **area** of **studies** with which he or she is known. The **relevance** of his or her contributions within the field of his or her studies must relate to the **needs** and **aspirations** of the **society**. Generally, professors in any field of study should constantly seek to push forward the **frontiers** of **knowledge** and they should be very active in publishing the **outcome** of their scholarships and research. The **outcome** of their scholarship and research should improve society or offer opinions on how we might proceed from now.

Mr. Vice Chancellor, I must say that I am very grateful to **LASU** for the **opportunity** given me to deliver another Inaugural Lecture. I feel happy and honoured on this occasion to stand before such an **august audience** as gathered here today. The topic of my first Inaugural lecture was "**From Bench** to **Bedside**: **Connective Tissue Proteins** as **Tumour Markers**." I was appointed the **first** or **foundation Professor** of **Chemical Pathology** in the College of Medical Sciences, University of Calabar, Calabar early in 1990.

Today's inaugural lecture is the fourth since the establishment of LASUCOM and it is the first from the Department of Chemical Pathology. It is particularly **unique** to me, being the **second** inaugural lecture in Chemical Pathology to be given by an **alumnus** of **two** very **old Universities** noted for **Nobel Prizes** in **Medicine** in **Europe**, **Szeged** School of Medicine in **Hungary** was founded in **1872** and **Oxford** University in **England** was founded in about **1100**. Szeged produced such great medical scientists for example, **Albert Szent-Gyorgyi**, who was an internationally renowned medical biochemist, and received the Nobel Prize in **1937** in Medicine. He was the first to identify **Vitamin C** or **Ascorbic acid** and its biochemical and physiological importance to the human body in the **Szeged Medical School** Laboratory. He also explained the role of adenosine triphosphate (ATP) and contributed to the understanding of actin and myosin in muscle contraction.

Oxford is one of the **most famous** Universities in the **world** and it is the **oldest University** in the **English-speaking world**. It is the **richest seat** of **learning** and it is full of **academic traditions**. It has produced a **sizeable number** of Nobel Prize **recipients** (up to date 47 Nobel Prize winners, 7 in the 21st century). It has the **highest international research standing** of all universities in the **UK**. **Students** from more than **140 nationalities** or **countries** are represented at Oxford, and they make up more than a **third** of the **total student body**. Most of the **Oxford** scientific research institutes have global outposts such as the Centre for Tropical Medicine in Kenya, Vietnam and Thailand. From Oxford sprang forth such prestigious and world-renowned universities as **Cambridge** in

England, **Harvard** and **Yale**, etc in the **USA,** others in **Canada**, **Australia**, and **New Zealand**.

In my preparation for becoming a research and professional pathologist I need to thank some people at **home** and **abroad**. **First**, Emeritus **Professor Thomas Adesanya Ige Grillo**, the **first African Professor** of **Anatomy** (of blessed memory) who was not only my **first teacher** in **anatomy** at the **University** of **Ibadan,** but was also my **African** or **Nigerian mentor**, as I had my **first** stint in university education in the **prestigious premier** University in Nigeria.

In my years in Szeged as a medical student, my then teacher and **Head** of the **Department** of **Pathology**, **Professor Ormos,** now Emeritus Professor, instilled in me the **discipline** needed in order to become a **successful medical researcher**, **academic** and **professional pathologist**.

I need to mention those who without whose **help** and **guidance** I would not have been standing in front of you today. Such people include: **Professor James O'Donnell McGee**, **Nuffield Professor** and Head of the Department of **Pathology** in the School of Medicine, Oxford. He was my teacher and the chief **supervisor** for my **D. Phil**. **Thesis** in Oxford University. Doctors **Ken Fleming**, **Ian Burns**, **Bryan Sykes** (now Professor of **Human Genetics** in Oxford), **John Morton** and Emeritus Professor **Sir Hans Krebs** (**Nobel laureate** in **Medicine** in 1953) of blessed memory. When I began my **postgraduate** studies in Oxford in **1976** I was influenced by this inspiring teacher; the **discoverer** of the enzymes that catalyze the processes of glycolysis or the citric acid cycle (or what is generally known as **Krebs cycle**).

The Oxford of my time was a wonderful university, with a long history that filled me with enthusiasm for **medicine** or caring for the **sick** and left an **indelible impression** on me, such as the need for **meticulous** and **relentless hard work** in **scholarship** and **research**, particularly in the field of **Clinical Medicine** or **Pathology**. Oxford has influenced me overwhelmingly and given me the **confidence** to carry on.

In the **USA**, these include **Professor George C**. **Fuller** (my **postdoctoral research supervisor** in **Searle Research** and **Development**, Skokie, **Chicago**, **Illinois**, USA). He was again my Dean at the **College** of **Pharmacy** and **Allied Health Professions**, **Wayne State University**, **Detroit**, **Michigan**, USA. Doctors **David Pitts**, **Eckstrom**, etc.

In **Finland,** I had the opportunity to work as **Sigrid Juselius Postdoctoral Research Fellow** in the **Department** of **Medical Biochemistry**, **University** of **Oulu**, **Oulu** with an international and eminent medical research scientist **Professor Kari I**. **Kivirikko** and his medical research team, which is made up of **renowned medical scientists**. With all the above I worked **long** and **tedious** but highly **satisfying hours**. To them I am very grateful but above all, I am thankful to **GOD** for the opportunity.

OBJECTIVE

In this **lecture,** I will try as much as possible to summarize my **experience**, my **modest contribution** in **Chemical Pathology** and the **use** of **recent biomarkers** in the **early detection** or **diagnosis** of **cancer**. I do hope that at the end of this lecture the audience would be able to **appreciate** the **under-listed questions:**

a. What is a **tumour** or **neoplasm**?
b. What is a **benign tumour**?
c. What is a **malignant tumour**?
d. What are the major **characteristics** of cancer?
e. What are **oncogenes** and **tumour suppressor genes**?
f. What is a **tumour marker** or **tumour index**?
c. **What** are the **role** and **importance** of **tumour markers** in?
    i. **Cancer Screening**
    ii. **Cancer Detection** or **Diagnosis**
    iii. **Therapeutic Monitoring** of **Cancer** and,
    iv. **Management** or **care** of patients with **cancer**.

CELL

At this juncture I wish to cite Max Delbruck who once wrote and I quote:

The curiosity remains, though, to grasp more clearly how the same matter, which in physics and chemistry displays orderly and reproducible and relatively simple properties, arranges itself in the most astounding fashions as soon as it is drawn into the orbit of the living organism. The closer one looks at these performances of matter in living organisms the more impressive the show becomes. The meanest living cell becomes a magic puzzle box full of elaborate and changing molecules, and far outstrips all chemical laboratories . . . in the skill of organic synthesis performed with ease, expedition and good judgment of balance.

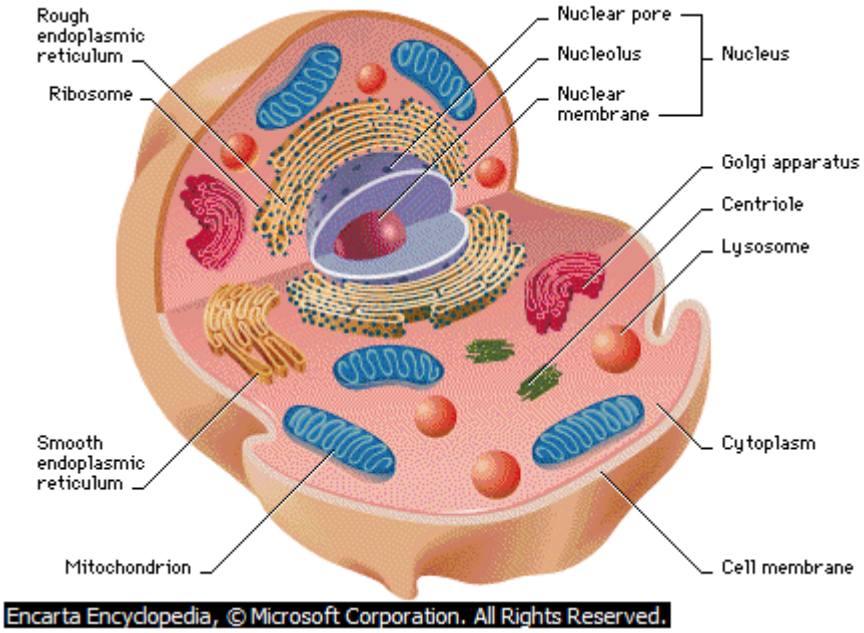

FIGURE 1: A normal **Human Cell** showing the **major Organelles**
Note that most cells in our body are highly specialized for their **specific functions** and so may differ from what has been shown above.

The cell is the **basic unit** of **structure** and **function** of our body. Thus, the cell is the **unit** of **tissues**, **organs** and the **system** of the body. Our body contains about **75 trillion cells**. Each of these cells performs **specific functions**.

An example of two different specialized cells in our body

a. The **red blood cell** is highly specialized to carry oxygen through our body in the blood circulation in order that life can be continued (Figure 2(a) below)
b. The **beta (β) cell** of **Langerhans** in our **pancreas** (Figure 2(b) below) does not go round our body; it stays in one place in our body in **an islet** or **group** of β cells called islets of Langerhans inside the pancreas. The **major duty** of this specialized endocrine cell is to secrete the **hormone** called **insulin** – a **protein**, which it releases into the **blood circulation**.

The functions of these two types of cells, that is, the red blood cell and the β cell of Langerhans are very different as demonstrated above, and these are reflected in the proteins these two cells synthesize. While the immature or young red blood cells synthesize **haemoglobin** but not insulin; the β cells of Langerhans produce insulin but do not make haemoglobin. These functions are programmed by **genetic differentiation**.

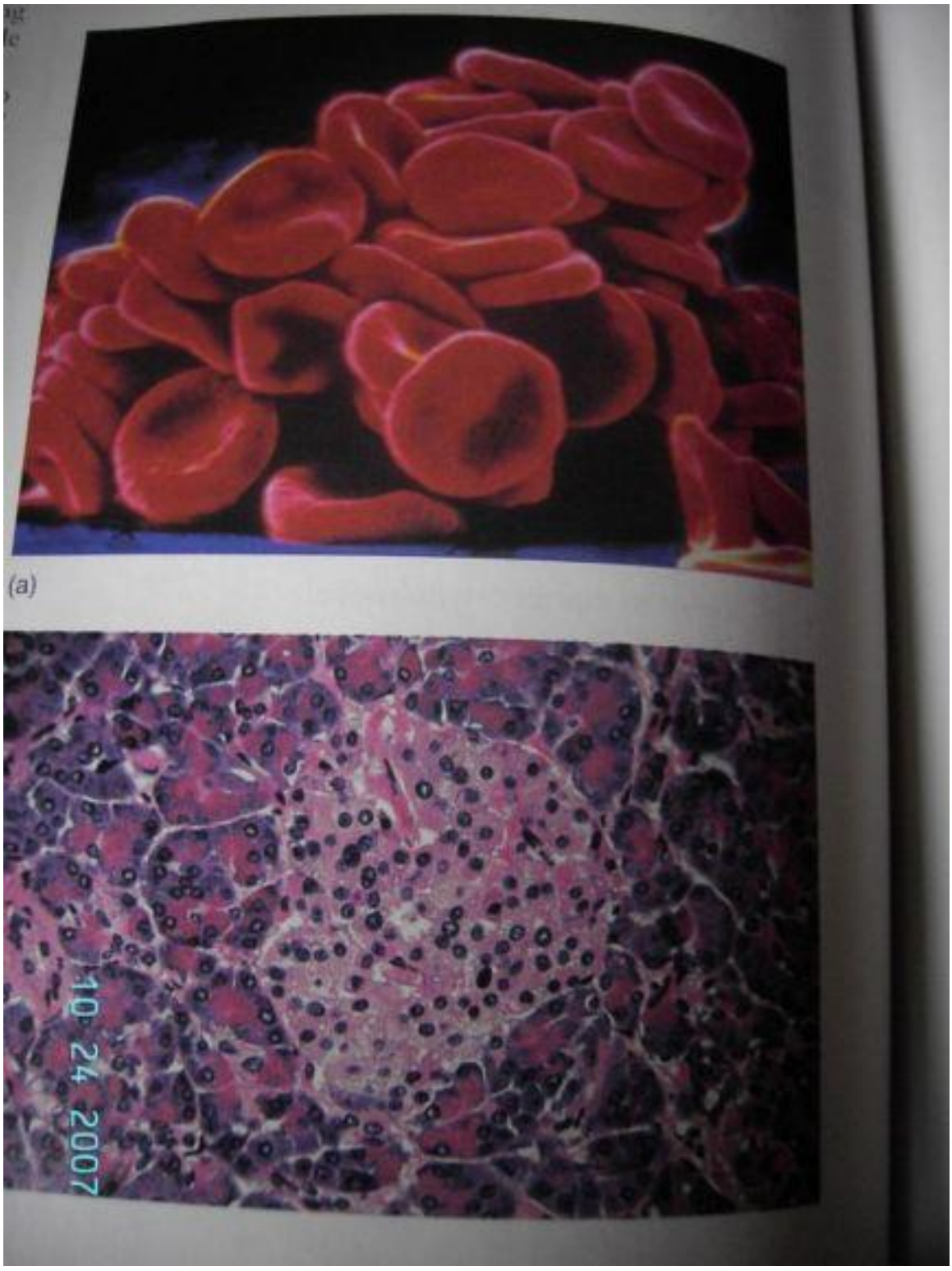

FIGURE 2: Normal histological picture of **Red Blood Cells** or **Erythrocytes** (a) above, which carry oxygen round our body and return carbon dioxide to the lung and below is a normal

histological picture of **Islet** of **Langerhans** in our pancreas (b) below which secretes or produces **insulin**.

The **mammalian cell** consists of **three basic parts** namely the **nucleus**, **cytoplasm** and the **cell membrane**. These **three major components** are very essential for the **survival** of the cell and of the **species**.

a. **Cell membrane**:
This is the **outer boundary** of the cell; it is a **selective permeable membrane**, for **intake** and **output** of **materials** compatible with cell function and survival). Cell membrane gives the cell its **shape** or **form**.

b. The **cytoplasm** and **Organelles**:
The cytoplasm is the **fluid** or **liquid content** of the cell and it is enveloped by the cell membrane. It surrounds the **nucleus**. The cell cytoplasm is composed of **organized cell components** or **organelles** and the **cytoplasmic matrix**. The organelles are **subcellular structures** within the cytoplasm that perform **specific functions**.

c. The **Nucleus**:
This is the **largest** of the **organelles** within a cell. The nucleus contains the **genetic material** or **DNA**, a long rope like structure, which is coiled and folded to fit inside the nucleus. The DNA directs the **activities** of the cell that is; the **DNA** is at the **centre** of every **body's cell.** The nucleus contains a **granular-looking chromatin**. The chromatin materials are **genes** which are lined on **tiny threadlike materials** known as **chromosomes**. Chromosomes are **pairs** of **threadlike bodies** (i.e. two **similar** or **homologous copies**) within the cell nucleus (see **Karyotype** below). The pairs of chromosomes differ from one another in **size** and **shape**.

Each cell in our body except the **gametes** or the **germ cells** that is, the **eggs** or **spermatozoa** contains the same number of chromosomes. The gametes (i.e. sperm and egg) are **haploid,** that is, they have **single set** of chromosomes (i.e. **half** of the diploid number), which is formed during **gametogenesis**. The somatic or body cells carry **two copies** of **each chromosome** – **Diploid** [(i.e. two haploid sets of chromosomes) (see Figure or the Karyotype below)]. Fertilization or union of the egg and sperm restores the diploid number of the chromosomes in zygote. There are **23 pairs** of chromosomes in a **man** or **woman** (**22 pairs** of these chromosomes are called **autosomes** and **a pair** of **sex** chromosomes). This means that, the nucleus of a **somatic cell** or any of our **body** cell (except our gametes or germ cells) contains a **total** of **46 chromosomes**, **23** of these **chromosomes** are **maternal** in **origin** (i.e. one chromosome from each pair from the **mother**) and **23** are **paternal** in **origin** (i.e. the other chromosome from the **father**). The **twenty third** (**23rd**) **pair** of chromosomes in the **female** consists of **two large X chromosomes** (i.e. **XX**, they are matched) but in the **male**, the **twenty third** (**23rd**) **pair** do not match and consists of **one large X chromosome** and **one small Y chromosome** (i.e. **XY**, see the Figure or the Karyotype below). The **Y chromosome** carries a **gene** for **maleness** and so the male is the **sex-determining sex**. Individuals of the make-up XY are males and ones with XX are females.

Genes

The **nucleus** directs and regulates the **cellular activities** through the **genes**. A gene determines **one element** in the **hereditary make-up** of an **individual**. A gene determines obvious **traits** such as the **colour** of our **eye** or **skin**, the **hair, blood groups** and other **characteristics**. Genes carry the instructions, which allow cells to produce specific **proteins**. Our body has about **40,000** genes. Many genes become permanently **inactive** as the cells mature. The **arrangement** of **active** or **inactive genes** in a cell determines which kind of cell it is and its function in the body. Human genomics (i.e. the human genome, which means the total of the genes in a cell) revealed that any two individuals share about **99.9 per cent** of their DNA sequences while our diversity is encoded in about **0.1 per cent** of our DNA.

The secrets to our **disease predisposition** (e.g. tumours or cancers) and response to **environmental agents** and our response to **drugs** may be found in these **0.1 per cent variable regions**. **Defects** in genes can result in **disease** or **cancer** (i.e. a defective gene gives rise to a defective polypeptide chain or protein).

Cancer Genes

In contrast to the other types of genetic disorder, for **most cancers** or **tumours**, the **genetic mutations** are rarely inherited but arise in **somatic cell** during **adult life** as a result of our **exposure** to the **carcinogens** in our **environment**. The mutations, which may be **acquired** or **inherited** commonly, involve **three types** of **genes** that include:

a. **Oncogenes**
b. **Tumour suppressor genes**
c. **Genes** involved in **DNA-repair mechanisms**

Oncogenes and tumour suppressor genes are usually involved in the **control** of **cellular growth** or **proliferation**, and **disruption** of such **control** is a **consistent feature** of cancer. Genes involved in **DNA-repair mechanisms** exist to correct DNA damage due to **environmental mutagens** and accidental **base misincorporation** at the time of DNA replication. **Inherited defects** of either system result in an increased frequency of cancer.

The proliferation of malignant cells is related to genes. Cancer often starts when a *carcinogenic agent* such as *tobacco smoke*, *ultraviolet light*, *ionizing radiation*, *parasites*, *bacteria*, *viruses*, etc. damage DNA of a **critical gene** in a cell. This DNA damage triggers abnormalities or ***mutations*** in these genes, leading to increased abnormal activity of the gene. The mutation causes the cell to behave in an abnormal manner and so become rebellious or ***malignant*** (i.e. ***cancerous***). The mutant cell multiplies and the offspring or succeeding generations of these cells aggregate to form ***cancer*** or ***malignant tumour***.

One of the most important protections we have against cancer is the death of cells that are not wanted by the body. This death mechanism is what we call ***apoptosis***. Apoptosis is induced in cells when they are (a) damaged, (b) unnecessary to the body, or (c) dangerous to the body. Many cells or may be all cells, can be triggered to commit

suicide or kill themselves, and in the process, to signal macrophages to engulf and degrade their corpses.

WHAT IS A CANCER OR TUMOUR?

At this juncture I wish to cite Pat McGrady (American geneticist) who once wrote of a cancer cell and I quote:

> ***A savage cell which somehow ….. corrupts the forces which normally protect the body, invades the well-ordered society of cells surrounding it, colonizes distant areas and, as a finale to its cannibalistic orgy of flesh consuming flesh, commits suicide by destroying its host.***

Although **deaths** from **heart disease** (but in addition to this, in **Nigeria** and other **developing countries**, **major infectious diseases,** including **HIV**, **AIDS**, **malaria** and **tuberculosis**) are more than cancer- or tumour-related deaths, cancer is one of the most feared and hated diseases threatening mankind. Cancer touches each of our lives in a different, personal way. To quote from a recent Oxford University Magazine (*Oxford Today*, 2007), which states and I quote:

> ***At least one in three of us will develop cancer; one in four of us will die of it. It's a disease that touches everyone. Cancer and heart disease are vying with one another to be the number one killer …. I think cancer is just ahead at the moment.***

Despite the scientific gains cancer remains a killer. The **doubt** associated with the **diagnosis** or **detection** of **tumour** or **neoplasia** was the **biggest single reason** why the **discussion** of this disease, for a long time was even considered **taboo**. Man fears and hates cancer more than any other disease. The **course** of the **disease** varies widely depending on the **origin** of the tumour and the **stage** in which it is **first detected** or **diagnosed**. Tumour means **swelling**. It is a **protuberance**. The term tumour can be applied to **non-neoplastic nodules** just as it applies to **neoplastic growths**. Thus, all cancers are tumours but not all tumours are cancers. However, in **oncology** we use the word tumour to mean **neoplasm**. **Continuous growth** is the **salient feature** or **characteristic** of neoplastic cells that distinguishes them from other **normal** or **non-neoplastic cells**. On account of the **nature** and **rate** of **growth**, tumours may be subdivided into **two broad groups**:

a. **Benign (simple)**
   Benign tumours are made up of **well-differentiated cells** that look very much like their normal counterparts. The benign tumour cells closely resemble the tissue from which they have arisen.

b. **Malignant**
   Cancer is derived from a **Latin word**. It means "**crab**". It appropriately describes the resemblance of the **cut surface** of the **cancer lesions** to a **crab**. The **body** of the crab resembles the main tumour mass while the **claws** of the crab being the invasive or the infiltrative tumour margins. Malignant tumours, which are made

up of **epithelial cells** (i.e. cells covering tissues such as skin and the lining of the mouth and the gastrointestinal tract, etc.), are called cancers or **carcinomas** (carcinoma is a term derived from the Greek word for crab). **Cancer** (i.e. crab-like in shape) is a **general term**, which refers to **all malignant tumours** irrespective or regardless of **types**

TABLE 1: COMPARISON of BENIGN TUMOURS and MALIGNANT TUMOURS or CANCERS

BENIGN TUMOUR	CANCER (MALIGNANT)
Adult type cell	**Most cancers have young type cell**
The cell is just like the parent cell	**The cells tend to be anaplastic (very different), that is less differentiated than the normal cells from which they arise (that is, loss of normal characteristics and differentiation).**
Grows slowly	**Usually grows rapidly**
They often have coverings or capsules (i.e. encapsulation), so can easily be removed surgically, just like removing beans from a pod.	**They never have coverings or capsules (i.e. not capsulated)**
They do not grow into the surrounding tissues (that is, expansive growth)	**They do grow or invade or spread into the surrounding tissues widely (that is, infiltrative growth)**
They always remain localized at the original or primary point or site.	**They form secondary growths by metastases through the lymph, bloodstream and body cavities, etc.**
When they are completely removed surgically they do not recur	**They tend to recur when removed surgically or by other treatment techniques or methods**
They harm the host only by pressure of growth on surrounding structure (e.g. uterine fibroid on surrounding structure or brain benign tumour – severe pressure effects on vital adjacent structures leading to serious effect or death), but the functional endocrine benign tumours do have serious systemic effects. e.g. benign tumours of the β-cells of the islet of Langerhans in the pancreas (a functional tumour), which produce excessive high insulin levels and	**They have local and systemic effects. Some of the systemic effects include:** **a. Malaise** **b. Weakness** **c. Weight loss** **d. Anaemia** **e. Cachexia, etc.** **f. Then Death.**

thus cause hypoglycaemia and its complications	

The **appearance** of a **mass** is the **predominant feature** that attracts **attention** in a patient or an individual. This remains **prominent** and **permanent** in the **patient's mind**. An **accurate diagnosis** or **detection** of this **mass** is very **important** or **essential**, because it determines the type of **treatment, management** or **care** to be given, which in turn influences the **clinical course** or **prognosis** of the condition. The **causes** of cancer or tumour are **multifactorial**. The major causes are particularly **environmental** and **host factors**.

Oncologist

Environmental causes of cancer include:

a. **Biological**

Among these are **viruses** (e.g. **Hepatitis B** or **C** and **primary hepatocellular carcinoma**, **Epstein-Barr virus** and **Burkitt's lymphoma** and **nasopharyngeal carcinoma, Epstein-Barr virus** may also be linked with Hodgkin's disease. **Human papilloma viruses** and **cervical carcinoma**, **HIV- 1** and **HIV-2** [**human immunodeficiency virus**] and **non-Hodgkin's lymphoma** and **Kaposi's sarcoma**, **HTLV-I** and **HTLV-II [human T cell lymphotropic** or **leukaemia virus]** and **leukaemia**, etc.), **parasites** (e.g. **Schistosomiasis haematobium** and **bladder cancer**, **Clonorchis sinensis** and **cholangiocarcinoma** [bile duct], etc.), **bacteria** (e.g. Helicobacter pylori suspected to cause **stomach carcinoma**) and other biological agents

b. **Chemical**

Whole variety of **hydrocarbons, cigarette smoke** [(cigarette smoke contains **3, 4-benzpyrene,** a **polycyclic hydrocarbon**) and **cancer** of the **lungs**, **oesophagus**, **urinary bladder** and **pancreas**], snuff taking causes cancer of the nose while pipe smoking is associated with cancer of the lip and other **chemical compounds** including **naturally occurring carcinogens** (mycotoxins, e.g. **aflatoxin** and **primary hepatocellular carcinoma**, **nitrosamines** and **nitrosamides**, **Nitrites** are ingested in our **foods** or taken in **drinks**, **Dietary factors** – e.g. **fat**, excessive **meat consumption**, and **cooking habits**, etc.). Inhalation of **wood dust** especially **hardwood** can lead to **adenocarcinomas** of the **nasal sinuses** and is common in workers in the **furniture factories**. **Chromates** and **nickel** are known to cause **lung cancer**. **Arsenic** may be associated with **basal** and **squamous cell carcinoma** of the **skin** and it is also associated with **lung cancer**. Industrial exposure to **vinyl chloride** monomer is associated with angiosarcomas of the liver

c. **Physical**

Among these are **X-ray** or other **ionizing agents** including **solar radiation**. Exposure to radiation, electromagnetic or particulate – these can all be damaging to the DNA. **Ultraviolet** (**UV**) **light** is also dangerous. Skin cancer particularly **malignant melanoma** and **basal cell carcinoma** are very common in albinos or light or fair skin individuals or subjects. Naturally dark or pigmented skin individuals are protected from the damage caused by UV light but sun injury to the skin or other tissues will lead to reduced ability of DNA repair and hence

leads to increased cancer risk. **Uranium** miners suffer high rate of lung cancers due to **radon gas** inhalation. Radiologists and radiographers have high rate of cancer due to ionizing radiation. **Chronic mechanical irritations** may also cause carcinoma, Skin cancers may arise from **scars** of **previous burn** and **scars** in the lung due to **previous tuberculosis** may give rise to **adenocarcinomas**. Cancers can arise from sites of **chronic venous ulcer** on the **lower limb**, etc.

TABLE 2: SOME EXAMPLES OF CARCINOGENIC AGENTS FOR HUMANS

AGENT	**OCCUPATION**	**SITE** of **CANCER**
Aromatic amines	Workers in the Dye and Rubber industries	Bladder
Arsenic	Copper and Cobalt smelters, Pesticide industries	Skin Lung Liver
Asbestos	Miners in asbestos mines, Handlers of asbestos insulators	Lung Pleura Peritoneum
Ionizing radiation	Workers in Uranium mines, Luminizers	Lung Bone
Polycyclic hydrocarbons	Exposure to tars and oils (roofers and asphalters)	Skin Lung Oral cavity Larynx Bladder
Ultraviolet (UV) light	Fair or light skin individuals exposed to sunlight (outdoor workers especially susceptible subjects or in albinos)	Skin
Wood dust	Workers in furniture factories	Nasal sinuses

TABLE 3: SOME EXAMPLES OF MEDICAL AGENTS THAT MAY CAUSE CANCER IN PATIENTS THAT ARE EXPOSED

AGENT	REASON for EXPOSURE	SITE of CANCER
Alkylating agents	Cancer chemotherapy	Bladder Bone marrow

Ionizing radiation	Isotope handling, thyroid irradiation	Site of handling or exposure
Oestrogens	Post-menopausal hormone replacement therapy or oral contraceptive	Endometrium
Diethylstilboestrol	Prevention of miscarriage	Vagina (off-spring)
Thorotrast	X-ray contrast medium	Liver (angiosarcoma)

Host factors

These include the identification of **oncogenes** and **tumour suppressor genes** which are two important genetic factors in tumour or cancer growth (aspects of this was discussed earlier in cancer genes).

Tumour Sites

Cancer can affect any **organ** or **tissue** or **cells**. Some cancers are very common. These include the following:

a. **Lung** cancer
b. **Breast** cancer
c. **Cervical** cancer
d. **Skin** cancer
e. **Gut** cancer
f. **Prostate** cancer, and
g. **Liver** cancer.

Others are very **rare**, especially those affecting the **youths** being among the **rarest**. Most of the cancers affect the **epithelial tissues** (these are tissues that bound or cover **surfaces** particularly of the **skin** and **mucous membrane)** because most of the known **cancer-causing agents** (i.e. **carcinogens**) are from **natural radiation**, in the **air** we breathe, and from the **foodstuffs** we eat. The **epithelial cells** are our **first line** of **defence** to the outside world in the skin, lung and gastrointestinal tract (GIT) etc.

Most of the **harmful effects** of malignant tumours or cancers are caused by their **local effects** on **neighbouring tissues**. Malignant tumours are **locally destructive** (i.e. they are savage) to the **tissues** they invade. They infiltrate and destroy the **walls** of the following:

a. **Lymphatic vessels**

b. **Capillaries**
c. **Venules**
d. **Arterioles**
e. **Arteries**

Tumours invade, encircle and obstruct the following **tubular structures**:

a. **Gastrointestinal tract** (**GIT**)
b. **Respiratory tract** (**RT**)
c. **Urinogenital tract** (**UGT**)

Importance of Host Effect

The **immune system** functions as a **continuous surveillance mechanism**, tracking down neoplastic cells on the basis of their **aberrant appearance** and hence prevents tumours from arising. The immune system is also **important later** in the **disease process** when neoplastic cells have escaped the above mechanism (i.e. their being tracked down and destroyed). This is why some patients with **good performance status**, which is associated with **good functioning immune system**, tend to have a more **favourable prognosis**.

Staging of Cancers or Tumours

Staging of ***cancer*** is an effort to describe the ***extent*** in terms, which are commonly understood. This staging of the cancer describes its ***size*** and also shows whether it has ***spread*** into the *adjacent tissues* or not or has ***invaded*** the *lymph gland* or *node* or via the *blood circulation* to more *distant organs* or *sites*.

The ***purposes*** of staging cancer include the following:

a. To choose the optimum ***treatment*** or ***therapy*** or ***care***
b. To assess the ***survival*** rates (i.e., it provides prognostic information)
c. To establish the ***relative qualities*** of ***different techniques*** or methods of treatment, and
d. To make the ***exchange*** of ***information*** among cancer treating centres or hospitals ***easy***

SIGNALS of CANCER

Certain **signs** and **symptoms** are commonly associated with cancer. These include the following:

a. ***Sudden*** rapid ***loss*** of ***weight***

b. A change in ***skin colour***, ***mole*** that starts to bleed or itch, changes in size or shape of mole
c. ***Sore***, ***scab*** or ***ulcer*** in the ***mouth*** or on any part of the ***body*** that fails to heal
d. ***Headache*** that becomes very severe for no obvious cause
e. ***Vomiting*** which starts suddenly and no preceding ***nausea***
f. ***Swallowing*** becoming increasingly difficult
g. For no apparent causes there are ***constant fainting spells***
h. There are ***visual problems***, which include seeing ***"haloes" around lights*** or ***blurred vision*** which is intermittent especially in dim light
i. Persistent ***hoarseness***
j. Persistent ***cough*** which continues to get worse
k. ***Blood*** in ***coughed-up sputum***
l. ***Shortness*** of ***breath*** which is very severe for no apparent cause
m. ***Vomiting blood*** or coffee grounds
n. Severe ***abdominal pain*** or persistent ***indigestion***
o. Sudden change in normal ***bowel habit*** which may be an alternating attacks of ***diarrhoea*** and ***constipation***
p. ***Bowel movement*** is ***blocked*** and ***tarry***
q. ***Bleeding*** from the ***rectum***
r. ***Urine*** is unusually ***cloudy***, ***pink red*** or ***smoky***
s. ***Difficulty*** and ***discomfort*** when ***urinating*** and ***frequency*** in ***men***
t. ***Lump*** or ***unusual thickening*** of a ***breast***, any ***alteration*** in ***breast shape*** as ***flattening***, ***bulging*** of ***skin*** in ***women***
u. In ***women*** whose ***breast bleed*** or ***unusual discharge*** from nipple
v. ***Vaginal bleeding*** that occurs between normal menstrual periods or after menopause

Actually none of the above constitutes **proof** of **cancer**; only that cancer is a possibility which should be investigated without **delay**. At this juncture, I wish to cite Pastor Adeboye, General Overseer, Redeemed Christian Church of God, who is one of our most revered religious leaders in Nigeria, and who wrote in the daily prayer book "Open Heavens", and I quote:

> ***Go for medical check up at least once or twice annually. This does not make you faithless. Some believers refuse to do so not because of faith but fear of a negative report.***

WHAT IS A TUMOUR OR CANCER MARKER?

Today, the treatment or management of patients with cancer has become more **complicated** and more **complex**; thus, the **need** for these **tests** or **assays** has become **essential** and very **important**. The use of **tumour** or **cancer markers** goes back to about one hundred and sixty two years ago. **Sir Henry Bence Jones** in **1847** first described a **protein** in **urine**, which could be identified or shown in the laboratory by its **unique thermal properties**. This **protein** today is known as "**Bence-Jones Protein**" (**BJP**).

"**Bence-Jones Protein**" (**BJP**) as the **first tumour marker** was used as a **definitive diagnostic test** for **multiple myeloma** about one hundred and fifty two years ago.

About **twenty years** after, another early application of tumour marker in the **diagnosis** of **cancer** was by **Sir Michael Foster** in **1867**. He reported the presence of **amylase** (an **exocrine digestive enzyme**) in blood of patients with **pancreatic tumour**.

Tumour or Cancer markers

The introduction of **radioimmunoassay** and the application of **immunoassays**, which permitted **quantitative measurement** of **minute** or **very small** concentrations of **analyte**, (i.e. protein or other molecules) led to the introduction of the term **"tumour marker"**. This term is now a part of our everyday clinical laboratory vocabulary.

Short Classification of Tumour markers

a. **Hormones**
b. **Enzymes**, **isoenzymes** and **protease inhibitors**
c. **Oncofetal products or antigens**
d. **Other macromolecules**, **genes**, **oncogenes and their products**, **growth factors**, proliferation products, **receptors**, **oncoproteins**, **differentiation linked markers**, **chromosomal changes** including those involving **tumour suppressor genes** (e.g. **p53**,) and **cellular degradation products**

Methods or techniques for determination or **demonstration of tumour markers**

These include:

a. **Immunological methods**
b. **Blood circulating tumour markers may be measured by biochemical methods**
c. **Aberrant** or **actual DNA genome** of **neoplasm** can now be determined using appropriate **molecular biological techniques** currently available. For example, modified differential **polymerase chain reaction** (**PCR**) can be used.

The objectives of biochemical monitoring system of cancer are:

a. **Screening tool** in **asymptomatic individuals**
b. **Early identification**, **detection** or **diagnosis** of primary cancers
c. **Differential diagnosis** from **non-malignant conditions**, **assessment** of the **rate** of **progression** of **established metastasis**, or as an **adjunct** in **clinical staging** of **malignant disease**
d. **Indicator** of the **response** of **patients** to **therapy**

e. **Prognostic indices**

Properties of an ideal cancer or tumour marker

An **ideal tumour marker** should have **certain properties**, which should include:

a. Provide **useful patient care information**
b. Have **high disease sensitivity**
c. Should be **positive** in **all patients** with the **particular neoplastic disease**
d. Should have an **abnormal serum** or **plasma** or **urine** or other body biological fluid **level** in the presence of **occult carcinoma** or **micrometastases**
e. Should be able to **predict** and **precede recurrences** of the **cancer** or **tumour** before it is **clinically detectable**.
f. Should have **high disease specificity** to the tumour or cancer being investigated or diagnosed and should be **associated** with **only** this **tumour**. It cannot be demonstrated in a normal healthy individual or patients with **benign diseases** or patients with **other types** of **tumours**, which are different from the cancer or tumour in question
g. If present in the **bloodstream** of **normal healthy subjects**, it should be **very low** or at **significantly lower level** than that detected in patients with **all stages** of **carcinoma**
h. **Concentrations** of the cancer or tumour marker should have a **positive correlation** with the **tumour** or **cancer size** or **volume** and its **levels** should **change** as the **status** of the **carcinoma changes** over a **period** of **time**
i. Should be **stable** and not be **subject** to **marked fluctuation without clinical** and **pathophysiological changes** in **tumour activity**
j. Its **concentrations**, both **initial** and **serial** should be **prognostic** or be able **predict** the **outcome** of the **patients**
k. Method of measurement should be **specific** and **sensitive** enough to measure very **small** or **low concentrations** of the marker. Methods or techniques of measurements should also be **simple** to perform and **cost effective**

Some examples of tumour markers

A. HORMONES

Hormones may be **appropriate** or **eutopic**, that is, the endocrine tissue that normally produce the hormone may produce the hormone in excess, such as **steroids** from **adrenocortical tumours**, **catecholamines** from **phaeochromocytoma** or **insulin** from **insulinoma** or tumour of the β-cells of the islet of Langerhans, or they may be **"inappropriate"** or **ectopic**. In the inappropriate or ectopic tumour markers the commonest are the production of **adrenocorticotrophic hormone** (**ACTH**), **antidiuretic hormone** (**ADH**) or **calcitonin** by **oat cell carcinoma** of the **bronchus** or **lung**.

Expression of the **tumour** or **cancer markers** is under **genetic control**. **Ectopic hormones** are generally derived from **non-endocrine organs** or **tissues**, that is, organs or tissues, which under normal physiological conditions do not

synthesize or secrete these hormones. These hormones may also be secreted by endocrine tissues but such endocrine organs do not secrete or produce them under normal physiological conditions. The hormones may not necessarily be **chemically identical** to the **native hormone** but may be very close to **cross-react** in immunoassay techniques or methods for the native hormone.

TABLE 4: SOME EXAMPLES OF NON-ENDOCRINE TUMOURS (ECTOPIC HORMONE PRODUCTION)

HORMONES or HORMONE-LIKE SUBSTANCES	SITES of NEOPLASM	CLINICAL FEATURES or SYMPTOMS
Adrenocorticotrophic hormone (ACTH)	Lung, thyroid, pancreas, etc	Cushing's syndrome
Antidiuretic hormone (ADH)	Oat cell carcinoma of the lung, etc	Water retention, Hyponatraemia
Serotonin	Enterochromaffin cells in most organs	Carcinoid syndrome
Parathyroid hormone	Bronchus, lungs, etc	Hypercalcaemia
Thyroid stimulating hormone (TSH)	Trophoblastic tumour, bronchial carcinoma, etc.	Hyperthyroidism
Gonadotrophin, androgens etc.	Hepatocellular carcinoma	Testicular hypersecretion
Erythropoietin	Haemangioblastoma of the cerebellum	Hyperplasia of erythroid tissue of the bone

B. ENZYMES

A wide variety of **enzymes** and **isoenzymes** have been shown to alter in the **tumour tissues** and in the **body fluids** of **cancer patients**.
Enzyme tumour markers may be subdivided into:

a. **Organ-specific enzyme tumour markers.** These include the following:

i. **Acid phosphatase -** 80 to 90 percent of patients with prostatic carcinoma have elevated serum acid phosphatase levels. The extent of increase varies considerably. **Acid phosphatase** total **protein** level in plasma or serum is now being measured or estimated instead of the **enzyme activity**. Commercial kits for this method of measurements are now available.

ii. **Creatine kinase** - High concentrations of BB **isoenzyme fraction** have been found in **prostatic carcinoma** and **metastatic carcinoma** of the **stomach**, in **Breast carcinoma**, **small-cell carcinoma** of the **lung**, etc.

iii. **Alkaline phosphatase** - Elevated levels of this enzyme have been found in cancers affecting the **liver** (both primary and secondary liver cancers) and those involving the **bone**. **Osteogenic sarcoma**, especially of **osteoblastic type** often produces large amount of alkaline phosphatase of bone origin into blood circulation. Bone metastases from carcinomas of the prostate and breast may be associated with an increase of serum alkaline phosphatase. These types of carcinoma deposits (e.g. prostate) in bone stimulate local **osteoblastic reaction**, which lead to high serum or plasma alkaline phosphatase level. Minimal increase in alkaline phosphatase is seen in breast cancer with bone metastases because of its osteolytic lesion. Radioimmunoassay or enzymeimmunoassay techniques using polyclonal or monoclonal antibodies can also measure bone specific alkaline phosphatase.

iv. **Regan isoenzyme -** An interesting change in **serum alkaline phosphatase** in **malignancy** is the appearance of an **isoenzyme** (**"ectopic" alkaline phosphatase**) that cannot be distinguished from **placental alkaline phosphatase**, called **Regan isoenzyme**, after the patient in whom it was first demonstrated. This isoenzyme is found in both **serum** and in the **tumour tissue**. Increased serum or plasma activity may be increased in these neoplastic conditions:

   α. Bronchus carcinoma
   β. Oat cell carcinoma of the lungs
   χ. Carcinoma of the ovary
   δ. Breast carcinoma
   ε. Colon carcinoma

v. **Neuron-specific Enolase** (**NSE**) - NSE is the form of enolase that is found in the neuronal tissue and in the cells of the diffuse neuroendocrine system, especially the **a**mine **p**recursor **u**ptake and **d**ecarboxylation (**APUD**) cells or tissues. It is increased in the following tumours
   α. Small cell carcinoma of the lung
   β. Neuroblastoma
   χ. Carcinoids

vi. **Prostate-specific antigen (PSA) -** This is a **glycoprotein** that is

secreted by the prostate into the **seminal fluid**. **Low concentrations** of PSA **protein** are normally released into **blood circulation** where samples can be taken for serum PSA tests. PSA is used in most hospital laboratories all over the world currently also for **response** of **therapy**, since it is a **sensitive assay**.

b. **Non-organ specific enzyme tumour markers.** These include the following:

i. **Lactate dehydrogenase** - It has been shown in a variety of cancers, which include:

α. Liver
β. Non-Hodgkin's lymphoma
χ. Acute leukaemia

ii. **Lysozyme** - This enzyme may be increased in the myeloid leukaemias and in particular monocytic leukaemia.

C. Oncofetal antigens

Typical examples** of **oncofetal antigens** include**:

a.	**Carcinoembryonic antigen (CEA)**	– colorectal, GIT, pancreatic, etc.
b.	**α_1-fetoprotein**	– Liver cancer, germ cell (nonseminomatous)
c.	**Pancreatic oncofetal antigen**	– Pancreatic cancer
d.	**β-oncofetal antigen (BOFA)**	– is produced by the cancer of the colon
e.	**Carcinofetal ferritin**	– Liver
f.	**Tissue polypeptide antigen**	– Breast, colorectal, ovarian, bladder

Some routinely measured examples of oncofetal antigens are:

a. **Carcinoembryonic antigen** (**CEA**)
b. **Alpha$_1$-** (**α_1-**) **fetoprotein**
c. **Carbohydrate antigens** or **Cancer antigens** (**CA**) - A large number of cancer or carbohydrate antigens have been detected in specific types of tumour. Cancer antigens represent clinically useful tumour or cancer markers. They are much more specific than the enzyme or hormone cancer markers. Measurement of serum CA 19-9 by radioimmunoassay or enzymeimmunoassay is of value in the diagnosis and monitoring of patients with **gastrointestinal tract carcinoma** including **carcinoma** of **pancreas** and **hepatobiliary system**. CA-125 is elevated in serum of approximately 82 percent of women with **epithelial ovarian carcinoma** and is mildly increased in serum of some women with

endometriosis and pelvic inflammatory disease. Other carbohydrate antigens include the recently developed assay of **CA 15-3**. This is used in the diagnosis of breast carcinoma.

D. Other **Macromolecules**

Proteins as Tumour or Cancer Markers

a. **Immunoglobulin**
b. **Ferritin**
c. **Melanoma-associated antigen**

Receptors as Tumour or Cancer Markers

Oestrogen and **progesterone** receptors – Oestrogen and progesterone receptors (**E+** [E for oestrogen] and **Pr+** [Pr+ for progesterone]) in breast are indicators for hormone or endocrine treatment.
Breast cancer patient with positive oestrogen and progesterone receptors (**E+** and **Pr+**) respond favourably to endocrine hormonal therapy while those with negative oestrogen and progesterone receptors (**E-** and **Pr-**) are treated with chemotherapy.

Genetic Markers

a. **Oncogenes**
   i. **N-ras gene**
   ii. **K-ras gene**
   iii. **c-myc gene**
b. **Tumour Suppressor gene**
   i. **RB or Retinoblastoma gene** - This was the first tumour suppressor gene to be identified. Retinoblastoma occurs in families and sporadically.
   ii. **p53 gene** - This gene is found in chromosome 17q. p53 mutations lead to the production of proteins that allow wild-type p53 protein and so allow cells to move through the cell cycle and contribute to autonomous growth of cancer.
   iii. **Adenomatous polyposis coli** (**APC**) **gene** - this gene is mutated in hereditary colorectal cancer syndromes, polyposis and non-polyposis types. Bowel cancer does occasionally run in families through the inheritance of a mutated APC gene.
   iv. **BRCA1 and BRCA2** - These are tumour suppressor genes which when mutated are implicated in the development of breast and ovarian cancers.

TABLE 5: SOME EXAMPLES OF TUMOUR AND SOME TUMOUR MARKERS USED FOR THEIR DIAGNOSIS

TUMOURS	TUMOUR MARKERS
Hepatocellular carcinoma	Alpha$_1$-fetoprotein, ferritin, enzymes of collagen synthesis (prolyl 4-hydroxylase, collagen glucosyltransferase, collagen metabolites, alkaline phosphatase (i.e., liver isoenzyme)
Gastrointestinal tract carcinoma	CEA, α_1-fetoprotein, CA 19-9, CA 242, CA 195, MCA, etc
Breast carcinoma	CEA, ferritin, calcitonin, CA 15-3, β-hCG, enzymes of collagen synthesis (prolyl 4-hydroxylase, etc.) creatine kinase isoenzyme (BB), mammaglobin, tissue polypeptide antigen (TPA), cytokeratin-19 (CK-19), Mucin-like Cancer Associated antigen (MCA) etc.
Prostate carcinoma	Prostate-specific antigen, Prostate acid phosphatase, CEA, TPS, etc
Germ-cell tumours of the testis and ovary	α_1-fetoprotein, β-hCG, creatine kinase isoenzyme, Parathormone, Regan isoenzyme, MCA, etc
Trophoblastic tumours (choriocarcinoma or hydatidiform mole)	β-hCG, inhibin, Lactate dehydrogenase, etc
Multiple myeloma, Waldenstrom's macroglobulinaemia	IgG, IgA, IgM, IgD, IgE, peptide chains of immunoglobulin, Bence Jones protein
Oat-cell carcinoma of the lung	Regan isoenzyme, ACTH, ADH, etc.
Renal cell carcinoma	Tu M2-PK an Isoenzyme of Pyruvate kinase
Ovary	Tumour Associated Trypsin Inhibitor (TATI), MCA, CA 125
Neuroblastoma, lung cancer (i.e., small cell carcinoma)	Neuron Specific Enolase (NSE)
Thyroid carcinoma (i.e. papillary and follicular)	Thyroglobulin

CONNECTIVE PROTEINS as **TUMOUR MARKERS**

The extracellular matrix is made up of various proteins and other compounds and can be divided into three main components:

a. Collagens
b. Proteoglycans, and
c. Glycoproteins

I. Collagens

Collagens are the main **insoluble fibrous protein** of **connective tissues** and constitute about **one third** of **all proteins** in the **body** (i.e., the **most abundant protein**). **Tissues** that are particularly rich in collagens are **skin**, **bone**, **tendon**, **cartilage**, **ligament**, and **vascular wall**, but collagens are found essentially in **all tissues**, and play a **dominant role** in maintaining the **structural integrity** of numerous tissues and **organs**. Collagens are involved in **many diseases** from **fatal heart** and **lung diseases** to **liver diseases**, **back pain**, and **minor skin disorders**. Physiologically, collagens are associated with **normal morphogenesis** in **embryonic development**, **growth** and **aging**, **coagulation**, **wound** and **fracture healing** (all conditions which prevent or inhibit collagen synthesis will delay wound or fracture healing).

TABLE 6: **SOME EXAMPLES** of **MAJOR COLLAGEN TYPES**

Types	**Constituent chains**	**Chain Composition**	**Location**	**Subgroup**
I	A1(I) α2(I)	$[\alpha1(I)]_2$ $[\alpha2(I)]$ $[a1(I)]_3$	Skin, tendons, bones, most tissues, etc.	Fibrillar
II	α1(II)	$[\alpha1(II)]_3$	Cartilage, vitreous humor, cornea Intervertebral disc	Fibrillar
III	α1(III)	$[\alpha1(III)]_3$	Skin, muscle, soft tissues, etc., frequently occurs together with type I	Fibrillar
IV	α1(IV) α2(IV) α3(IV) α4(IV)	$[\alpha1(IV)]_2$ $[\alpha2(IV)]$ $[\alpha3(IV)]_2$ $[\alpha4(IV)]$	All basement membrane	Network forming
V	α1(V) α2(V) α3(V)	$[\alpha1(V)]$ $[\alpha2(V)]$ $[\alpha3(V)]$	Most interstitial tissues associated with type I	Fibrillar
VI	α1(VI) α2(VI) α3(VI)	$[\alpha1(VI)]$ $[\alpha2(VI)]$ $[\alpha3(VI)]$	Most interstitial tissues associated with type I	Beaded filament forming
VII	α1(VII)	$[\alpha1(VII)]_3$	Epithelia	Anchoring fibril forming

Collagen synthesis follows the same basic principle of **protein synthesis** in **general**, but **collagen** is **unique** in that there are unusually large numbers of **post-translational modifications** involved in its biosynthesis.

Summary of general steps in collagen synthesis:

a. **Transcription**
b. **Translation** of **mRNA** on **polysomes** in the **cytoplasm**
c. **Post-translational modifications,** which take place **intracellularly** and **extracellularly**

Biochemical Markers** of **Collagen Metabolism

a. ***.Assays** of **Collagen Synthesis***

i. **Prolyl 4-hydroxylase**
ii**.** **Collagen glucosyltransferase activity**

b. **Procollagen propeptides:**
Type III and **I collagens** are synthesized as **type III procollagens** and **I** respectively. Once the procollagens are secreted into the **extracellular space**, the **propeptides domains** are no longer needed and are subsequently cleaved off by **two specific endopeptidases**. The collagen molecules resulting from this cleavage **spontaneously assemble** into **collagen fibres**. In principle both **amino-** and **carboxyterminal propeptides** are produced at the **same molar-rate** as the **type I** or **III collagen** proper. The segment that is removed from the **carboxyterminal end** is termed the **carboxyterminal propeptide** of **type I procollagen** (**PICP**), while the segment cleaved from the **aminoterminal end** is called **aminoterminal propeptide** of **type I procollagen** (**PINP**). PICP is measured in serum or plasma, with commercially available radioimmunoassay kits.
Aminoterminal propeptide of type III procollagen (PIIINP) can be measured by commercially available **radioimmunoassay kits**. The serum assay for the measurement of aminoterminal propeptide of type III procollagen has been used in various liver disease including malignant diseases.

Summary of my **contribution:**

In summarizing my contribution, I wish to start by quoting **Christian de Duve** (1987)

> ***Most of us are bricklayers. We are happy to add a stone to the edifice of science and we consider ourselves fortunate to contribute a cornerstone, or the base of a column, or a keystone of an arch. A rare few have the vision of an architect. They***

somehow see the whole building long before it is completed.

1. .**Assays of Collagen Synthesis**

A. Study in Primary Hepatocellular Carcinoma (i.e., **liver cancer**) or **Hepatoma**

a. In **serum** of **patients** with **malignant diseases**:
Serum immunoreactive prolyl hydroxylase protein (**S-IRPH**), serum Galactosylhydroxyllysyl glucosyltransferase (i.e. **SGGT** or **Collagen glucosyltransferase**) and amino-terminal propeptide of type III procollagen [**S-Pro**(**III**)**-N-P**] were studied in **24 patients** with **primary hepatocellular carcinoma**, **18** with **secondary liver neoplasms** and **35** with **other malignant diseases** but no **liver evidence** or **liver involvement**; this latter group included **13 patients** with **Burkitt's lymphoma**, **11** with **breast cancer** and **11** with other **neoplasms**. Control values were determined for **60** apparently **healthy Nigerians**.

The summary of the results showed that **S-IRPH** was above the **upper normal limit** (defined as the mean + 2SD of the controls) in **all** the **patients with primary hepatocellular carcinoma** and in **all** but **one** with **secondary liver neoplasms** or **cancers** was high in one patient only in the group of patients with other malignant diseases. The data suggest that primary and secondary malignant neoplasms of the liver have a higher rate of collagen biosynthesis. The **assay** of **S-IRPH** may be used as a **tumour marker** in the **diagnosis** of **primary hepatocellular carcinoma** and **secondary liver involvement** in other **malignant diseases** and in **monitoring** the **treatment** provided.

The results also showed that the mean **serum Galactosylhydroxylysyl Glucosyltransferase** (i.e., **S-GGT** or **collagen glucosyltransferase**) was above the upper limit, defined as the mean + 2SD of the controls, in **all** the **patients** with **primary hepatocellular carcinoma** and **all** but **one with secondary liver neoplasm**, whereas only three S-GGT values exceeded this limit in the patients with other malignant diseases. The data suggest that the **assay** of **S-GGT** may be used as a **tumour marker** for the diagnosis and detection of **primary hepatocellular carcinoma and secondary liver involvement** in other malignant diseases and in monitoring the therapy of this disorder.

The mean **S-Pro** (**III**)-**N-P** was highly elevated in the **primary** and **secondary liver neoplasm cases**. It was also elevated in **other malignant neoplasms**; about one third of the patients with no evidence of liver involvement had a concentration exceeding the upper normal limit. This marker can be used as a **general tumour** or **cancer marker** as it is not specific for **liver tumours** or cancer (**primary** and **secondary**) as the enzymes of collagen biosynthesis or the procollagen III analytes are minimally increased in other disease conditions.

Reference for this work can be found in Debayo M. Bolarin et al. **Int. J. Cancer** 1982; 29: 401-405.

b. **Study** in **Human Liver Tissue**

i. **Liver Immunoreactive Reactive Prolyl Hydroxylase Protein in Human Primary Hepatocellular Carcinoma**:

Liver prolyl Hydroxylase protein was measured in **hepatic tissues** of **8 patients** with **primary hepatocellular carcinoma** (**PHC**), **5** with **acute viral hepatitis** and **5** with **cirrhosis** (**3 alcoholic** and **2** with **other causes**). The mean values were compared with the mean control of **10 normal hepatic tissues**. The mean values were all highly significantly elevated about 5 times the control mean in patients with PHC than the other liver diseases. The **greatest elevations** were seen in individuals with primary **hepatocellular carcinoma** (i.e. **liver cancer**). Minimally elevated levels were seen in individuals with other liver diseases. The findings of this study showed that this enzyme may be used as a **tumour or cancer marker** for **early identification** or **detection** of **primary hepatocellular carcinoma**.

Reference for this study can be found in Debayo M. Bolarin et al. **Hepato-gastroenterol**. 1983; 30: 230-232.

ii. The activity of **Liver-GGT** was determined in **human primary hepatic cancer**, **acute viral hepatitis** and **cirrhotic liver tissues** and compared to the mean level of enzyme activity in **normal liver tissues**. The results showed that the mean levels of L-GGT activity in **primary hepatocellular carcinoma** (**PHC**), **acute viral hepatitis** and **cirrhotic tissues** were **7.78**, **2.69** and **2.16** times the **mean level** of **enzyme activity** in **normal human tissues**. The mean level of L-GGT activity in **PHC** was **3.61** times the mean level of L-GGT activity in **cirrhosis** and **2.90** times the mean value of liver enzyme activity in **acute viral hepatitis**. The **greatest elevations** were seen in individuals with primary **hepatocellular carcinoma** (i.e. **liver cancer**). Minimally elevated levels were seen in individuals with other liver diseases. The findings of this work provide the basis for the highly elevated serum values of this intracellular enzyme in patients with **primary hepatic cancer** and the data confirm the enzyme as a **tumour** or **cancer marker** for the **early identification** or diagnosis of primary hepatocellular carcinoma.

Reference for this work can be found in Debayo M. Bolarin et al. **Int**. **J**. **Biochemistry** 1983; 15:1291-1293.

B. Study In Human Breast carcinoma

Breast cancer tissue and serum:

Prolyl hydroxylase activity, **immunoreactive prolyl hydroxylase** and **Collagen glucosyltransferase** were measured in **primary human breast tissues** and **sera** of the **same patients** and compared to the level of **enzyme activities** and **protein** in **normal breast tissues** and **control sera**. Our results showed that there was **no difference** in the levels of **serum immunoreactive prolyl hydroxylase protein** in **breast cancer patients** and the **controls**. In the primary breast tissues enzyme activity and protein were **13.86** and **5.3** times the mean levels in normal breast tissues. The results suggest that the **enzyme activity** and its **total protein levels** are **elevated** in the **primary breast tissues**. The result shows that the enzyme could be used as a **marker** in **breast cancer tissues** but not **in primary cancer patients' serum**.
As in the above result for prolyl hydroxylase, **collagen glucosyltransferase activity** in **primary breast cancer tissues** was **5.00** times the mean level in **normal breast tissues**. There were no differences in the levels of the **serum enzyme activity** in breast cancer patients and the control. The result shows that the enzyme could be used as a marker in breast cancer tissues but not in primary cancer patients' serum, like the serum prolyl hydroxylase above.

Reference for this work can be found in Debayo M. Bolarin, **Research Communications in Chem**. **Path**. and **Pharmacol**. 1983; 39: 493-502.

C. In experimental Primary Liver carcinoma

a. In **Serum** of **Rats** with **Experimental Liver carcinoma**

Serum total Prolyl Hydroxylase Protein was measured in serum of **rats** fed with **0.06 %** of **azodye**, **3-methyl-4-dimethyl-aminoazobenzene** (**3-MeDAB**). Serum enzyme protein values in the group progressing to primary hepatocellular carcinoma or hepatoma and those which had the tumours were significantly different ($p < 0.001$) from the controls. The serum enzyme protein was progressively elevated in all animals progressing to cancer of the liver. The results suggest that the assay of **serum prolyl hydroxylase protein** may be an **additional useful tool** (i.e.,

a tumour or cancer marker) in the **early identification** and **diagnosis** of **primary hepatic cancer**.

Reference for this study can be found in Debayo M. Bolarin. **Acta Physiologica Hung**. 1983; 71: 55-59.

b. In **Liver carcinoma tissue** and **serum**

Liver collagen glucosyltransferase activity

Collagen glucosyltransferase activity was measured in **experimentally induced liver carcinoma**, **murine schistosomiasis mansoni-induced liver fibrosis** and compared to the level of enzyme activity in **control liver samples**. Enzyme activity in hepatoma and fibrotic tissues were **12** and **5** times the mean level of enzyme activity in the **control liver tissue** respectively. The level of enzyme activity in the primary hepatocellular carcinoma or hepatoma tissue was two times the level of enzyme activity found in the fibrotic tissue. Greatest elevations were seen in the individual animals with primary hepatocellular carcinoma or hepatoma while minimal elevations were seen in individual animals with other lesions. The findings in this study confirm that the enzyme may be used as a **cancer** or **tumour marker** for the early identification or diagnosis of **primary hepatocellular carcinoma**.

Reference for this study can be found in Debayo M. Bolarin. **Acta Physiologica Hung**. 1990; 77: 55-59.

c. **Serum Collagen glucosyltransferase Activity**

Serum collagen glucosyltransferase activity was used to examine the **sequential changes** of **serum collagen glucosyltransferase activity** levels with the **evolution** of **experimental hepatocellular carcinoma**. Rats were fed with 0.06 percent of the azodye, 3-methyl-4-dimethylaminoazobenzene (3MeDAB). A **significant increase** in the serum enzyme activity levels was observed in the experimental animal groups **four weeks** into the experiment, which **rose progressively** over the duration of the study. The serum **enzyme activity levels** in the **carcinogen-fed animal group** increased **five times** the **control mean** enzyme activity levels at 0 week to 18 weeks and also about **five times** its mean enzyme activity at **0 week**, when hepatic cancer appeared in the liver. There was a progressive increase in the serum enzyme activity. The data thus indicate that the serum collagen glucosyltransferase may be a useful tumour marker in the diagnosis of primary hepatoma.

Reference for this study can be found in Debayo M. Bolarin**. Central African Journal of Medicine** 1986; 32: 213-217.

2. **Assays of Collagen Degradations**

a. **Hydroxyproline**

Almost 14 percent of the amino acid content of collagen is **hydroxyproline**. It is a **post-translationally modified amino acid**. It is modified from some **prolyl residues** in the procollagen by the action of the **intracellular enzyme prolyl hydroxylase**. This amino acid has been used as a **urinary marker** for **bone degradation** or the **bone metastatic tumour**. Urine hydroxyproline can also be derived from the **diet**. Urinary hydroxyproline is measured in most laboratories by **colorimetric** or **high pressure** or **performance liquid chromatography** methods. This is an old marker for bone disorders especially bone resorption and malignant tumour metastases.

b. **Urinary pyridinoline** (**Pyr**) **and deoxypyridinoline** (**D-Pyr**)

These markers are released from bone only during **resorption** or **degradation**. D-Pyr is more bone specific. **Pyr.** occurs widely in **connective tissues**, including **bone** and **cartilage**. D-Pyr and Pyr can be assayed in **urine** and **serum** by **high-pressure liquid chromatography** (**HPLC**) and by **immunoassays**. The immunoassay methods have been used to measure these markers to confirm **bone metastasis** of **prostate carcinoma**.

c. **Cross-links** of **aminoterminal** and **carboxyterminal telopeptides** of **type I collagen (NTX, CTX)**

NTX and **CTX** are highly **bone specific**. Both markers are measured in **urine** and **serum** using **radioimmunoassay** and **enzymeimmunoassays**. They are both used as **tumour markers** to confirm **bone metastases**.

II. **Fibronectin**

Fibronectins are **high molecular weight glycoprotein** found in **body fluids** and **connective tissues**. Fibronectins are distributed widely in the human body. They are **large adhesive proteins** found on **cell surfaces**, **extracellular matrices** and **basal laminae** are present in **soluble form** in the **plasma** and other body fluids. It has been shown that fibronectins play a role in **tumour invasion** and **metastasis**, thereby making circulating fibronectin or its isoforms **potential tumour markers**. Increased plasma concentrations of fibronectin in various carcinomas including **breast**, **colonic**, **lung** and **ovarian carcinomas** have been reported.

FERRITIN AS TUMOUR OR CANCER MARKERS

Ferritin

Ferritin is primarily an intracellular **iron-storage protein** with a high molecular weight of approximately **450 kD** and it is found in all **tissues**, but in particularly high concentrations in the **liver**, **spleen**, and **bone marrow**. With the development of sensitive **immunoradiometric assays** and **enzymeimmunoassay** for ferritin, it has become possible to detect small amounts of ferritin in normal serum and to record changes in the serum ferritin concentrations in **patients** with a variety of **pathological conditions**. High serum ferritin concentrations have been found in **anaemia** of **chronic diseases**, acute as well as chronic **liver damage**, in **haematological malignant diseases** and in **solid tumours** or **cancers**.

Serum Ferritin in Nigerian Patients with Burkitt's Lymphoma and other Malignant Diseases

Serum ferritin was studied in 4 patients with abdominal Burkitt's lymphoma, 6 patients with facial Burkitt's lymphoma, 10 with primary hepatocellular carcinoma, 6 with secondary hepatic cancer, and 8 with primary breast cancer, 4 with Hodgkin's disease, 3 with chronic lymphocytic leukaemia and 6 with other neoplastic diseases. Control values were determined for 23 apparently healthy Nigerians. Serum ferritin was significantly elevated in patients with Burkitt's lymphoma (facial and abdominal combined), primary hepatocellular carcinoma, secondary hepatic cancer, chronic lymphocytic leukaemia ($p < 0.00001$), Hodgkin's disease and in other neoplastic diseases as compared to the control ($p < 0.0004$). Serum ferritin levels were significantly elevated ($p < 0.00001$) in abdominal Burkitt's lymphoma but less dramatically elevated values or even values within the reference range (mean ± 2 Standard Deviations of the controls) were seen in the values of serum ferritin in the patients with facial Burkitt's lymphoma. The assay of serum ferritin may be of some value in the diagnosis and classification of patients with Burkitt's lymphoma, and in monitoring treatment provided.

Reference for this work can be found in Debayo M. Bolarin, **Acta Tropica** 1983; 40: 71 – 77.

PROSTATE-SPECIFIC ACID PHOSPHATASE AS TUMOUR OR CANCER MARKER

Prostate-Specific Acid Phosphatase

Prostate cancer is one of the most frequent cancers in men and is accountable for more **deaths** than any other form of cancer except **lung cancer**. Prostate cancer is at present the most common cancer of the elderly Nigerian man.

Prostate acid phosphatase is an enzyme capable of hydrolyzing **phosphate ester** in **acidic medium**. Following the original **findings** by Gutman et al and Huggins and Hodges many years ago, that serum acid phosphatase activity is markedly elevated in **patients**

with **prostate carcinoma**, determination of this **enzyme activity** has been widely employed to identify prostatic cancers and **follow-up therapy** of patients with the disease. **Immunological quantification** of the total **enzyme protein** of acid phosphatase seems to be clinically more useful when compared with measurement of catalytic activity. It has now been possible to measure concentrations of serum **immunoreactive prostate-specific acid phosphatase** by direct **radio-immunoassay** (**RIA**) and enzyme-**immunoassays** (**EIA**). High values have been found in patients with prostatic cancer.

Prostate-Specific Acid Phosphatase in Nigerian Patients with Prostate Carcinoma

Serum immunoreactive prostate-specific acid phosphatase was studied using a radioimmunoassay (RIA) technique in 10 patients with prostate carcinoma including occult prostate carcinoma, 6 with benign prostate hyperplasia, 16 with other malignant diseases, and 10 with chronic schistosomiasis haematobium. Control values were determined for 12 apparently healthy Nigerians. Serum immunoreactive prostate-specific acid phosphatase was above the normal limit defined as the mean ± 2 Standard deviation of the controls, in all the patients with prostate carcinoma. Whereas only two values slightly exceeded this limit in the patients with benign prostate hyperplasia, there was no value that exceeded this limit in patients with either other malignant diseases or chronic schistosomiasis haematobium. The data suggest that prostate carcinoma contain and release a high concentration of prostate-specific phosphatase. The use of RIA or EIA in the evaluation of this enzyme protein is a useful, non-invasive, diagnostic tool and is well suited for differential diagnosis of urogenital diseases in the tropical or endemic areas of schistosomiasis haematobium.

Reference for this work can be found in Debayo M. Bolarin and O. A. Badejo. **Acta Tropica** 1983; 40: 71 – 77.

At this juncture, I wish to cite **Charles Brenton Huggins**, who was a co-recipient with **Peyton Rous** of the **Nobel Prize** for **cancer research** in **1966**. He was a **dedicated physician** who **worked tirelessly** to return **cancer patients** to **active** and **useful lives**; and yet as a **research scientist**, he also provided **insight** into the **nature** of **cancer**. He was indeed a champion in the fight against cancer, a man who has done great service for the health of the whole world. Throughout his life, Charles Huggins has found **great joy** in posing **difficult questions** and seeking to **answer** them. He once said and I quote,

Doing science in the Universities is one of the most pleasant vocations of man. One must give everything, but one receives much in return. One pits his wits against apparently inscrutable nature, wooing her with ardour. Nature is blind justice who cannot recognize personal identity. She can refuse to speak, but cannot give a wrong answer. She is an unsophisticated, buxom lass who can be cajoled but not forced; her vocabulary consists of three words – yes, no, and perhaps. It is the genius of research to frame a question so simply that a conditional answer is prohibited.

(Please, note that **emphasis** in the **quotation** are **mine** and not in the **original text)**

I want to stress again that the **whole clinical management** of cancer would be transformed only if it is possible to secure **early evidence** (i.e. **early detection** or **diagnosis**) of the **upgrowth** of a **malignant tumour** in the body – especially a **tumour** of the **internal organs**. This is the only current practical means for reducing the morbidity and mortality rates of cancers. A major proportion of **cancer research** in the world (i.e. in the USA, Europe, Canada, Japan, etc.) today is directed towards a solution of this problem. The main goal of cancer research is to identify individuals at risk. Recently an International Cancer Genome Consortium (ICGC) was set up to deal with the genetic make-up of human cancers. ICGC is the oncology equivalent of the Human Genome project. It takes global approach to search for major gene mutations. This is aimed to enhance the detection, treatment or therapy and prevention of cancer in the world.

Mr. Vice-Chancellor, distinguished guests, in the opening I said that cancer is about the second among killer diseases, coming after heart disease or AIDS and tuberculosis, etc. (in Nigeria or sub-Saharan African countries). Yet it is the most dreaded of diseases. Much of these fears stem from lack of good information or knowledge of cancer – for cancer is **curable** if detected or diagnosed early as I have mentioned. Other **reassuring features** are that cancers are not contagious not even in their **terminal phase**.

We need **facilities** and **funds** for **basic research** in **cancer** in Nigeria. The fundamental goal of such research will be to give a greater understanding of cancer and eventually facilitate more effective cancer treatments. Basic research in cancer should go hand in hand with **new methods** in **cancer patient care**. Research discovery will lead to **targeted therapies**, more specific to the **malfunctioning cells** seen in cancer. The traditional cancer treatments of **surgery**, **radiotherapy** and **chemotherapy** are being gently modified with **modern** and **new methods** of cancer patient care.

In the industrial or **developed countries** in Europe, USA, Canada, Australia, New Zealand and others where intensive cancer researches are carried out, **new cancer treatment** methods are being applied by exploiting the knowledge of **molecular cell biology** of **cancer** (Fast DNA sequencing technology and high density genotyping are now available).

Philanthropy

Philanthropic Foundations are vehicles for channeling **private wealth** into **public purposes**. Philanthropies bear heavy societal responsibilities by virtue of their wealth, their central role in our civil society and their power to help. They are exemplars of private initiative in the service of the public good. The philanthropic foundations are evidence that it is not necessary if not dangerous to serve public needs solely through the state (i.e. Federal and State Governments).

At this point I may say that we need a **funding philanthropy** for **cancer research** in this country. Nigeria needs **people** or **families** or **organizations** (**NGOs**) who would bequeath income from their estates for **charitable causes**. These **bodies** or families or organizations may give money for example for the set up of **cervical** and **breast cancer screening services** to all at-risk **women**, irrespective of their **socioeconomic status**. This can be replicated for **prostate cancer screening services** to all at-risk **men** and also

irrespective of their socioeconomic status, since **early detection** will facilitate successful treatment and therefore **save lives**.

Legislation On Cancer

Finally, I wish to advise that the country's Federal and State legislative houses should pass an enabling law for the Federal and State Governments to embark on an initiative by declaring **war** on **cancer** now. Such a law should make provision for adequate **resources**, **manpower**, **facilities**, and the **development** of a coordinated **national programme** for the conquest of cancer. It should include many important provisions in the areas of **research**, **education**, **early detection** or **diagnosis** and therapy. It should also provide for special budget for the establishment of a **National Cancer Institute** of **Nigeria**, which should conduct cancer control activities and to establish national research and demonstration centres. These centres will develop innovative approaches to the detection or diagnosis and treatment of cancer. The Government of the Federation should appoint a **National Cancer Advisory Board** and a **director-general** for the National Cancer Institute of Nigeria.

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I started the lecture by mentioning the various persons who were instrumental to the development of my special interest in Pathology. I wish to end the lecture by acknowledging those who supported my research efforts.

I thank the many international institutions and research granting bodies which supported my research effort during my appointment as postdoctoral research fellow from 1980-1984 and 1995 to 1997: **Searle Research** and **Development**, Skokie, Chicago, USA, **Wayne State University**, Detroit, USA, and **Sigrid Juselius Foundation**, Helsinki, Finland; these have at various times supported my **research effort**. I appreciate their support and I am most grateful.

Above all, I thank **Almighty GOD** for giving me **Bimpe** (a **professor** in her own right, through hard work, quality and quantity research outputs, community and social services) and the children.

Mr. Vice-Chancellor, with **apologies** to **my children**, **Tope**, **Lola** (late), and **Tunde**, I say and do request that those after me should **please pass** on the **torch**.

I wish to end with the following quotation, which is from a paper presented during Albert Szent-Gyorgyi commemorative presentation in Szeged Medical School, Szeged, Hungary in September, 1993, by Professor Egon Dicsfalusy, an internationally renowned medical scientist who worked in Karolinska Institute, Stockholm, Sweden. The paper's title was "World-Population and Reproduction Health: Quo Vadis Homo Sapiens?"

It is not disaster to be unable to capture your ideal, but it is a disaster to have no ideal to capture. It is not a disgrace not to reach the stars, but it is a disgrace to have no stars to reach for. Not failure, but low aim is sin.

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