Inaugural Lecture Series 128

HEREDITY, GENES AND EVOLUTION

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Professor of Zoology

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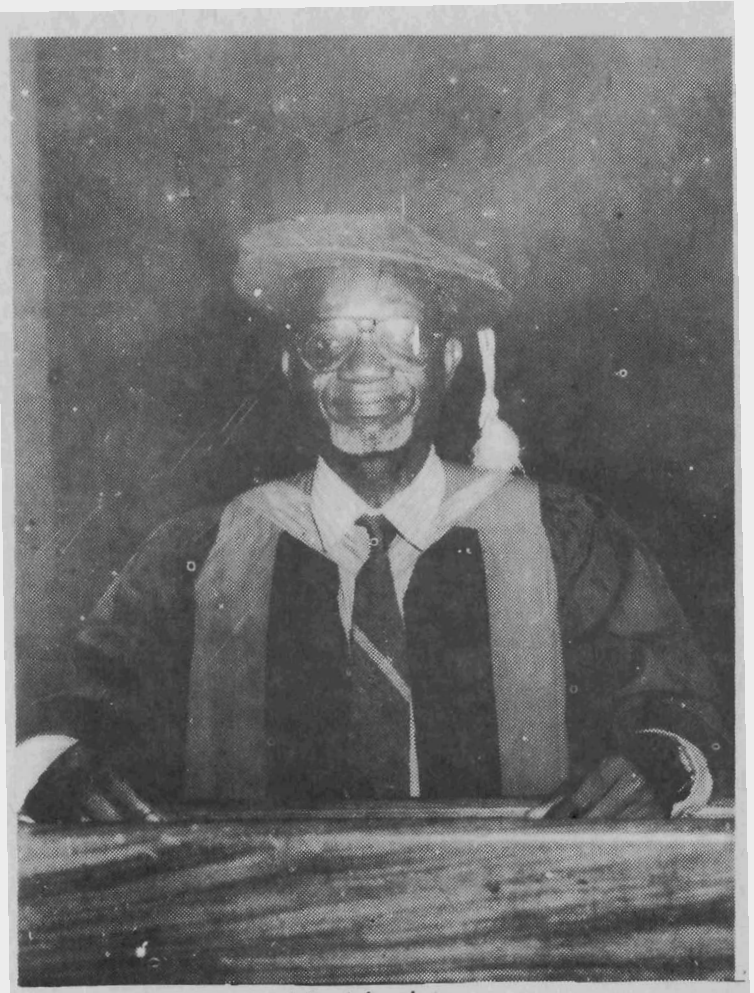

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HEREDITY, GENES AND EVOLUTION

INTRODUCTION

Mr. Vice Chancellor Sir, fellow academicians, staff of Obafemi Awolowo University, distinguished ladies and gentlemen; it gives me great pleasure to have this opportunity to present to you a minuscule of information on the wide and crucial science of genetics under the title, **Heredity, Genes and Evolution**. In preparing the address, I have taken a cue from a similar one published in the *Annual Review of Biochemistry* in 1990 by Oliver H. Lowry, a great biochemist and physiologist, and in so doing, I will discuss those events that paved the way to my involvement in academics and in particular, genetics studies; give a brief overview of basic genetics; discuss my activities in the fields of cytogenetics and molecular genetics at Ife and elsewhere; make a brief excursion into nature's biological engineering designs; and finally, consider the important issue of organic evolution including the evolution of humans.

Growing Up

Being the second to the last child of a large peasant family, it is not difficult to see that to be sent to school, by the family, was clearly providential. The march to being an academic started in August 1956, with an admission to College Africa, the way Government College Ughelli was popularly referred to at that time. After completion of the Cambridge West African School Certificate Examinations in December 1961, and with no funds to pick up the offer of a Higher School at Ughelli, I took up a job between January and October 1962 in the Western Region's Ministry of Lands and Housing as a Survey Draughtsman. The experience here was significant in the life of a young man, such as I was then, because it exposed me not only to the responsibilities of life out of school, but also to the micro- and macro-politics, within the strictly hierarchical civil service, in the Region, and the country at large. These experiences reinforced the desire not to relent until one had a university degree with all its implications at that time. A stint of one year at the Technical College, Ibadan, as an Electrical Engineering student with full sponsorship from the Ministry of Works and Transport, was abruptly but freely terminated during a practical session in September 1963, when it was confirmed to us that the diploma of the institution had then not been recognized. A day after leaving the Technical College I secured an appointment as a pupil teacher at the Premier Grammar School, Lafenwa, and immediately commenced an evening class for the GCE (A level) at the Abeokuta Evening Institute.

Having qualified for admission into any of the Nigerian Universities by 1965, attention was turned to looking for funds. The Western Region, with its unparalleled education policy, came to the rescue in 1966 with a full scholarship to study Zoology in any Nigerian University! Ife naturally became the institution of choice when I recieved admission offers from Ibadan for Biochemistry, Lagos for Biology and Ife for Zoology. I have since had every cause to thank God for that choice.

The Ife Experience

In 1969, Ife, under the dynamic tutelage of Professor Oluwasanmi, was carrying out some progressive reorganization of the Zoology and Botany departments into a Biological Sciences Department with five semi-autonomous units, of Biochemistry, Botany, Genetics, Microbiology and Zoology. This was in line with such progressive steps elsewhere. I was thus recruited into the Genetics Unit as an Assistant Lecturer some three months after graduation in June of that year. Although Genetics was always regarded as a difficult area (in retrospect, I now know that that view was held out of ignorance about the subject matter), nevertheless I had preferred that to the alternative post of Fisheries Officer in the Civil Service. This saw me taking my postgraduate degrees in Molecular Genetics to complement my other colleagues in the Unit (Professor Olorode, cytogenetics and systematics and Dr. Awopetu, population genetics and human genetics). Unfortunately, the idea of Biological Sciences did not go beyond 1978 when only the Genetics Unit was dissolved and the academic staff redeployed to the departments in which they obtained their first degrees, which were either Zoology or Botany. Today the genetics group has survived in the two departments, and I make bold to say that Ife has since been the source of highly trained geneticists for the research institutes, the government and other tertiary institutions in the country. One of the students that graduated under the Genetics Unit of the Biological Sciences dispensation, and who is one of the group's several doctorate graduates, is Dr. Julius Faluyi, Reader in Botany, and currently Vice Dean, Faculty of Science.

THE RISE OF GENETICS

Genetics is described as a crucial science because it involves studying the elements of life in all living systems, from viruses through unicellular organisms to the higher plants and animals. It is also about studying the way in which the general and unique characteristics or traits of individuals in any group *are* transmitted faithfully from generation to generation. This is **Heredity**. No living organism or being is created *de novo*. Every organism is derived from pre-existing forms, which are its parents, and the *totality* of any particular organism is what it is because of the genetic information or hereditary attributes handed down to it by its parents.

In the contemporary context, genetics may be described as a new science, since the name **genetics** came into being only in 1901, following the rediscovery of the work which Mendel did in the 1860s. Gregor Mendel (1822-1884) was an Austrian monk who took particular interest in, and studied how characters were transmitted from generation to generation. His experiments were carried out in his garden on the garden pea, *Pisum sativum*. He obtained results that gave him definitive ratios when he considered one, two or three pairs of contrasting non-interacting character states, and from these results, Mendel proposed two rules of heredity. One, that individuals carried character-determining particles (now to be known as *genes*), in pairs and that these genes segregate into gametes (sex cells) that would participate in the production of offspring for the next generation. Two, that the segregation was a random and independent event. These rules have been sustained by studies on the behaviour of chromosomes during the processes leading to the production of gametes (gametogenesis) and fusion of these gametes (fertilization) to form a new organism. Furthermore, Mendel posited that the pair of genes controlling a trait existed in two forms/alleles, the dominant and recessive alleles, such that when the two alleles are of the dominant, or one dominant and one recessive, only the dominant trait is expressed, and the recessive trait is expressed only in the absence of a dominant gene.

Today, from the molecular studies of genes and their alleles, it is known that the dominant genes are those with the right blue-print to specify functional proteins while the recessive genes contain a changed blue-print which products do not function as the dominant counterpart *or* do not function at all. All living organisms, including humans carry a number of such recessive genes which are either expressed immediately, or are latent, to be expressed several generations later.

In nature, the expression of a trait is often affected or modified by other genes, hence any one character state may have several variants. Also, several genes may participate in the expression of one character state, for example, several genes probably participate in the determination of natural skin colour in humans, where the colour ranges from ebony black to almost paper white. One skin colour phenotype that is common to all human races is albinism. Albinos are perfectly normal individuals in whom one of the genes involved in the synthesis of the skin pigment, *melanin*, is changed (recessive), and fails to produce any pigment because one of the genes involved in the chemical pathway from the amino acid tyrosine is faulty. This trait, like all other genetic attributes in humans, can be studied by analysis of pedigree and

the person in which the condition was first observed in the pedigree is the propositus if male, and proposita if female.

Since the turn of the century, genetics has blossomed tremendously. Today, the amount of information on genetics that is available to the scientific community and the world community at large is enormous. In humans, a number of hereditary diseases have been identified and are being studied at the chromosomal and molecular levels, and genetic counselling is an important aspect of the management of such diseases. Genetics studies have shifted from being mainly descriptive, to solving the problems associated with the mechanics of the processes that had been observed and described. Thus the parallel between inheritance and behaviour of chromosomes in cells established *cytogenetics*. Chromosomes are a complex combination of the macromolecules, Deoxyribonucleic acid (**DNA**), and proteins, especially the basic proteins. The ability to fractionate cells and study individual molecules in the cell gave birth to *molecular biology* of which *molecular genetics* is an important aspect. Today most problems in biology are studied using the molecular biology approach.

MY ACTIVITIES IN THE FIELD OF GENETICS

Since 1970, my studies and research have largely been in the area of Molecular Genetics, with additional studies in Cytogenetics, of diverse animals. The highest denomination of my studies therefore is the cell, and hence my data have come from direct microscopic observations of chromosomes, readings made from UV spectrophotometer to detect and measure amount of DNA, and assessment of radioactivity incorporated into DNA in scintillation counters or on photographic films, all in the laboratory.

The Animal Cell

The cell is the smallest building unit of multicellular organisms. It consists basically of cytoplasm which is enclosed by a semi-permeable membrane. The cytoplasm is filled with various cell products including proteins, fats, carbohydrates, other membranes, *et cetera*, and the organelle, mitochondria which is the source of the energy molecules for driving the various biochemical reactions on which the cell's life, indeed the organism's life depends. A double membrane delimited nucleus occupies a somewhat central position in the cytoplasm, and contains the chromosome complement of the cell. The life of any multicellular organism starts from a single cell, the **zygote**, which results from the fusion of two gametes, one of which is contributed by each of the parents. The nucleus of the zygote carries the genetic blue print for all of the organism's growth and development through adult-hood to death. The zygote develops to an adult by repeated equal cell divisions known as *mitosis*, in which all the products carry the same genetic make up as the zygote. The life of an organism behaves like an automated system, which once activated proceeds from one stage to another, to a logical end (death), unless of course terminated by any of many courses. An intriguing question that has caught the attention of researchers for long is whether the genetic blue print also contains information that determines the onset and progress of ageing and consequently death, or ageing is the culminative result of wear and tear of the body tissues. Regardless of the contribution of the latter, it is apparent that ageing has a genetic basis since different animals have life spans that are species specific. Most animal species have life spans that are less than half of that for humans, while tortoises may live for four to five times as long as humans.

The adult organism may consist of billions or trillions of cells. Each cell has a specific task to accomplish, and represents a working unit. The multicellular organism has specialised tissues and organs which perform various functions, all geared towards the survival of self, and perpetuation of the kind (species) via the process of reproduction. To fulfil this injunction therefore, an animal's activity while alive is devoted first and foremost to feeding, then reproduction. You can confirm this by observing your domestic animals or the insects around you. Rest, shelter and other activities may come later.

The Cell Division Cycle and Cytogenetic Studies

The CellDivision Cycle

Actively dividing cells, such as found in the bone marrow of vertebrates, the ganglia of insect larvae, the testes of all animal groups, (and for plant enthusiasts, in the root tips and young shoots), go through a cycle known as the *cell division cycle*. There are four broadly define phases, designated G_1, S, G_2 and M. Cells that complete mitosis go into G_1, when lots of proteins and other cell components are made and the cell increases in volume. Cells normally perform their functions in tissues and organs at this phase, and they are prevented from advancing to the next stage by being held at a point towards the end of the phase called the *arrest point*. The duration of the cell at this phase is highly variable. Zygotic cleavages (division), lack this phase, while liver or skin cells may stay at this stage for thousands of hours. From the G_1, the cell advances into the S phase when the whole DNA, and by implication, the gene complement is duplicated exactly *once*, and the cell passes into a short G_2 phase during which the cell prepares for the actual division into two, i.e. *mitosis*, M.

The reproductive organs which in animals are, testis in the male, and ovary in the female carry out a special type of cell division, called *meiosis*, during which the cell undergoes two rounds of division after only one round of DNA duplication. The result is the production of haploid sex cells or gametes which carry only half the number of chromosomes present in the body cell. Significantly, all of the products of this division are genetically different because all the genes on the paternal and maternal chromosomes have been shuffled by *recombination* events during the meiotic division. This important behaviour is universal, and it is the source of the paradox that progenies and parents are alike, yet no two individuals in a family are identical, except for monozygotic siblings. In short, meiosis is the source of variation among living things and a crucial prerequisite for organic evolution in organisms that reproduce by sexual means.

Over the years I have been involved in research spanning two aspects of the cell cycle. The first were cytogenetic studies carried out at Ife on the types and behaviour of chromosomes in the mitotic and meiotic division phases in one species of fruit bat, and eight reptilian species, while the second were molecular studies on the programming of DNA synthesis during the S phase, carried out at the Institute of Molecular Biophysics, Florida State University, U.S.A.

Cytogenetic Studies

The cytogenetics procedures currently in use in my laboratory were acquired during a three month study leave to the Department of Pediatrics, East Tennessee State University Medical School in 1982. The technique was that used for determining the karyotype in cells extracted by amniocentesis, or the blood, and then cultured in the laboratory. The procedure has been adapted in my laboratory for studying mitotic chromosomes from the bone marrow of vertebrates. With materials bought from grant 1425FX, we were able to describe the chromosome complements of the African fruit bat, *Eidolon helvum*, and significantly identified the Y chromosome as a minute chromosome (often called microchromosome), and we established the 2n number as 34 instead of the previous suggestion of 33/34 for the male and female respectively (Adegoke and Nadesan, 1986).

In the suborder Lacertilia of the class Reptilia, we have published the karyotypes for the Rainbow lizard, *Agama agama agama*, 2n=44, (22 of which are microchromosomes). (Adegoke, 1988). Others are the wall gecko, *Hemidactylus brookii angulatus*, 2n=40, the chameleon *Chameleo senegalensis* (?) 2n=18, the skinks, *Mochlus guineensis*, 2n=30, including four species of *Mabuya*, *M. blandingi*, 2n=32, *M. affinis*, 2n=32, *M. maculilabris maculilabris*, 2n=32, and *M. quinquetaeniata sharica*, 2n=32 (Adegoke, 1984; 1985;

Adegoke and Ejere, 1991). All these karyotypes, like other reptilian karyotypes contain a sizable number of microchromosomes, often about half of the chromosome number. The reptiles share this feature with birds. Interestingly, the karyotype in the genus *Mabuya* shows a high level of homogeneity. Nine species, including the four karyotyped at Ife, out of ten species karyotyped worldwide, have 32 chromosomes each, the exception being one species, *M. striata*, with 2n=28 (Dalfai and Talluri, 1969).

These reptilian karyotypes are first time determinations, and up till date, probably represent the only reptilian species karyotyped in this subregion. This explains why the only West African listed on the Registry of the over five thousand strong World Herpetologist League is the speaker. This is a rather poor reflection of our interest in our environment since the region has a plethora of reptilian species waiting to be studied. Meanwhile this group of animals is seriously threatened with extinction through the efforts of humans who destroy their habitats, kill them for food or simply kill them on sight just because they are reptiles!

Apart from the detailed descriptions of the chromosomes, we also observed that some cells consistently violated the control normally in place at the end of the metaphase stage, i.e when the chromosomes are ready to segregate equally into the two halves of the cell, prior to the actual division of the cell into two. Such violations yielded cells containing more than the usual 2n number of chromosomes, such as 4n, 8n and even 16n! These are great numbers indeed, and such cells are called *autopolyploids*. They were observed in the bone marrow cells of the bat, but not in the bone marrow of any of the reptilian species. However, autopolyploids were found in large numbers in the testes of all the reptilian species but not in the testes of the bat.

As mentioned earlier, the total DNA complement is duplicated exactly once before the cell reaches the division phase, but autopolyploidy indicates several rounds of DNA duplication without the cell going through a division. Thus we coined the concept of "*anaphase failure*" as being responsible for autopolyploidy in both the bat bone marrow and the testes of the lizards. Recent findings have shown that a mitotic block actually does exist just before the onset of anaphase, and cells may choose to keep this block in place and hence prevent anaphase, as shown: ***prophase - metaphase -*anaphase - cytokinesis*** (cell separation). (* = block)

We have explained these results as follows; that autopolyploidy as seen in these cells is a strategy to produce several cells rapidly while saving energy for several rounds of anaphase which may then occur in series, utilising the same energy molecules simultaneously in a polyploid cell. The fruit bat with its daily long flights to search for food uses polyploid cells to produce very large number of red blood cells to cope with respiratory demands, since

the cells extracted for study were erythrocyte precursor cells. Mice and rats kept in cages at the Biological Gardens Unit did not have polyploid cells in their bone marrow. In similar manner, the testes of the reptiles studied undergo active spermatozoa production at limited periods of the year, so that the polyploid cells would enhance their spermatozoa production capacity during the limited period (Ejere, 1997). This is plausible because: 1. No abnormal pairings were observed in these cells as would be expected if the polyploidy originated as an error in the division cycle. 2. The incidence, up to 5%, is higher than would be expected if the polyploidy was due to an abnormality. 3. Polyploid cells were observed in the process of completing the meiotic division, a situation that will not be observed if the cells were abnormal. These views were published in 1988 and they have not been challenged, but rather got international support.

Molecular Basis of Heredity

The S-Phase and DNA Synthesis

For my doctoral research, I chose a topic that had direct bearing on the main research focus of my supervisor, Prof J. H. Taylor. Taylor (1960, 1973, 1974), had been working on the mode of replication of DNA in eukaryotes following the elucidation of the process of DNA replication in bacteria in 1958 by Messelson and Stahl. Specifically I had to design experiments to test whether DNA synthesis was programmed such that the same molecules always replicated at the same period during every cell division cycle. The experiments were rather complicated and I will discuss only the essentials. One of the experiments involved feeding radioactive ^{14}C-labelled thymidine to cultured Chinese hamster cells synchronized to the G1 arrest point with hydroxyurea aided by mitotic selection, for 30 minutes, and then resynchronizing them to the second, third or fourth cycle G_1 arrest point also with hydroxyurea and mitotic selection. Once released from the arrest point, the cells were followed through the whole cycle by feeding them with a second type of radioactive thymidine (^3H), at 30 minute intervals over a period of 30 hours. A good alarm clock was always an essential companion especially in the small hours of the morning!

The results from the experiments showed reasonably clearly that the programming hypothesis was true, and the findings, which were published in 1977 generated a lot of interest world wide (Adegoke and Taylor, 1977). But the results could probably not have been otherwise, because more recent findings have shown that the whole cellular functional mechanism is highly *automated* such that for a cyclic event as the cell division cycle, a strictly controlled and ordered pathway must have evolved for the cell to follow.

Movement through every step in the cycle is controlled by a menu of gene products. A fault developed in a gene controlling one of the steps in the series may lead to untoward consequences. For example, if a step in the sequence of events which causes the cell *to stop* at the G_1 arrest point is faulty, then the induced signal remains permanently turned *on* in that cell, and so continues to divide infinitely since all its progeny also carry the fault. The consequence could be a tumor or a cancer

The Gene, Cloning and Sequencing

What is a gene?

Earlier in this address I stated that genes were DNA molecules, which form complexes with proteins to form chromosomes. It is also known that particular genes are consistently located at particular loci on chromosomes hence it is possible to map genes on a chromosome. This property made earlier researchers to assert that genes were located on chromosomes like beads on a string. With the information at our disposal, a gene can be *defined* as a stretch of DNA molecule which specifies a particular protein or peptide chain. The first genes put together at the inception of life must have been simple, and specified proteins necessary for self reproduction. The gene *per se* does not participate in the physical determination of a phenotype, but rather, it acts as a repository of information necessary to determine the appropriate protein whose action, or non-action, determines the particular trait/s.

Structure of DNA molecule

Structurally, DNA consists of two strands wound on each other in a double helical fashion. Each strand is made up of units called nucleotides, each nucleotide consisting of a phosphate, a ribose sugar and a nitrogenous base attached to the sugar. There are four different types of these bases, adenine (**A**), guanine (**G**), thymine (**T**), cytosine (**C**), and the **order** or **sequence** of these bases in the DNA molecule *dictates the existence* of life itself. One recognizes the weight of such a statement, but in so doing, I would like to call attention to one fact, that DNA, from whatever source, has the same components and general characteristics as DNA from any other source. This is why it is possible to integrate a viral DNA into bacterial, plant or animal DNA; why it is possible to isolate a human gene (DNA) and integrate it into bacterial DNA where the product of that gene is expressed as if it were a bacterial gene. Such a product can be purified, for example in biotechnology drug production. As far as is known, DNA is the only molecule that is capable of replicating or duplicating itself. This property underlies the process of cell division which is the basis of development, growth and heredity.

Expression of a gene

When a signal is received by a cell that the product of a particular gene is desired, the gene is faithfully copied into an RNA molecule (messenger RNA or mRNA for short) in the nucleus. The mRNA is transported to the cytoplasm where the information is translated into a covalently bonded sequence of amino acids (protein), using the genetic code system (Appendix I), in a process called *translation*. The process is much more complex than shown in the figure, and has a series of control mechanisms which regulate the amount of product. Quite often, the nascent gene product may undergo processing to give the active form. The protein may be an enzyme which catalyses a reaction, or just a structural protein component of the cell.

Organization of DNA in Chromosomes

Studies on the organization of DNA in chromosomes of eukaryotes indicated that the DNA is highly packaged by proteins into chromatin fibers. (DuPraw, 1974). The packing is such that 1 micron or one millionth of a meter, of the chromatin fibre contains up to 100 micron of DNA. The folding pattern of the DNA within the fibre is still not quite understood yet. But, so compact is the folding that in one human cell, with a total DNA length of about 1 meter, is packed into a nucleus of 10 micron in diameter. Indeed the DNA in the trillion cells of an average man is estimated to be about 320 million kilometers long! So thin is the DNA molecule that the DNA of T_2 has several folds even though it is only 0.056mm long. The total DNA in a human cell is estimated to have at least 100,000 to 200,000 genes, taking into consideration the presence of some 30 to 40% highly to moderately repetitive DNA. That is, sequences that occur in multiple copies, sometimes up to 1 million copies, per haploid genome and whose functions are still not quite fully understood.

Repetitive DNAs

This highly repetitive species of DNA fascinated me considerably, and I have spent considerable time studying them in a few animals. Between 1971 and 1972 I determined the proportions of the four nucleotides in the highly repetitive DNA of the Chinese hamster, *Cricetulus griseus*, a rodent, as part of my masters degree project. Using thin layer chromatography, the highly repetitive DNA which accounted for about 8% of the genome, had a base composition of 49.2% GC, which was a much higher proportion of guanine and cytosine than the 41.9% for the total DNA. The base composition of the total DNA was in consonance with figures obtained for other mammals. In interpreting these results, cognisance was taken of the fact that other results

from Taylor's laboratory and elsewhere had shown that the DNA synthesized at the beginning of the S phase of the mammalian cell cycle was always rich in G and C, and so it was hypothesised that the highly repetitive sequences probably have some role to play in the initiation of DNA synthesis. This hypothesis has however not been followed further, since the whole process of DNA synthesis is now fairly well understood.

At Ife, my research on the highly repetitive DNA of eukaryotes got a boost in 1981 when, with a modest grant of N15,000, I was able to purchase some much needed pieces of equipment and analytically pure chemicals direct from overseas using the University Indent System. With these I was able to equip my lab for molecular genetics experiments. The first highly repetitive DNA investigation done in the new lab was on the genome of the African fruit bat, *Eidolon helvum*. In collaboration with a postgraduate student, Oyenuga, the complete reassociation profile of the total DNA of the bat was determined, and it had a $Cot_{1/2}$ of 1,570 nucleotides x secs./liter, indicating a genome complexity similar to those of other mammals (Oyenuga, 1989). The reassociation profile effectively describes the complexity of the genome, and by implication that of the organism. The properties of the highly repetitive DNA which constitutes 7% of the total genome were also investigated, and the sequences were found to contain a GC rich component, the base composition of which was similar to that of Chinese hamster (Adegoke, 1982).

Working with two postgraduate students, Ighavini and Onuigbo, we investigated the reassociation profile of the total DNA and also the properties of the highly repetitive DNA of the Rainbow lizard, *Agama agama agama*. Approximately 15% of the genome of this animal is highly repetitive, and it contains a GC rich stable fraction which accounts for 8% of the genome. The reassociation profile for the total DNA of the animal has a $Cot_{1/2}$ of 370 This is a much lower figure than that obtained for mammals, and indicates a lower level of complexity in this animal than mammals.

In addition to the genome of *Agama*, we also investigated the behaviour of the DNA of the gecko, *Hemidactylus brookii angulatus*, on hydroxyapatite columns, and compared these with similar DNA from the albino mouse *Mus musculus* and the bacterium, *Escherichia coli*. An interesting finding from the experiments was that the total DNAs from the reptiles could be fractionated into two basic components, while similar DNA from bat and mouse (mammals) or *E. coli* under similar fractionation conditions gave only one band each. An innovation introduced into the technique of DNA fractionation on hydroxyapatite columns was the use of 1M urea in the phosphate buffer. This improved the reliability of the results and one could obtain particular DNA fractions without recourse to expensive gadgets (Adegoke *et al.*, 1991).

In 1983, the university research committee approved a grant of N30,000 for my research, based on the report of the previous grant. The ambition was high. the lab was going to be launched into the biotechnology age. Proforma invoices were obtained from various suppliers overseas, revalidated many time over, lots of paper work, memos here and there. Finally the elusive Import License was obtained. The ambition was however not to be realised after all, as SAP descended heavily on us in September 1985 while the university's Central Stores' bureaucracy stalled the utilisation of the Import License. With the naira then exchanging at four to a dollar, the whole grant could no longer purchase any one of the key equipment. For any further meaningful research then in molecular genetics, I had to turn to some overseas laboratories, since the isolation of highly repetitive DNAs, or any species of DNA for that matter, was now done by the more precise method of restriction digestion which produced reproducible DNA fragments.

DNA cloning and Restriction Enzyme Digestion

In 1990, Dr. Ulfur Arnason of the Department of Molecular Genetics at the Institute of Genetics, University of Lund in Sweden applied for, and obtained a Swedish Institute Fellowship on my behalf for a nine-month stay in his laboratory. Dr. Arnason had also been studying the highly repetitive DNAs in some whales and carnivores (Arnason, *et al.*, 1988; Arnason and Widegren,1989). This was my first practical contact with the gene cloning methods of molecular genetics. In this technique, a fragment of DNA obtained after digesting total DNA with one or more *restriction enzymes* is ligated onto a plasmid (small circular DNA molecules which carry a few genes and are found in bacteria and which are capable of transferring from one bacterial cell to another) or small virus, and the chimaera is allowed to infect a bacterium which replicates several times to produce enough progeny for use in infecting several more bacteria which, after growing for 5 to 6 hours at 37^{0}C, would have produced several hundred thousand copies of the same sequence (cloned!) which can be utilised for further experimentation, such as the determination of the nucleotide sequence, or in biotechnology.

Restriction enzymes bind to, and cut double stranded DNA at specific sites within or outside of a specific nucleotide sequence known as the *recognition sequence*. In majority of the enzymes, the recognition sequence is some 4, 5 or 6 nucleotides long and display two-fold symmetry. Restriction enzymes are normally isolated from microorganisms which have evolved them as protection against infection by viruses and other extraneous DNAs that may get into their cell. The specificity of these enzymes has been exploited to obtain desired sequences or genes from total DNA of any organism.

With genetic probes already developed from highly repetitive DNA isolated by the previous methods, it was possible to isolate, clone and determine the nucleotide sequences of the repetitive DNAs from the total DNA of *Balaena mysticetus* and *Eubalaena glacialis*, and also in conjunction with Arnason, similar sequences, from the remaining eight species of the extant mysticete whales. Characteristically, all the sequences are GC rich, with nucleotide composition corresponding approximately to those of the stable fraction from the highly repetitive DNAs from hamster, the fruit bat, Rainbow lizard, gecko and mouse investigated by me (Adegoke, 1982, 1984; Adegoke *et al.*, 1991; 1993). Other workers have also since reported GC rich highly repetitive DNAs from all animals investigated.

Some of the other salient features of these sequences were that the repeats which were estimated to have evolved and amplified some 20 million years ago, i.e, before the diversification of the mysticete whales, had a highly conserved portion in which the sequence hardly varied between species. This is an example of slow sequence evolution. All the sequences have a unique portion which is typically 212 bases long in all the mysticete whales except *Caperea marginata*, the pigmy right whale in which the sequence is 211 bases long. One factor that is probably responsible for the slow evolution rate is the relative stability of the oceanic environment in which these animals live and which saves the genomes from undue environmental stress. Furthermore, the seas provide one big common environment with no barriers against interbreeding. Following the unique portion is a series of repeating hexamers, ie, six-base long motifs or units. Prominent among these haxamers is TTAGGG which constituted 35% - 50% of the total repeats. Indeed a close observation of the other hexamers would indicate that these other motifs apparently arose from a basal TTAGGG motif by changes which were mostly base substitution events, and a few by deletion or addition of bases. For example, TTTGGG, TTAGGC, TTACGG, TCAGGG, and so on. A boost for a possible *in vivo* function for these highly repetitive DNAs came with the finding that the TTAGGG motif and its derivatives were closely associated with the telomeric or subtelomeric portions of chromosomes, where they are speculated to play a stabilising role. Interestingly, the TTAGGG and its associate repeating motifs have been found to be present in the chromosomes of all animal groups, including the Chinese hamster and humans (Moyzis *et al.*, 1988; Meyne, *et al.*, 1989; Vogt, 1990). Recently however, Highly repeated sequences in form of hyper variable mini- and microsatellites have been applied in DNA finger printing forensic investigations, such as determination of parenthood or as convincing evidence in a serious crime such as the celebrated murder case resolved by the use of DNA minisatellites, and reported in *Nature* by Hagelberg and colleagues in 1991.

Mitochondrial DNA

Towards the end of the 1980s, great interest was being generated in the mitochondrial genomes of eukaryotes as possible clues to solutions of problems in evolution and systematics. The mitochondrial genomes were found useful for the following reasons. 1. The genome is reasonably easy to isolate by first isolating the organelle, and then the mtDNA from these. 2. The genome is haploid, and hence easier to analyse in terms of mutant genes. Most of the features have thus been worked out. 3 More significantly, mitochondria are maternally inherited, and hence it is possible to trace the history of a species through the molecule (Irwin, *et al.*, 1991). The first mitochondrial DNA to be completely sequenced was the human mtDNA, in 1981. It contains 2 ribosomal RNA genes, 22 transfer RNA genes and 13 protein coding genes. All subsequent mammalian mtDNAs sequenced so far have the same number of genes in the same sequence.

Thus in 1992 and also in 1997, I had the opportunity of carrying out some investigation on mitochondrial DNA in Arnason's laboratory. The analysis in 1992 involved the sequencing of the cytochrome *b* gene and the control region from six species of cervids using universal primers, the polymerase chain reaction (PCR) technique and restriction enzymes to isolate the genes. The sequences of cytochrome *b* gene vividly illustrate one point, that a gene can tolerate a number of changes in the information it carries and still specify a functional protein. This is due to the fact that some changes in DNA do not produce a change in the amino acid sequence because of the degeneracy of the genetic code, which in some cases allows more than one code to specify an amino acid. Also in some cases, even when there is a change in the amino acid, the replacement amino acid may not affect the activity of the protein. Indeed while all cytochrome *b* from different animals perform the same function in the energy transducing pathway of the cell, it is highly unlikely to have two genes specifying this protein having the same DNA sequence, even within the same genus. A general rule however is that portions of the genes that are essential to the **integrity** of essential proteins are conserved, and have only very little room for variation. Should an intolerable change occur in such a region, then the organism does not normally survive past that point of its life when the product of the gene is required, and hence such variants are not seen in the population.

The mtDNA of pangolin (Manis tricuspis)

In 1997, Arnason and I decided to look at the (mtDNA) of the pangolin, *Manis tricuspis* , following consistent discrepancies in the systematics of the animal. Pangolins (*akika*) are limited to Africa south of the Sahara, and southeast Asia. And so between May and September of that year,

I took along the liver from a male pangolin to Lund and determined the entire 16,564 nucleotide sequence of the mtDNA of the animal. The restriction digestion pattern of the mtDNA was first determined using a menu of nine restriction enzymes. Thereafter, a total of 5 restriction enzymes, SpeI, XbaI, BamHI, BclI and BlnI, were used to generate the clones for direct ligation and sequencing. SpeI and XbaI were the primary cleaving enzymes, while the others were used as secondary enzymes to create cloneable fragments in some of the large fragments obtained from the primary cleavage. The sequence like others have been deposited at the European Molecular Genetics Gene Bank. A preliminary computer analysis of the genome, using nine out of the thirteen protein coding genes gave a provisional phylogenetic. The tree which indicated that *Manis*, which has hitherto been classified with armadillo may indeed have its own separate order. This way, DNA analysis is being used to reevaluate previously determined phylogenies, and resolve controversial phylogenetic cases. Also, all the information accumulated in form of DNA nucleotide sequences determinations are part of the important and necessary job of germplasm conservation in which vital information on the genomes of our biosphere are safely stored for posterity. In this regard it is my wish to see the establishment of an African Gene Bank for proper documentation of African Germplasm. I am sure the OAU Computer Centre has the wherewithal for such a task.

CHANGES IN GENES AND EVOLUTION

In nature, perhaps one phenomenon that is universally recognized as permanent is *change*, that is a change of one form to another, often slowly, sometimes accelerated. This is **evolution**, and we see it around us all the time, in our culture, religion, profession and so on. When the study of changes pertains to living forms, it is called **organic evolution**.

Spaceship Earth and Life

The earth on which we live behaves like a space ship hurtling through the void at about 107,000 km/hour, spinning like a top at a velocity of about 1,700 km/hour at the equator, and never static for a moment. With life originating under such conditions, the dynamism and variability of the molecule of life, ie DNA, is a **sine qua non**. Life forms have thus subsisted within the outer 20 km of the earth's mass where nature has, on a continuous basis, been molding and remolding the same elements, particularly carbon, nitrogen, hydrogen, oxygen, silicon, *et cetera* into various designs through *changes* induced into DNA molecule. Such changes in the molecule include addition or deletion of one or more nucleotides, substitution of one or more

nucleotides, and inversion of some nucleotide ...ll these changes have the effect of changing the *sequence* of the nucleotides in the molecule.

The changes that are induced in any DNA sequence/s, are called *mutations*. A mutation that occurs in the somatic (body) cell of a multicellular organism is not transmissible to progenies, and either kills the cell in which it occurs, kills the organism in case of cancerous mutation, or as happens in most cases, remains latent in the organism till death. Only those mutations that have a probability of being transmitted to the next generation, that is, that occur in gametocytes are of consequence in the determination of subsequent life forms. Such consequential mutations accumulate, and are continuously but faithfully redistributed among the population by recombinati... events every generation, and produce subtle modifications in the phen...type. Such modifications will eventually produce varieties, and when varieties of a common stock are effectively separated from each other such that they are prevented from interbreeding among themselves, then, over time they may evolve into separate species which will no longer interbreed freely. Thus if two varieties were so separated, then two species would have evolved from the original stock whose representative may only be seen as fossil. Alternatively, the environment, with all its various meanings, may change to favour the survival of one variety over the other, and the surviving variety reproduces abundantly to replace the original stock and the unfavoured variety. In this case only one species has evolved from the original stock. In the absence of a barrier or drastic environmental change, forms are continuously changing imperceptibly such that over several generations, the existing forms come to differ from their progenitors.

Causes of Mutations

Scientific evidence point to the fact that several factors are responsible for changes in the DNA. These include: 1. the earth's natural activities such as volcanoes, quakes, magnetic field, vagaries of weather, and other purely natural disasters. 2. The sun's and other cosmic rays which continually bombard the earth. 3. The food and feeding habits of living organisms. 4. Activities of naturally occurring transposable DNA elements which move from ... site to other multiple sites on chromosomes, causing changes to gene sequences, especially the gene regulatory sequences, such that they may ... the timing, level or spatial pattern of expression of structural genes. These elements account for at least 10% of the genome in higher plants and animals. 5 And lately, man's immense contribution from industrial and technological advances in which the amount of radiations in the environment is increased by direct generation from all types of commercial and domestic machines, and from advanced weapons explosions (in this regard it is notable

that medical reports in 1997 showed that incidence of cancer increased, up to six-fold, in Iraq as a direct consequence of the weapons used in the 1990 Gulf War). Also, the millions of tons of industrial wastes, radioactive materials, cigarette smoke, and so on, dumped or infused into the environment, have been variously identified as mutagen in animals and various categories of people (Adegoke, 1980). One lesson to be learnt here is that while it is important for us to prevent over exposure to some of the factors that we know can cause changes in DNA (smoking for example), nevertheless it is not possible to escape from ...se changes ...t are purely due to the earths behaviour.

ANIMAL EVOLUTION

The earth, our earth, has played host to life in various forms at one time or the other since some 2 billion years ago. This was when the first fossil protozoa and sponges (two cell layered animals) were detected, and spanned some 1.4 billion years, before fossils of the first invertebrates comprising molluscs, crustacea and echinoderms were observed on earth some 600 to 500 million years ago. The first vertebrates appeared about 500 million years ago. Since then the vertebrate groups have at one time or the other risen and dominated the earth, and then fallen. Thus it was the age of fishes 500 400 million years ago, the age of reptiles, 200 to 65 million years ago, and the age of mammals since approximately 65 million years ago till present, and man reigns supreme.

The human species shares so many features in common with all other living things that it is difficult not to see the link and lineage. All the religions of the world realise and accept this fact, for example see *Ecclesiastes 3, 19 - 21*. However, just as each animal group has its own inherent characteristics, so does human. The human brain is primarily his unique characteristic, being bigger than that of any other animal, and having the quality of *reasoning* and ability to learn. His power of speech, emotional outlay and cultural activities including religion are also unique, and set him aside from other animals. Nature has carefully engineered his genes for all those characteristics over several million years. His genes are however changing, and soon, perhaps less than half a million years hence, he would have taken a completely different form. And what that form would be been the subject of a number of science fiction paperbacks.

Evolution of Humans

Human evolution has, from the beginning of the proposition of the theory of evolution in the seventeenth century, generated a lot of controversy,

and there is no let up on the arguments. Fossil remains of primates have been collected largely from East and South Africa, and others from Europe and Asia. Information from these collections indicate that about 9 to 12 million years ago, the human-chimpanzee-gorilla lineage diverged from that of the orangutan. Thereafter, about 5 million years ago, the tripartite stock diverged into the human lineage and that of the gorilla-chimpanzee. Since then at least three different types of hominid fossils have been identified that existed between 3 and 1 million years ago (Wood, 1992). These were the Australopithecines (3 million to 800,000 years ago), *Homo erectus* (800,000 to 300,000 years ago) and the neanderthals (300,000 to 100,000 years ago). The Neanderthal man, apparently the closest to modern man, was first unearthed in Neander, Germany in 1856, and more specimens have since been found in Africa, Europe and Asia. There is evidence that it coexisted with modern man before it became extinct. The Neanderthal fossil dating was corroborated recently with the analysis of mitochondrial DNA fragments from the fossil type specimen by Krings and his team in 1997. Mitochondrial DNA analyses have also consistently indicated that the first *H. sapiens* was African. These are based entirely on studies carried out by Europeans or Americans who had access to DNA samples from a few Africans. No doubt the West African subregion which is home to about half of the world's Black Africa population, and with a diverse and robust cultural heritage definitely has its rich historical antecedents underground. These information need to be dug up, and properly identified and compared with those from other parts of the world. One may never be too certain what the meaning of the Caucasian cacophonous support given to the African origin of modern man is, since the older race would have to be more *primitive*! However, today, the differences between races are being minimised due to contemporary civilization which enabled more people to accept the universal equality of mankind, and also to the improved means of transportation which allow peoples of different ethnic nationalities to interact and exchange genes.

Had the world adopted the type of apartheid philosophy such as practiced in South Africa prior to 1994, then with time, and considering the spread of humans over the globe, a number of distinct human species could emerge. But perhaps it would not be too difficult to see that, like our progenitors probably did to the neanderthals, only one of the species, the fittest, would remain.

ANIMAL CLONING

Since the invention of agriculture by human, he has been using his intellect to speed up nature's genetic engineering designs through deliberate breeding programmes. This way, he has been manipulating the genes of plants

and animals for his own needs. He has advanced these designs to cloning whole animals. The antecedents of animal cloning probably have their roots in the experiments of Boveri in 1889, when he fused spermatozoa with the eggs of sea urchins *in vitro*, and found that the cytoplasm of eggs lacking nuclei could also develop into viable larvae. This reasonably simple basic principle has been elaborated to facilitate cloning of higher animals, though it may be complex in accomplishment. Since all the body cells carry the same genetic blue print as the zygote, a transfer of the nucleus of a body cell into an egg devoid of its haploid nucleus, transforms that egg into one with zygotic properties. When such egg is transplanted into an appropriate womb, a new animal which is presumably a replica of the adult from which the body cell was extracted is conceived and given birth to. Recently cloning projects have yielded successes in sheep, cow and mice. If it can be done for these animals, it can be done for humans. Apparently only ethical considerations have so far prevented humans from engineering his kind. How much longer such considerations will hold is difficult to guess.

However, I would like to submit that the disadvantages of doing that far outweigh the advantages for the following reasons: 1. Nature is a better genetic engineer, always with time on its side, than humans, and if cloning were advantageous, then nature would have engineered it a long time ago. In fact the closest to cloning in nature for vertebrates is found in the reptilian genus *Cnemidophorus* in which some species reproduce parthogenetically, wherein an egg is laid without fertilization, and the egg develops into an adult. In these animals, the population size is small and all the members are females! Even here the oocyte undergoes a pseudomeiosis with mixing of its set of genes but producing a diploid egg instead of one with half chromosome set. 2. The somatic cell which will be used in cloning an individual already carries several mutations, and a clone from such a cell inherits all the mutations incurred from the environment as stated earlier, and this means that the new individual starts life with a load of mutations, to be passed on through subsequent generations. Already, human technological prowess has allowed some genes that would have been eliminated by natural selection to be retained in the population. The direct consequence of human cloning therefore will be weaker human physique and possibly also intellect.

SUMMARY

Mr. Vice Chancellor Sir, over the last hour or so, I have tried to convey to you and the audience an overview of some of the information available on some aspects of the general study of genetics, as well as my modest contributions in the field of cytogenetics and molecular genetics of animals in the past 28 years. Genetics straddles all areas of the natural

sciences, basic and applied, because of its universality. Today, any breeding programme (plant or animal) has its base in genetics, selecting those individuals that carry particular genes designed by nature and which we feel are suitable for us - high yield, disease resistance, fast growing, are some of the traits we *select* for in these organisms. Genetics has led to the understanding of some of the basics of life and its constant transfigurations within the outer 20 km or so of the earth's crust into various designs of microbes, plants and animals, following the dictates of the genetic blue print designed for each type. No wonder Orunmila said God made man not to die, but he is only recalled every now and then for renewal so that he sheds the old body and puts on a new one - within the crust or dust!

Mr. Vice Chancellor Sir, virtually all the major scientific discoveries till date have emanated from the Caucasian race, making that race arrogate intellectual superiority to itself. To date, there is no genetic evidence whatsoever to show that the Black race is in any way intellectually inferior to any other race. But no other race can prove this to us but ourselves. In this regard, and in view of the possible dawn of a new era in the country, I would *recommend* that we allow and encourage our brilliant youths to vent their youthful intellectual exuberance in researching into the basic physical and biological sciences. This is where scientific discoveries can be made. In zoology, such researchers should be given the necessary financial support and free hand to dissect worms; cut up the gut of bed bug; collect toads; study the movements of birds; study the shells of snails; assay for the nucleases in grasshopper; study relationship between various animal groups; collect, identify and name all the beetles of Nigeria, and so on and so forth. Such studies will unearth many information not yet available to science, and thereby generate credible hypotheses and theories which may sooner or latter find application in agriculture, pharmacy or medicine. The other races do *not* do more than these! The tropical Africa environment is endowed with fauna and flora richer than any other part of the globe. Nigeria as a country in the subregion is endowed with qualified personnel. The basic information needed to start and prosecute research projects, even at the molecular level are available to us, and all that is needed is the *will* to see a reason for carrying out research in basic biological sciences.

It is also recommended, Sir, that every active scientist in the nation's universities must be given the opportunity to compete for, and obtain some grant every year for his research, with funds set aside annually by the government of the Federation for that purpose as is done in the developed economies. All evidence point to the fact that this country has the financial resources to accomplish this. The N15,000 modest grant I got in 1981 and which was used to equip my laboratory then will today be equivalent to at least N1.8 million. On average, such modest grants from 1 billion naira will get to over 500 academic staff at N1.8m each! At this juncture, I would like to restate, that our applied sciences, natural or physical, will continue to be *wobbly* until the foundation is made *firmer* with continuous research at the basic science level, for example, no meaningful genetic counselling can be done by the most brilliant physician without the ground knowledge of Mendelian genetics as applied to animal and plant species, nor can the most brilliant agricultural expert carry out gene transplant without knowing how to adjust the pH of a buffer.

Today, it is routine to clone DNA. The groundwork for cloning individual mammals has been laid, and it is a matter of a short time before the first human is cloned. It will not surprise me a tiny bit and it will not be a big deal.

Mr. Vice-Chancellor, distinguished, ladies and gentlemen, I thank you for your attention.

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TABLE OF UNIVERSAL GENETIC CODE

Amino Acid	Abbrev.	m-RNA Transcription
1. Alanine	ala	GCU GCC GCA GCG
2. Arginine	arg	CGU CGA CGG AGA CGC AGG
3. Asparagine	asn	AAU AAC
4. Aspartic Acid	asp	GAU GAC
5. Cysteine	cys	UGU UGC
6. Glutamine	gln	CAA CAG
7. Glutamic Acid	glu	GAA GAG
8. Glycine	gly	GGU GGC GGA GGG
9. Histidine	his	CAU CAC
10.Isoleucine	ilu	AUU AUC AUA
11.Leucine	leu	UUA UUG CUU CUC CUA CUG
12.Lysine	lys	AAA AAG
13.Methionine	met	AUG
14.Phenylalanine	phe	UUU UUC
15.Proline	pro	CCU CCC CCA CCG
16.Serine	ser	UCU UCC UCA UCG AGU AGC
17.Threonine	thr	ACU ACC ACA ACG
18.Tryptophan	try	UGG
19.Tyrosine	tyr	UAU UAC
20.Valine	val	GUU GUC GUA GUG
Terminating triplets		UAA UAG UGA