N E T W O R K

THE MAGAZINE OF THE INTERNATIONAL NETWORK FOR CANCER TREATMENT AND RESEARCH

INCTR

Volume 10, Numbers 1 and 2, Special Issue : Ethiopian Pediatric Oncology

THE PRESIDENT'S MESSAGE

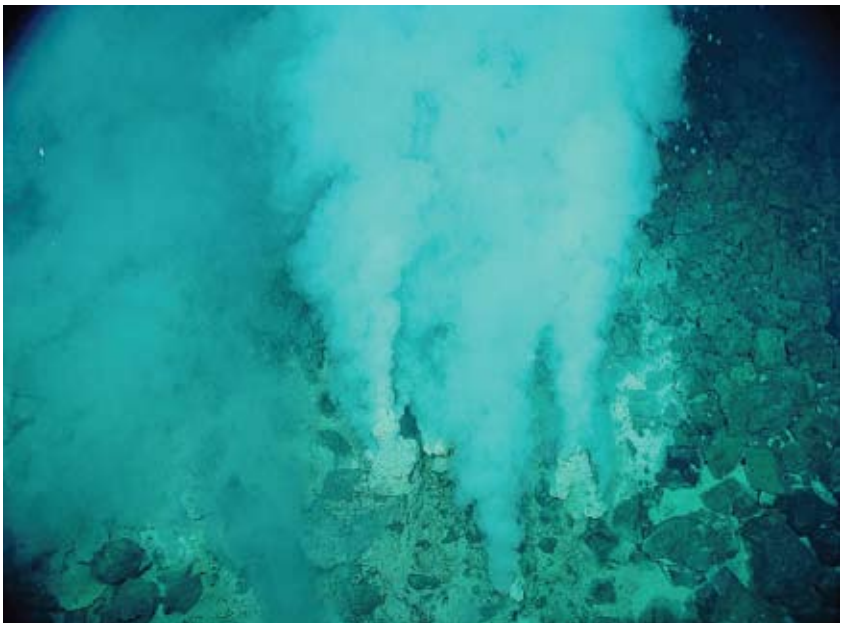
THE CELL

Part 4. Complex Cells

by Ian Magrath

Life on Earth is a dynamical system that, since its origin in self-replicating molecules approximately four billion years ago, has continued to evolve through a process of adaptation to the ever-changing environment – which is both modified by and includes Life itself. The most rapid evolution has taken place in the last two billion years, creating in the process ever more complex systems known in the field of biology as *biomes* or *ecosystems* – the sum total of living organisms in a specific habitat. All existing biomes, which are interconnected, together comprise the *biosphere*.

Complexity implies an increase in the number of interacting component parts of a system or in the number of component parts in each element of the system (which in the case of Life may be systems in their own right), or both. Eukaryotic cells are only comparatively more complex than prokaryotic cells – the development of which was the point at which Part 3 of this series of articles describing the evolution of cells ended. In reality, prokaryotic cells are immensely complex and there is much that remains to be discovered about them. But eukaryotic cells are enormously more diverse in their structure and functions and also able to cooperate in the formation of the complex multicellular systems that we refer to as animals, plants and fungi, and which comprise the elements of the next higher level of biological organization. Moreover, each organism is an ecosystem in its own right, such that Life consists of ecosystems within ecosystems (the human body, for example, contains ten times as many



A hydrothermal ocean vent, known as Champagne, emitting liquid carbon dioxide (so-called "white smokers") and minerals such as barium, calcium and silicon as well as acetyl thioesters, which, along with the heat, can form organic molecules – a potential location for the origin of Life. Picture from the *U.S. National Oceanic and Atmospheric Administration*

microbial cells, known as its *microbiome*, as human cells) and Life is probably the most complex system in the universe. There can be little doubt that had eukaryotic cells not evolved, Life on Earth would still consist of "simple cells" rather than the present rich profusion of multicellular organisms. The more complex among the latter have developed awareness, and in the case of humans, rational thought. Had this not been the case, and unless there is Life beyond Earth, the Universe itself would in effect, have never existed, for what is existence without the perception of existence?

THE EMERGENCE OF EUKARYOTIC CELLS

There is a great deal of debate regarding both the processes that led to the formation of eukaryotic cells, and precisely when, on an evolutionary time-scale, the first eukaryotic cells emerged. The most generally accepted hypothesis, supported by a considerable amount of scientific data as well as the fossil record, is that eukaryotic cells arose from the fusion of many small prokaryotes with a much larger prokaryotic cell, approximately 1.6 to 2 billion years ago, close to 2 billion years after the emergence of prokaryotic cells (a date that is also uncertain but likely to be in excess of 3.5 billion years ago). The conditions required for the development of eukaryotic cells can only be hypothesized, but it is highly probable that two events were of critical importance: the evolution of *oxygen photosynthesis*, making oxygen available from water molecules, and the development by some prokaryotes of metabolic pathways enabling them to use oxygen as a source of energy. *Aerobic respiration*, the process of obtaining energy from intracellular chemical reactions involving oxygen, is much more efficient than anaerobic respiration or fermentation, thereby permitting the emergence of greater complexity. Organisms could develop alternative, active means of obtaining food, including preying upon, or becoming the parasites of other life-forms. Initially, single eukaryotic cells *(Protista)* were able to prey upon prokaryotes, but as Life evolved, the possibilities expanded enormously, and photosynthesis ensured that the high levels of energy required could be obtained from the sun, by at least some life-forms, and passed on to others by processes such as parasitism or predation.

The advent of molecular genetic analysis led Carl Woese and George Fox, in 1977, to subdivide prokaryotic cells, on the basis of differences in their ribosomal RNA, into two types, the *Archaebacteria*, subsequently referred to as *archea* and the *Eubacteria* or "true" bacteria. Although it is now believed that these subgroups are no closer to each other at a genetic level than each is to the *Eukarya* (i.e., all of the organisms whose cells are eukaryotic), both are still prokaryotes, since this term refers to the absence of a true cell nucleus; prokaryote comes from the Greek meaning "prior to the presence of a nucleus (actually, nut or kernel)." Presumably both bacteria and archea evolved from a single precursor, and some (notably Carl Woese) favor the hypothesis that this precursor may also have given rise to the eukaryotes, hence Woese's three "domains" of life, *Bacteria, Archea* and *Eukaryota*, in which case, eukaryotes could be of more ancient lineage than proposed. An early date for the evolution of eukaryotic cells, however, seems unlikely if, indeed, their development required the ability to use oxygen in order to obtain sufficient energy for their needs, for the evidence suggests that oxygen did not become available for use by prokaryotes, at least in significant quantities, until perhaps 2.5 billion years ago.

Evolution by Fusion

Molecular analysis has led to the recognition that eukaryotes more closely resemble archeons with respect to their DNA and genetic machinery (e.g., the enzymes involved in transcription and translation), although they contain mitochondria - membranous organelles that closely resemble bacteria in several respects. This strongly supports the hypothesis that it was a fusion event that gave rise to the eukaryotic cell, as proposed by Lynn Margulis - probably between an archeon and several smaller prokaryotic cells with which it was interdependent *(sym-*

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Volume 10, Numbers 1 and 2
December 2010 - March 2011

biotic). Perhaps the prokaryotes that underwent fusion had previously contributed to each other's metabolic processes, as occurs today in bacteria which produce acetic acid, from which archeons, which would otherwise have access only to longer chain

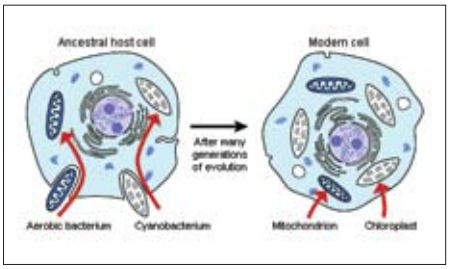

Figure 1. Diagrammatic representation of endosymbiosis which is thought to have led, through endosymbiont evolution, to the presence of mitochondria (aerobic bacteria) and chloroplasts (cyanobacteria) in eukaryotic cells.

fatty acids, are able to produce methane. Regardless of the mechanism, and whether one or many episodes of fusion took place, stable cells with an *endosymbiotic* relationship arose, i.e., the bacteria were able to survive, indeed, benefit from their location in the cytoplasm of a much larger archeon, while the latter similarly benefited from the presence of the bacteria (Figure 1). This must have entailed the replication of the bacteria becoming synchronized with the archeon chromosome (DNA), a process which may already have existed since it is known that prokaryotes are able to transfer DNA to each other through a process known as conjugation. The transferred extrachromosomal DNA, which may contain a gene, for example one that confers antibiotic resistance (bacteria themselves make antibiotics which have a role in regulating mixed bacterial populations, such as those in the gastrointestinal tracts of animals), is passed from one prokaryotic cell to another and retained over generations. Extrachromosomal DNA, often in the form of circular DNA molecules, known as plasmids, can also be incorporated into (or removed from) the bacterial chromosome, in effect, adding one or more genes to the latter. Almost certainly, some of the genes of the endosymbiotic bacteria were transferred to the nuclear *genome* of the archeon, at the time of the creation of the eukaryotic cell, although genes involved in the production of proteins involved in energy production and some other cellular processes remained in the bacterial chromosome, and persist today in the mitochondria of eukaryotic cells, which are the main source of *adenosine triphosphate* (ATP), the molecule in which energy is stored in all life forms. Mitochondria resemble, in many ways, the bacteria from which they are believed to have originated – they use, for example, a variant genetic code that is also used by the group of diverse bacterial genera known as *Proteobacteria*, and in particular, the Rickettsia.

PHOTOSYNTHESIS

How the first cells obtained the energy required to form the carbon polymers from which they were constructed is unknown. At least some of the essential chemical reactions may have been driven by the very inefficient process of using heat from the Earth's core, available at volcanic hydrothermal vents under the sea. The earliest cells were probably *hetero-trophs*, i.e., they used available organic molecules present in the sea around them as a source of raw materials and energy. Heterotrophs, which include modern animals, fungi, most protists and prokaryocytes, are unable to "fix" carbon, i.e., use carbon dioxide for the production of the carbon polymers essential to life. An important step towards both the development of eukaryotic cells and the expansion of the habitats that could support life was the development of *autotrophs* – cells able to create their own complex carbon compounds (essentially, food) from carbon fixed from carbon dioxide present at high levels in the atmosphere and dissolved in the sea. Although little is known of the details of the chemical pathways, they may have involved a primitive form of photosynthesis, in which the necessary electron donors were inorganic molecules such as sulphur, metal ions, methane or hydrogen, which could be used to fix carbon by reducing carbon dioxide, leading to the synthesis of sugars and other organic molecules with the production of energy (ATP).

These processes were probably available to prokaryotic cells some 3.5 billion years ago, and their relative inefficiency could have imposed an upper limit on the size and complexity of prokaryotic cells, except perhaps in exceptional circumstances. Some 2.8 billion years ago, perhaps as much as 3.5 billion years ago, the *cyanobacteria* emerged (Figure 2). It was probably much later – 2.3 to 2.4 billion years ago – that cyanobacteria developed photosynthetic pathways in which water was the electron donor and energy was derived from the sun. Little is known about the evolution of chlorophyll, a green pigmented protein located in the cell membrane of cyanobacteria, and able to absorb energy from light, particularly from the blue and red parts of the electromagnetic spectrum, but this, in its several forms, has probably been the major photochemical pigment for at least 2-2.5 billion years. Less efficient light-absorbing

Figure 2. A large bloom of modern cyanobacteria (also often referred to as blue-green algae) on Lake Atitlán, Guatemala. The filamentous strands are clearly visible in the lake, which is surrounded by forest and cultivated fields. Sewage agricultural run-off is thought to have caused the bacterial growth. Picture from NASA Earth Observatory.

pigments may have preceded chlorophyll. Chlorophyll never developed in the Archea, although some are able to use another pigment, *retinal*, which is able to absorb green light that can then be used for carbon fixation and carbohydrate production.

THE OXYGEN CATASTROPHE

A problem for the cyanobacteria, and, subsequently other prokaryotes, was that photosynthesis in which water is used as the electron donor produces oxygen as a waste product. Oxygen entered the surrounding sea water and was trapped by the large quantities of dissolved minerals, particularly ferrous iron, which precipitated out as ferric oxides that can still be seen in "banded iron formations" in sediments in Minnesota. It may have been another billion and a half years before most of the oxygen-trapping minerals were "rusted" or oxidized (creating, incidentally, a major diversification of minerals in the Earth's crust), such that oxygen could build up in the atmosphere – a process believed to have begun approximately 900 million years after the evolution of oxygen photosynthesis. This triggered the mass extinction of anaerobic prokaryotic cells, but some were able to develop mechanisms not only for protecting themselves against free oxygen radicals, but also for using oxygen as a means of generating energy through oxidation of glucose (glycolysis). A major metabolic pathway, namely, the *citric acid* or *Krebs cycle*, which is universally present in living organisms, is central to this process, although it participates in many other reactions such that even anaerobic (non-oxygen-using) organisms make use of it. The Krebs cycle is so important that it has even been suggested that it evolved prior to the evolution of nucleic acids and genes. Whether or not this is correct, the development of oxygen photosynthesis increased the ability of living organisms to produce energy via oxygen-based (aerobic) metabolism, which is estimated to produce 30 ATP molecules per molecule of glucose reduced, as opposed to 2 ATPs per molecule of glucose in anaerobic respiration. This very large increase in the efficiency of energy production from organic molecules may have been an essential requirement for the emergence and evolution of eukaryotic cells.

Another factor may have been the onset of one of the periods known as *snowball Earth*, for atmospheric methane would have been oxidized. Methane is a powerful greenhouse gas which had been trapping heat, preventing its loss into space, and its elimination produced a period of cooling of the Earth, and the formation of the so-called Huronian glaciations, which essentially covered the Earth some 2.1 to 2.4 billion years ago, giving rise to one of the longest ice ages (300-400 million years). When it eventually subsided, the melting of the glaciers led to glacial sediments that contained increased levels of nutrients and phosphorus, an environment favorable to the cyanobacteria, thus raising even more rapidly the oxygen levels in the atmosphere and favoring the rapid evolution of eukaryotic cells.

At some point in their evolution, some eukaryotic cells developed

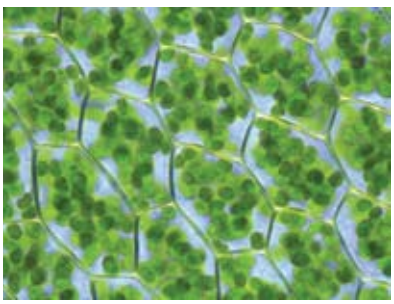

Figure 3. Chloroplasts in lamina cells of *Plagiomnium affine*, a plant that grows in close proximity to water. Photograph by Kristian Peters.

an endosymbiotic relationship with cyanobacteria, which, presumably as a consequence of mutations, became able to survive in their cytoplasm and evolved into *chloroplasts* (Figure 3). This theory is supported by the fact that chloroplasts, like mitochondria, still contain their own DNA, separate from the nuclear DNA, which genetically resembles the DNA of cyanobacteria. Chloroplasts also contain ribosomes and are capable of synthesizing proteins that are involved in the reactions involved in photosynthesis. Eukaryotes (algae) that contained chloroplasts and were eventually to give rise to plants, also contributed to the addition of oxygen to the Earth's early atmosphere.

MULTICELLULARITY

Eukaryotes still account for only a small proportion of all life-forms (Figure 4), but although there are many phyla (perhaps 30 or 40) of single-celled eukaryotes (Protista), which sometimes form colonies, eukaryotic cells have also given rise to all forms of truly multicellular life – i.e., complex biological systems in which the component cells undergo a process known as *differentiation*, primarily during the process of development of the multicellular organism from the *germ-cells* which gave rise to it, a process known as embryogenesis. Some would refer to colonies, such as the large colonies of bacteria that formed the earliest known fossils, stromatolites, perhaps as much as 3.5 - 3.8 million years ago, – as multicellular, but within such colonies there is minimal differentiation, although differences in gene expression may occur in the outermost compared to innermost parts of the colony. True multicellularity is extremely rare in prokaryotes, and even when it does occur, it is limited in its potential. For example, in Myxobacteria, a simple form of multicellularity involving the formation of a fruiting body, rather like that of the eukaryotic slime-molds, occurs. With these rare exceptions, essentially all multicellular organisms have evolved from eukaryotic cells - and in a remarkably brief period on an evolutionary time scale - emphasizing the enormous differences in the potential for prokaryotic versus eukaryotic cells to evolve into multicellular organisms. It has also been postulated that the rapidity of eukaryotic evolution was due to a similar period of glaciations to the Huronian period, perhaps precipitated by environmental factors that led to a further rapid rise in atmospheric oxygen and a second *snowball Earth* episode some 650 million years ago, "triggering" the development of multicellular organisms from eukaryotic cells and subsequently the *Cambrian explosion* in which essentially all animal groups (phyla) emerged in the course of a mere 10 million years (figure 4). The melting of the glaciers, as before, may well have caused a population explosion in cyanobacteria, as well, on this occasion, of protists and a further increase in the level of oxygen in the atmosphere (and hence seas), providing a second major leap in the availability of the energy required for evolution and the number of organisms neaded to ensure the necessary mutations.

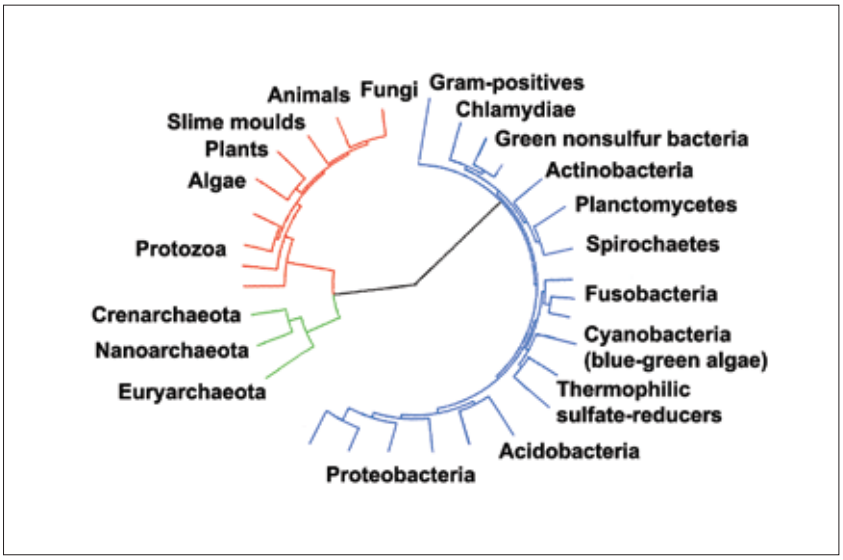

Figure 4. A simplified classification of Life. Eukaryote: red, archea: green, bacteria: blue. Based on whole genome sequencing. Protozoa are Protists.

CHARACTERISTICS OF EUKARYOTIC CELLS

The Nucleus

The defining element of eukaryotic cells, which tend to be much larger than prokaryotic cells, perhaps because of their larger genomes and cell organelles, is the presence of lipoprotein membranes within the cell (Figure 5). The most important of these is the double membrane that surrounds the nucleus (it is the well-formed, or true nucleus, *eu-karyon*, from the Greek, which gives the cell type its name). The membrane is

pierced by large numbers of "pores" that regulate the traffic of proteins in and out of the nucleus, and their access to DNA. Many of these proteins are involved in the regulation of the expression of genes. Large differences exist in the arrangement of the DNA, for the much greater number of genes need to be accessible when needed – this applies particularly to multicellular organisms where the gene expression in different tissues may need to be entirely different.

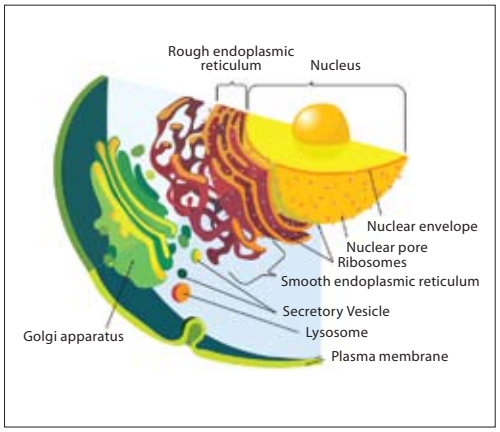

Figure 5. Diagrammatic depiction of the endomembrane system of eukaryotic cells. Not all of these structures are discussed in the text. Plasma membrane is an alternative term for the cell membrane. Created by Mariana Ruiz Villarreal.

Eukaryotic DNA is divided into several chromosomes, and the meter or so of DNA (the quantity varies greatly among different species) is packaged around histone proteins to form a linked chain of *nucleosomes*. The coiling of DNA around histones reduces the length of the DNA molecule by a factor of seven; further reduction is achieved by secondary coiling to create a shorter, thicker fiber, referred to, because of its diameter, as a 30 nanometer fiber. The precisely packaged DNA is held in place by links to the inner nuclear membrane, thus positionally stabilizing the packaged DNA and ensuring that DNA replication and transcription is carried out in a highly organized and reproducible fashion. In contrast, the prokaryotic cell generally has only a single DNA strand, or chromosome (occasionally up to four, which may be linear or circular), located in a region known as the nucleoid, which is in continuity with the cytoplasm. Prokaryotic DNA is supercoiled but not packaged around histones, although archeons do contain histones and form nucleosomes.

The processes of transcription and RNA processing occur within the nucleus in eukaryotic cells. Translation takes place in the endoplasmic reticulum, which is a system of interconnected vesicles and cisternae (sac-like structures) connected to the outer layer of the nuclear membrane and held together by the fibrous proteins that make up the cell's *cytoskeleton*. The rough endoplasmic reticulum is the major site of translation of messenger RNAs into protein and the smooth endoplasmic reticulum, the location of the synthesis of lipids and steroids. The endoplasmic reticulum is also the site of protein folding, and modification, e.g., by the addition of sugar molecules (glycosylation). Proteins destined for transportation to other parts of the cell, including, for example, the cell nucleus, are packaged in vesicles and contain specific sequences that function as "addresses" to ensure that they are correctly distributed. Further processing and packaging, especially of large molecules for export from the cell (e.g., hormones and other molecules that influence the behavior of adjacent or distant cells), take place in the somewhat similarly structured *Golgi apparatus*, named after its discoverer, which also secretes the proteoglycans that comprise a major part of the intercellular matrix in multicellular organisms.

These complex but highly efficient mechanisms for regulating the transcription, translation, processing and transportation of proteins must have evolved in concert with the complexities of form and physiology that emerged during the evolution of multicellular organisms, which range from simple sponges and Cnidaria, such as the hydra, to the intricacies of highly evolved animals, such as primates, including humans. It is important to recognize that in the truly multicellular *metazoans*, the vast range of differentiated cells must all arise from a single cell during the process of embryogenesis. Each cell contains the entire cellular genome, and programmed within its DNA must be the information required to regulate gene expression in such a way that only necessary genes are expressed at various stages of its development (e.g., larva, pupa, imago in insects), in different tissues, or during responses to internal or external conditions that the cell encounters. It must be able to sense these changes via a range of cell surface and cytoplasmic receptors.

The number of protein-coding genes (which in many organisms comprise only a few percent of the entire genome) is less important (assuming that a required threshold is exceeded) than the way in which the contained information is retrieved and processed – as evidenced by the fact that sea-urchin cells contain a similar number of genes to human cells (20-25,000), and flies and nematode worms about half the number. This is probably because a set of some tens of thousands of genes can give rise to a variable, but potentially

enormous range of functional attributes, not only through the production of specific proteins, but via their modification, e.g., glycosylation and phosphorylation, their assembly into a wide variety of protein complexes, that may contain large numbers of subunits, and the interactions that occur in protein networks. Thus, the genome, *transcriptome* and *proteome* work together in a complex three-dimensional dance that must take account of the precise role that the eukaryotic cell subserves in a broad range of environments orders of magnitude more complex in organisms such as animals, plants and fungi than in simple prokaryotic cells.

Gene expression is governed by a broad array of mechanisms that include chemical changes in the chromatin, which governs physical access to genes, or chemical modification (e.g. methylation) without sequence changes to DNA, and the binding of proteins and protein complexes to the sequences that act as *promoters* and *enhancers* of the expression of specific genes. Yet the genetic dance does not end with the synthesis of messenger RNA. Such messages are also subject to regulation, and their lifespan, and whether or not they are translated, are governed by various small untranslated RNA molecules. These processes are much less developed in prokaryotes, although there is evidence of an ancient RNA interference system that may have had, as its major function, protection against foreign RNAs, e.g., derived from viruses.

This level of genomic complexity and the evolution of efficient mechanisms for the use of the information contained in the genome, took millions, if not billions of years to evolve, and consumes a considerable amount of energy. This may account for the flowering of the eukaryotic cell only after the evolution of oxygen photosynthesis and aerobic metabolism.

Building a Genome and a Transcriptome

A major difference between the DNA of eukaryotic cells and prokaryotic cells is the much greater frequency of introns, or intragenic sequences, which are interspersed among the coding sequences of genes. Introns permit such phenomena as *differential splicing* whereby different cassettes of coding sequences, known as exons, can be expressed in a protein, such that, in effect, genes can be superimposed upon one another in the genome, or give rise to proteins that differ with respect to the presence or absence of certain *domains* according to which exons were transcribed, thereby modifying their folding, their location in cells (which is governed by specific sequences within the protein), or adding (or subtracting) specific functions to proteins or protein networks. Introns and other non-coding DNA sequences are also the site of various regulatory elements that govern the expression of genes, whether or not they are translated into proteins. The origin of introns remains obscure, but they may have arisen early in eukaryotic cell evolution.

There are various ways in which introns can be created, but the likeliest possibility is that they were inserted into the genome. This phenomenon is well known and is responsible for a considerable amount of the non-coding DNA that makes up the bulk of the human genome (perhaps as much as 98%). For example, transposons, which comprise some 45% of human DNA, also often referred to as "jumping genes" (such as Alu or LINE sequences) because of their ability to copy themselves from one location in the genome to another, and retroviruses are well known to insert themselves into genomes. Retroviruses comprise some 8% of the human genome. Another mechanism involves the breakage of the DNA, e.g., under the influence of enzymes *(endonucleases)* followed by the repair of the broken strands but with the addition of many more nucleotides to the gap. Whatever their origin, introns must contain specific DNA sequences which delineate the intron/exon border, so that they can be cut out of the gene during transcription, for introns, necessarily, are not present in the messenger RNA copy of the gene that will be translated into protein. The complexity of regulatory mechanisms is much more important than the absolute amount of DNA per cell, as evidenced by the observation that some simple organisms, such as the amoeba, *Polychaos dubium*, have approximately 200 times the amount of DNA per cell than humans!

The breaking up of genes into exons, or coding regions separated by introns, also has many advantages. Exons, for example, can be duplicated and incorporated into other genes in the course of evolution, creating possibilities, via additional structural changes to the genes which encode them, for modifying the function of proteins, their location in the cell, or creating a new member of a family of proteins. Similarly, whole genes or segments of chromosomes containing multiple genes can be duplicated. Such duplicated genes may not initially be functional, or they may, in the course

of time, perhaps millions of years, undergo various degrees of modification to create related genes with slightly different functions, or proteins that can form dimers or other types of complex compounds which may create new functional possibilities (a good example is the alpha and beta globin genes, believed to have arisen from the duplication of a single globin gene half a million years ago in a jawless fish related to the lamprey). Rarely, the wholesale incorporation of new genes into the cell genome may occur as a result of cellular fusion, as is believed to have happened at the time of creation of eukaryotic cells. The possibility that genes are also derived from intracellular parasites, or via the fusion of single-celled eukaryotes, cannot be excluded. Whatever its origin, DNA added to the genome forms the raw materials from which additional genes can be constructed.

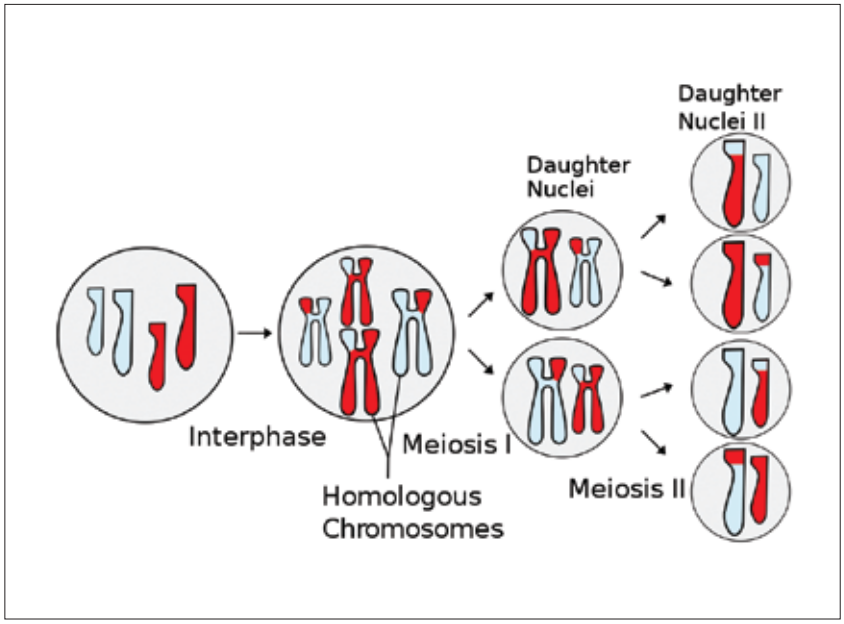

Figure 6. Diagrammatic depiction of meiosis. Chromosomes or regions of chromosomes of different color are from different parents. For simplicity, only one pair of homologous chromosomes is shown here. Image from National Institutes of Health.

Genetic Reshuffling via Sexual Reproduction

The evolution of multicellular organisms made possible yet another method of genetic variability, although precisely when, or how it evolved remains unknown. Sexual reproduction is of vital importance to both the maintenance of genetic integrity, and reshuffling of genes derived from males and females among daughter cells. Most animals and plants practice sexual reproduction, but asexual reproduction does occur, particularly in plants, while parthenogenesis in animals, in which the female gamete, (germ cell) is not fertilized by a male gamete also occurs, although usually as a temporary phenomenon.

Meiosis

The chromosomal complement of germ cells, which pass the genome on to the next generation in multicellular animals is derived from both parents, such that there are generally two copies of each chromosome and a double complement of genes (the so-called "diploid" state, comprising two haploid sets, one derived from each parent), although polyploidy (e.g., three, four or more copies of the haploid number of chromosomes) is also found naturally in nature, especially in plants. In general, polyploid plants can only reproduce with polyploid plants, such that although they may resemble their diploid cousins very closely (e.g., the Silver Birch tree, *Betula pendula* is diploid, its almost indistinguishable cousin, the Downy or White Birch, *Betula pubescens*, tetraploid), they are, by definition, separate species.

The presence of two copies of each chromosome in diploid species provides additional possibilities for the genetic reshuffling of genes, and has an important role in ensuring that organisms become increasingly adapted to their environment (or, alternatively, fail to survive or reproduce). This is because of a process known as *meiosis* (from the Greek, meaning "lessening"). Meiosis, unlike the standard mode of DNA and cell replication, called *mitosis*, is unique to germ cells and requires two cell divisions (meiosis I and meiosis II). Immediately after the replication of DNA, homologous chromosomes (i.e., equivalent chromosomes, but of male and female origin), each having been replicated, such that each chromosome in the pair now consists of two *chromatids*, undergo a process known as *crossing over,* whereby variably sized homologous fragments of the chromosomes are exchanged by the paired chromatids of male and female origin. The replicated chromosomes (chromatids), each of which now constitute a mixture of genes of male and female origin, are drawn into the daughter cells-to-be and a subsequent cell division results (in males, at

least) in four daughter cells, each containing a different mixture of genes from maternal and paternal origin (in females, three of the resultant cells usually undergo degeneration and form small *polar bodies*) (Figure 6).

This form of genetic variation, exclusively available to eukaryotes, can be seen to occur at the level of groups of genes rather than single genes. It is also confined to a single individual, capable, through sexual reproduction and the process of meiosis, to mix his or her genes with those of other adult individuals, producing offspring that differ genetically from their parents and from each other (except in the case of uniovulate twins). Meiosis creates much greater genetic variety in the offspring (the parents die after a variable period of time) than would otherwise be the case, permitting adaptive evolution to occur at a much faster rate. Crossing over randomly mixes many genes derived from different individuals that usually differ only slightly from each other (as a consequence of point mutations that may develop during replication, or as a consequence of environmental mutagens). Some of the offspring may prove to be better adapted to the environment, or more likely, for other reasons, to make attractive mates. But many offspring fail to survive as a result of inheritance of multiple mutations that have a negative effect on survival. Although a major problem for human societies, meiotic crossing over can be seen as a mechanism for a population to rid itself of individuals with mutated genes that have negative survival value while at the same time, producing at least some individuals with advantageous gene mixtures.

We are only now beginning to identify gene combinations that mutations may predispose to certain illnesses in humans, for although some may strongly predispose to diseases, including cancer, most diseases are polygenic, in which many genes each exert only a small positive or negative effect, such that their influence on the selection process – positive, negative or neutral – depends very much upon the genetic company in which they find themselves (and, of course, the environment).

MITOCHONDRIA

Mitochondria are present in most eukaryotic cells and it is here that most of the ATP (and hence energy) of the cell is produced via the Krebs cycle. Mitochondria can be transferred from one part of the cell to another (or to daughter cells), rather like mobile generators, such that the changing energy needs of different regions of the cell can be met as needed. This is made possible by proteins known as *kinesins*, which function as engines that take mitochondria in tow, and transport them via the cytoskeleton – that can function as tracks which guide the mitochondrion to its destination. The circular (intron-free) DNA molecules of mitochondria, that can occur in several copies (sometime varying from one tissue to another in the same organism), encode for only a small number of genes in a particular species, but perhaps a few thousand across species. In addition, they encode a small number of ribosomal RNAs (which are structurally similar to those of bacterial ribosomal RNAs) and the 22 transfer RNAs.

They also play an important role in *apoptosis* (programmed cell death), a process that does not exist in prokaryotes, although proteins bearing varying degrees of homology with the apoptotic pathways of multicellular organisms have been found in bacteria (although not archea). It is possible that ancient vestiges of these pathways were present in prokaryotes, but had a very different function at that time – e.g., involvement in signaling pathways, possibly related to stress reactions. Certainly it is difficult to envisage a mechanism whereby apoptosis could evolve via natural selection in single cells! Apoptosis, is, however, of considerable importance to multicellular organisms, since it is a means by which the organism can be precisely sculpted during embryogenesis, ensuring that various structures are correctly shaped and of appropriate size. It is also set in motion in cells in which errors occur during differentiation, or which are damaged for other reasons (e.g., invasion by microorganisms or genetic damage caused by external or internal factors). This is crucially important to the integrity of the organism, since some defects may be potentially carcinogenic, i.e., cause the cells in which they reside to fail to respond to the signals that control their location(s) and functions in the context of the organism). Thus, apoptosis is vital to multicellularity and its evolution by natural selection is easily comprehensible in multicellular organisms.

ANIMALS AND PLANTS

The earliest known, bizarre (by modern standards) multicellular organisms were first discovered in the Ediacara Hills in Australia (under water at the time of the emergence of the earliest fossils) and have since been found in many other sites across the world (Figure 7). They have been dated to the 40 million years before the *Cambrian Period*, some

Figure 7. Edicarian fossil resembling an Echinoderm.

635-542 million years ago, interestingly, again, just after a major ice age. This implies that the first metazoans arose some time before 635 million years ago – perhaps several million years before. The Ediacaran fossils bear little relationship to modern fauna, although brave palaeobiologists have attempted to liken some to the members of

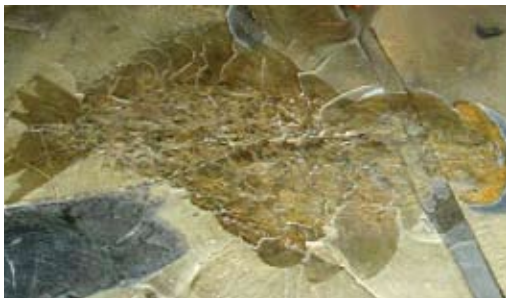

Figure 8. The first Anomalocaris (a shrimp-like animal) found in Walcott Quarry, part of the Burgess shale. Photograph by Keith Schengili-Roberts.

modern phyla. In contrast, by the mid-Cambrian period, animals that show strong resemblances to animals in most of the modern phyla had appeared, and can be found in regions in which conditions were such that soft-bodied as well as shelled animals could be preserved, such as the Burgess Shale Formation in the Rocky Mountains of British Columbia, whose fossils date to over 500 million years ago (Figure 8). The animals in such deposits must be considered as remnants of the much broader range of animals that existed at the time, and even earlier, but which were not preserved in the fossil record because the conditions in which they lived were not suitable for their preservation. Thus, it is not unreasonable to surmise that soft-bodied multicellular organisms arose sometime in the first quarter of the last billion years, perhaps a billion years after the emergence of the eukaryotic cell. Those which bore chloroplasts became algae, from which plants evolved, while the remainder evolved into animals or fungi. Many eventually colonized the land, although some time after the prokaryotes, which "paved the way" as it were, by providing both oxygen and a source of food for the earliest land organisms.

LIFE AS A COMPLEX SYSTEM

Life functions in many ways as a unit, albeit as an extremely complex system in which some elements (particularly the most recent additions, such as humans) are expendable. Indeed, our concept of an evolutionary hierarchy may well be erroneous. Without prokaryotes, Life as we know it would presumably never have existed. Prokaryotes, which still comprise the bulk of the biomass of Earth, might be seen as the substrate on which all else is built – they represent, in many senses, the biochemists who created the basic genetic mechanisms (the construction of a genome and its transcription and translation) and metabolic pathways (e.g., photosynthesis and aerobic respiration) that are still used in all organisms. Eukaryotes, particularly multicellular organisms, could be seen as a superstructure, built by the fusion of prokaryotic cells which then, through their transformation into mitochondria, became the engines of the generation of diversity. Having much more available energy, the genomes of eukaryotic cells could be much more rapidly and dramatically modified, while they also provided a host of new habitats for both prokaryotes and eukaryotes, thereby dramatically increasing the range and quantity of life-forms that can be borne by the planet.

One thing is certain. Humans, regardless of their ability to reason and imagine, could not survive in the absence of the prokaryotes that inhabit their bodies – indeed, prokaryotes remain critical to the survival of all organisms derived from eukaryotic cells. But whether the human characteristics of reason and imagination will be of value to Life in general, or will cause the extinction, not only of humans, but of many other life-forms – a process already well underway - remains to be seen. Humans, or their descendents, could eventually populate the Universe, but equally, they could return their planet to a condition resembling that of hundreds of millions or even several billion years ago. The evolution of the eukaryotic cell, and hence of consciousness, a process that has required approximately half of the lifespan of the solar system, has given us the ability to observe, and partially to understand, the miracles of Life on Earth and of the greater universe; this is a privilege of inestimable worth, but also one that carries the seeds of destruction of Life itself. Nevertheless, whatever Life's origins, or its destiny, it has permitted the Universe, after 13.7 billion years of existence, to observe itself, at least briefly; to open its eyes and to wonder, even if it then slips quietly back into its deep and dreamless sleep. ■

PEDIATRIC ONCOLOGY SYMPOSIUM IN ADDIS ABABA

The First International Symposium in Pediatric and Adolescent Oncology in Ethiopia was held in Addis Ababa, from January 18-21, 2011. The conference, locally sponsored by Mathiwos Wondu the YeEthiopia Cancer Society, marked the launch of a collaborative initiative to improve survival rates for children and adolescents with highly curable cancers in Ethiopia. The collaboration is between INCTR USA, the Division of Pediatric Hematology Oncology, Georgetown University Hospital, Washington DC, the Federal Ministry of Health, Addis Ababa University Faculty of Medicine and Black Lion Hospital (also know as Tikur Anbessa Hospital) in Addis Ababa.

The symposium brought together physicians, residents, nurses and pharmacists from Black Lion Hospital and other hospitals from around the country for an introduction to the field of pediatric oncology. Symposium topics covered the spectrum of the pediatric cancer experience, from diagnosis to treatment, supportive care, palliative and end of life care, and family education and support.

Conference faculty, who came from the US, Europe, Israel, Asia and Africa, volunteered their time to participate in the symposium. The presenters brought clinical and research expertise in pediatric oncology, palliative care, oncology nursing, infection control and patient/family support. Many of the faculty members have been engaged in oncology initiatives in developing countries, and several serve on the Strategy Planning Group that is helping to shape and direct the collaborative initiative.

The symposium opened with welcoming remarks from Dr. Milliard Derbrew, Dean, Medical Faculty, Addis Ababa University, who highlighted the commitment of the medical faculty and Black Lion Hospital to the development and success of the pediatric oncology program. Dr. David Nelson, Chair, Department of Pediatrics, Georgetown University Medical Center, welcomed the conference participants and thanked the visiting faculty for volunteering their time, expertise and commitment to the initiative.

Dr. Shad from Georgetown University and Dr. Michael Weintraub from Hadassah-Hebrew University Medical Center, gave presentations providing context to the challenge and opportunity of pediatric cancer in developing countries. Dr. Weintraub highlighted epidemiological differences between adults with cancer vs. children and adolescents, difficulties in estimating the burden of childhood cancer in low-income countries, patterns of care, barriers to care, dramatic improvements in pediatric cancer survival in high-income countries, and the genetic basis for cancer.

INTRODUCTION TO THE DISCIPLINE OF PEDIATRIC ONCOLOGY

Several foundational presentations were given on the infrastructure and clinical requirements of a pediatric cancer unit. Dr. Shad provided an overview of the essential elements of a pediatric cancer care unit (PCU). Initially developed by SIOP and more recently updated by INCTR, the classification of PCUs in levels I, II and III, is based on diagnostic and treatment capacity, support services and clinical staff. Dr. Carlos Rodriguez-Galindo, Dana-Farber Cancer Institute and Children's Hospital Boston, discussed early signs of childhood cancer. Dr. Sameer Bakhshi, from the Dr. B. R. A. Institute Rotary Cancer Hospital, AIIMS, New Delhi, presented case studies from his clinic on the diagnosis and staging of several common childhood cancers.

Dr. Nina Hurwitz, Director, INCTR Pathology Education, highlighted the need to adopt diagnostic tools and methods to the locally available therapeutic options and the need

Mary Louise Cohen, osteosarcoma survivor, Dr. Carlos Rodriguez-Galindo, Wondu Bekele and Aziza Shad.

Faculty and participants outside the meeting room.

for better communications between pathologists and hematologists, in the context of hematological malignancies, to minimize delays and ensure accuracy in determining a diagnosis. Dr. Hurwitz also introduced the iPath tool, which allows for on-line review of cases and development of a consensus diagnosis by multiple pathologists.

DISEASE-SPECIFIC PRESENTATIONS

Conference faculty gave a series of presentations on common childhood cancers. Each session began with an overview of the specific disease, followed a review of strategies for management of the disease in a developing country and panel discussions of the experience of the clinicians. In addition, the Ethiopian doctors in the audience shared their perspective on particular challenges in Ethiopia and there was discussion concerning similarities and differences and the fact that most patients in Ethiopia would have much more advanced disease, and therefore need potentially more toxic and expensive therapy. Thus, emphasis on earlier diagnosis, and therefore on improving public awareness as well as that of primary care physicians to the existence and potential curability of childhood cancer would be very important. Diseases discussed included retinoblastoma, Wilms tumor, acute lymphoblastic leukemia, chronic myeloid leukemia, non-Hodgkin lymphoma and bone and soft tissue sarcomas. In addition to the participants mentioned so far, Dr. David Korones, Rochester School of Medicine and Dentistry, Dr. Shamvil Ashraf, Children Hospital of Karachi, Dr. Cristina Stefan, Tygerberg Children's Hospital, Stellenbosch, and Dr. Amha Gebremedhin, Black Lion Hospital gave presentations on specific malignancies. Dr. Patricia Scanlan, INCTR's coordinator for pediatric oncology in East Africa, concluded the session with her experience in building a pediatric cancer center of excellence in Tanzania.

Julia Challinor, PhD, UCSF School of Physiologic Nursing, and Melissa Adde, RN, MS, Director of the INCTR Clinical Trials Office, reviewed the value of clinical data to advance research and care, along with misperceptions about clinical research and barriers to standardized collection of clinical information. The need to base care on evidence, particularly evidence obtained in the context of limited resources, and to take into consideration local attitudes and beliefs was emphasized.

SUPPORTIVE CARE / PALLIATIVE CARE

Building capacity to deliver appropriate supportive and palliative care is an important goal of the INCTR Ethiopia program. The symposium included a series of expert presentations on supportive care, along with palliative and end of life care. Topics included co-morbidities in children with cancer (Dr. Stefan), oncologic emergencies (Dr. Korones), management of febrile neutropenia (Dr. Bakhshi), transfusion of children undergoing cancer treatment (Dr. Prassana Kumar, Oman Medical College) and immunizations in immunocompromised children (Dr. David Nelson).

Dr. Gayatri Palat, MNJ Institute of Oncology and RCC, Hyderabad, India, presented the range of needs - medical, emotional, psycho-social and financial - that patients and families face, and the acute nature of the problems in many developing countries. Dr. Palat also presented on the management of pain, and Dr. Barbro Norrstrom Mittag-Leffler, from Lund, Sweden, explored symptom management at the end of life.

The conference concluded with a session on communications skills, led by Dr. David Korones, Dr. Julia Challinor and Dr. Savitri Singh-Carlson, California State University, Long Beach. The audience engaged actively in a discussion around the need for effective communication with pediatric patients, parents, and siblings.

Participant evaluations of the symposium were extremely positive, giving high marks for the breadth and level of content, and quality of presentations. Attendees were clearly grateful for the commitment of everyone involved with the project. One attendee said, "I believe the seed you are sowing today will grow much bigger tomorrow." ■

Aziza Shad and Craig Lustig,
Georgetown University Hospital
and INCTR USA

PEDIATRIC CANCER NURSING TRAINING: TIKUR ANBESSA HOSPITAL

In January 2011, a team of five nurses visited the Tikur Anbessa Hospital in Addis Ababa, Ethiopia, at the invitation of Dr. Aziza Shad, President of INCTR USA. The purpose of the visit was to provide training based upon needs specified by the hospital's nursing leadership in a questionnaire that was completed prior to the team's visit. The local nurses requested information about the most common pediatric cancers seen at the hospital, chemotherapy preparation and administration, and safety and organization. Cecelia Rose ("CR") English, from Georgetown University Hospital, Washington, DC, Kelly Bergfeld, from Children's National Medical Center, Washington, DC and Lauren Tytler, from the Children's Hospital of Denver in Colorado – all highly experienced pediatric oncology nurses and familiar with nursing in Ethiopia – created teaching modules based on the questionnaire results.

Visiting and local nurses at the First International Symposium in Pediatric and Adolescent Cancer in Ethiopia.

Nursing staff at Tikur Anbessa Hospital, Addis Ababa, Ethiopia.

(Left to right) Cecelia Rose English, Lauren Tytler and Kelly Bergfeld during the First International Symposium in Pediatric and Adolescent Cancer in Ethiopia.

CR arrived in Addis Ababa on January 3rd and spent time on the two pediatric units at the hospital in order to learn how nursing care is delivered to children with cancer through observing the nurses at work. Julia Challinor and Savitri Singh-Carlson, representatives of INCTR's Oncology Nursing Program and experienced nurse educators, joined CR on the 13th and began discussions with the head nurses of both units.

Lauren and Kelly joined the visiting nursing team on January 17th for a tour of the pediatric units. The tour was followed by a focus group for the nurses about the strengths and challenges of pediatric oncology nursing at the hospital. A questionnaire addressing the topics of the focus group was also distributed for completion by nurses unable to attend the group or those who wanted to write their answers. From the focus group and questionnaire, it was learned that the nurses identified patient and parent comfort issues as one of their biggest challenges.

On January 18th, 28 Ethiopian nurses – not only from Tikur Anbessa Hospital, but from other surrounding

Visiting nurses teaching at Black Lion Hospital.

Ethiopian hospitals - attended a day of didactic teaching on chemotherapy preparation, administration and the management of side effects. The Ethiopian nurses were given manuals containing information about common chemotherapeutic agents and their side effects. The following day, the visiting nursing team went to the pediatric units to observe chemotherapy preparation and administration by Ethiopian nurses and to interact with the children. They also distributed donated textbooks, supplies, including stethoscopes and gloves, to the nurses and toys for the children. Interviews were conducted with one nursing instructor and five students from the nursing school who were on the pediatric unit. The nurses from the hospital and surrounding hospitals attended the last two days of the First International Symposium in Pediatric and Adolescent Cancer in Ethiopia that were devoted to palliative and supportive care.

The following week, Lauren and Kelly visited the Adult Hematology/Oncology Unit where they met with Dr. Amha Gebremedhin, Head of the Adult Hematology and the adult hematology/oncology nurses. The nurses were given educational materials. Medications and supplies were also donated to the unit. Kelly and Lauren gave a teaching session on chemotherapy administration and afterwards observed chemotherapy administration by the nurses. Comments and advice were given to the adult nurses regarding data management and documentation, as well as safe practices of chemotherapy administration.

Plans were made for a return visit in May 2011 to assess the care of children for whom cure is no longer possible and to address nutrition, infection control, and nursing education. This initial visit marked the beginning of the collaboration between INCTR and the nurses at Tikur Anbessa Hospital to improve nursing care of pediatric cancer patients seen at the hospital. ■

Julia Challinor,
University of California,
San Francisco, USA and INCTR
Kelly Bergfeld,
Children's National Medical Center,
Washington, USA
Lauren Tytler,
The Children's Hospital of Denver,
Colorado, USA
CR English,
Georgetown University Hospital,
Washington, USA
Savitri Singh-Carlson,
California State University Long Beach,
Long Beach, USA and INCTR

PEDIATRIC ONCOLOGY IN ETHIOPIA – AN INCTR INITIATIVE

The International Network for Cancer Treatment and Research, USA (INCTR USA,) in collaboration with the Division of Pediatric Hematology Oncology, Blood and Marrow Transplantation Program, Lombardi Comprehensive Cancer Center, Georgetown University Hospital, Washington DC, has entered into a partnership with the Federal Ministry of Health, Ethiopia, Addis Ababa University Medical Faculty and the Tikur Anbessa Hospital (Black Lion Hospital), Addis Ababa, to demonstrate that a significant number of pediatric cancer patients in Ethiopia can be cured when treated by physicians trained to recognize cancer early, diagnose it correctly, and treat it according to standard chemotherapy protocols and supportive care regimens specifically designed for developing countries.

Figure 1. Temesgen Gamacho, the young man with osteosarcoma who inspired the initiative.

The Pediatric Oncology Initiative in Ethiopia is the result of the desire of the Cohen family in Washington DC, to honor the memory of an extraordinary 16 year old young man from Ethiopia, who fought a valiant battle against metastatic osteosarcoma, in part at Georgetown University Hospital, where he was transferred after he was adopted by the Cohen family. He passed away more than two years ago. (Figure 1). Knowing that most children with cancer in Ethiopia die from their disease as a result of lack of resources and expertise in diagnosis and treatment, Mary Louise Cohen, a Board member of INCTR USA, decided to spearhead an effort to make a difference in the lives of children with cancer in Ethiopia.

BACKGROUND

Ethiopia has long been known to the outside world as Abyssinia. It is located in the North-eastern part of Africa, also called Horn of Africa and is bordered by Eritrea (N), Kenya (S), Djibouti and Somalia (E) and Sudan (W). (Figure 2).

Ethiopia is one of the world's poorest nations. It has a population of 83 million people, with more than half the country under the age of 18 years; 49.7% are females, 44.7% of the population is less than 15 years of age, and 40% is under the age of 5 years (Figure 3). It rates as the 171st out of 182 countries on the United Nations Development Program's Human Development Index. Most people live on less than $2 a day.

HEALTHCARE IN ETHIOPIA

The Ethiopian Government is the country's main health care provider with 138 hospitals and 635 health centers. Only two of these hospitals, Tikur Anbessa and Yekatit 12 in Addis, have dedicated pediatric wards. Treatment is provided free. However, with the per capita expenditure of $2.31/day on health (as compared

Figure 2. Map of Ethiopia and surrounding countries.

to $9/day in India and $100/day in South Africa), resources are few and care sub-optimal. The doctor/nurse to population ratio is 1:42,700 and 1:4200 respectively. Neonatal mortality rate is 49 deaths/1000 live births and the under-five mortality rate is high at 77 deaths/1000 live births with 1/6th of the children dying before their 5th birthday. More than 70% of these deaths are due to communicable diseases such as measles, pneumonia, malaria, HIV/AIDS, diarrhea and severe malnutrition. Recently, with the institution of immunization programs all over the country, there is a trend towards decreased mortality from communicable diseases.

PATTERN OF CANCER IN ETHIOPIA

There is no cancer registry in Ethiopia. Extrapolation from clinical records from Tikur Anbessa Radiotherapy Center estimates that there are 120,500 new cancer cases/year, although Globocan estimates are much lower (51,000 per year). Most patients present with advanced disease, and there is a high rate of abandonment of treatment. Morphine is not readily available

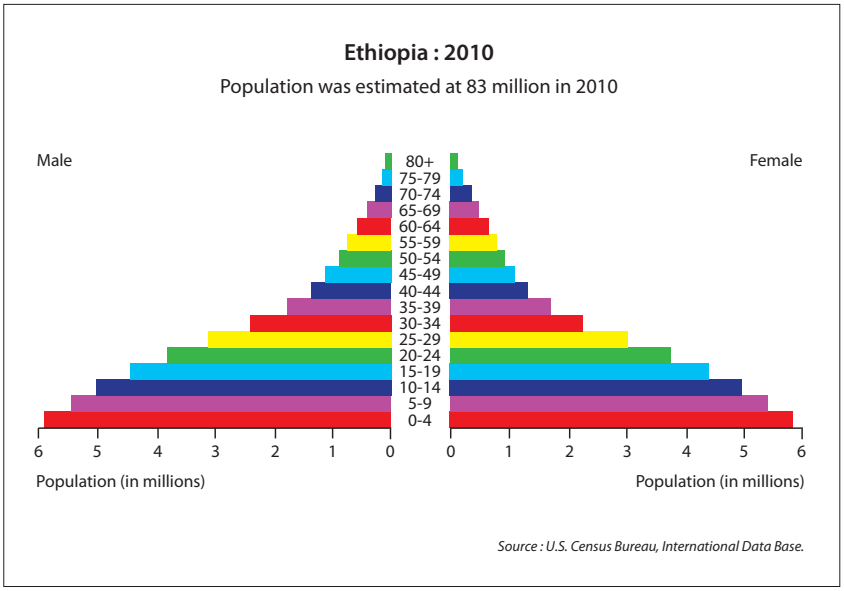

Figure 3. Ethiopian Population Pyramid for 2010.

for cancer patients. The top 10 cancers are listed below. (Figure 4).

PEDIATRIC ONCOLOGY IN ETHIOPIA

Based on extrapolating estimates from another East African nation, Tanzania, with an incidence of pediatric cancer of 134 cancer cases per million, Ethiopia probably has close to 6,000 new cases of pediatric cancer each year. The commonest childhood cancers seen at Tikur Anbessa Hospital include leukemia, lymphoma, retinoblastoma, Wilms tumor and bone and soft tissue sarcomas. Most children present late, with advanced disease, and in pain.

Cancer of Cervix
Cancer of Breast
Head and Neck Cancer
Sarcoma
Leukemia/lymphoma
Colorectal Cancer
Kaposi's Sarcoma
Skin Cancer
Bladder Cancer
Esophageal cancer

Figure 4. Pattern of Cancer in Ethiopia.

With a per capita income of approximately $2 a day, resources devoted to health and health care in Ethiopia are limited. Ethiopia has no pediatric oncologists. Mortality rates for most pediatric cancers are close to 100%. In contrast, in developed countries, the survival rate for children and adolescents diagnosed with the most treatable cancers, including leukemia, lymphoma, retinoblastoma and Wilm's tumor is rapidly approaching 90%.

The situation in Ethiopia is similar to that of other developing countries where cancer patients often receive incomplete, inadequate, or no care and those with incurable disease are frequently sent home to die without palliative care. Ethiopia lacks the trained medical personnel, adequate facilities, a sufficient supply of essential chemotherapy drugs and simple pain medications necessary to treat cancer patients. As a result, there is little public awareness that cancer can be cured, little public demand that health systems address cancer, and consequently, few government medical resources devoted to cancer treatment.

However, all this is changing rapidly as the world slowly wakes up to the burgeoning problem of non-communicable diseases (NCDs). Even though NCDs were not mentioned in the Millennium Development Goals written in 2000, NCDs were responsible for 60% of global deaths in 2005 (35 million), with 80% in low- and middle- income nations, and are projected to increase by an additional 17% over the next decade. Cancer is now recognized as an important health problem in developing countries. The WHO Assembly resolution WHA58.22 (2005) has done much to bring this about, and now even the governments of the poorest countries recognize that cancer is an important health problem. Resolution WHA58.22 urges countries to develop programs tailored to their socio-economic status, aimed at reducing cancer incidence and mortality and improving the quality of life of cancer patients and their families through the systematic, stepwise implementation of evidence-based strategies for prevention, early detection, diagnosis, treatment and palliative care.

Similarly, a 2006 Institute of Medicine (IOM) report also recommends focusing on pediatric cancers as an ideal target for capacity building in developing countries, as: a) most childhood cancers are highly curable if detected early; and b) successful, low cost, treatment protocols that utilize inexpensive, generic, chemotherapy drugs, adapted for use in low-income countries (such as the ALL and lymphoma protocols devised by INCTR) are readily available for use.

PROPOSAL TO BUILD CAPACITY TO TREAT CHILDHOOD CANCER IN ETHIOPIA

THE GOALS FOR THE ETHIOPIAN PROJECT ARE TO:

1. Increase capacity to recognize and treat children and adolescents with cancer in Ethiopia through training of doctors, nurses, pharmacists and social workers.
2. Increase survival rates for children with curable cancers by training a core group of pediatricians to treat patients using cost-effective protocols designed for developing nations.
3. Establish a dedicated Pediatric Oncology Unit (POU).
4. Improve diagnostic capacity through INCTR's i-Path program.
5. Improve supportive care and infection control practices through training and ensuring a supply of necessary antibiotics and anti-fungal agents.
6. Introduce palliative care for all patients, particularly those with incurable disease.
7. Help establish a sufficient supply of essential chemotherapy drugs to prevent interruption of treatment.
8. Provide a mechanism for family support to decrease rate of abandonment of treatment.

Eventual Goal: Establish a Center of Excellence for Pediatric and Adolescent Oncology at the Tikur Anbessa Hospital in Addis Ababa.

THE MECHANISMS THAT WILL BE USED TO ACHIEVE THESE GOALS INCLUDE:

1. The establishment of a Twinning program with Georgetown University and INCTR for training and education.
2. The development of a curriculum for a Fellowship Training Program in Pediatric Oncology and Palliative Care.
3. The development of a curriculum for Pediatric Oncology Nursing.
4. Telecommunication: use iPath to provide training and consultative services in pathology.
5. Hold focused Training Workshops targeted to specific cancers and their management.
6. Establish a Data Management Program to capture data on demographics, presentation, patterns of disease and outcomes of treatment.
7. Create a Visiting Faculty Program: INCTR faculty and other experts to participate in hands-on and distance learning.
8. The development of a Family Support Program to be established in collaboration with other agencies in Addis with the aim of providing housing, nutrition and financial support to families in order to reduce abandonment during treatment.

PROGRESS TO DATE

1. The INCTR Program for Ethiopia was inaugurated in January 2011 with the 1st Pediatric and Adolescent Oncology Symposium held in Addis. It was attended by physicians, nurses and other allied health care professionals from Tikur Anbessa Hospital and other academic institutions around the country.
2. Strategy Planning Committees have been established in INCTR as well as Ethiopia that meet regularly to implement the plans. Program coordinators are in place in INCTR USA and Addis.
3. Several needs assessment visits have been made by members of the INCTR Strategy Planning Committee and other experts.
4. The Curricula for the Pediatric Oncology Fellowship Program and the Nursing Oncology training are nearing completion.
5. Treatment protocols for common, curable pediatric cancers are being finalized.
6. An microscope equipped with a digital camera is already in place and the iPath program for training and diagnosis is already functional.
7. A separate cancer unit has been designated for the patients and is currently undergoing renovation.
8. Additional nurses have been hired for the Pediatric oncology unit.
9. Plans are being discussed for the family support and nutrition program.
10. Ward rounds and teaching by visiting faculty in medicine and nursing have already begun.

Goal: To officially initiate the two-year Fellowship training in January 2012.

Figure 5. Temesgen Gamacho and his oncologist, Aziza Shad, Georgetown University Hospital.

CONCLUSION

This program has been the collective effort of numerous Ethiopian and INCTR faculty, administrative staff in Ethiopia, Washington DC and Brussels without whom this huge endeavor would not be possible. Finally, a special thanks to Mary Louise Cohen – it was largely her vision, enthusiasm and determination to make a difference in the lives of children with cancer in Ethiopia that led to the creation of the program (Figure 5). ■

Aziza Shad,
Georgetown University Hospital
and INCTR USA

NETWORK

MATHIWOS WONDU – YEETHIOPIA CANCER SOCIETY

From the grief of parents who lost their youngest son to leukemia eight years ago, a ray of hope emerged for their fellow Ethiopian families facing a cancer diagnosis. The Mathiwos Wondu-YeEthiopia Cancer Society (MWECS), named in memory of their son Mathiwos Wondu, is one of the four non-governmental organizations (NGOs) in Ethiopia dedicated to cancer and the only one specializing in pediatric cancer.

Mathiwos Wondu, born June 17, 1999 in Addis Ababa, was diagnosed with acute lymphoblastic leukemia (ALL) just after he turned two. He was under intensive care at the Black Lion Hospital, the country's only cancer treatment hospital, for 26 months. Despite the valiant efforts of his carers and family, Mathiwos lost his battle with cancer at the tender age of four.

"I joined the war on cancer after I lost my beloved son," says Wondu. "I can't tell you how much cancer affected my family: emotionally, physically and financially. I don't have the right words to tell you how much we all miss Mathiwos."

Wondu Bekele is one of founding members of the newly formed the Ethiopian NCD Consortium. In addition to his work to save the lives of children, he is trying to develop and implement the first palliative and hospice care project for pediatric cancer patients.

"The society is working to improve cancer awareness," says Wondu Bekele, who, with his wife Amsale Beyene and 13 other supporters, established the NGO in 2004. "We are also ardently working to improve treatment facilities to help alleviate the suffering of pediatric cancer patients and to increase their survival rate."

Mathy's parents vowed to support other families with children diagnosed with cancer, and to address the lack of cancer treatment options, medicines and specialist care in Ethiopia. Thanks to improvements in cancer treatment, the cure rate in pediatric cancer in developed countries surpasses 75%, but in Ethiopia the rate is estimated to be below 20%.

In Ethiopia, cancer is considered an incurable disease. "Because of limited financial resources," Wondu says,"the Ethiopian government has not been able to give sufficient attention to cancer. Until recently there was no national strategy or program for the prevention and management of chronic diseases. NGOs working on non-communicable diseases (NCDs) in general and cancer in particular have been struggling to survive without meaningful support from within or outside Ethiopia."

A professional with a degree in government affairs and more than 30 years of experience in human resources and personnel administration, Wondu now serves as General Manager of the Mathiwos Wondu-YeEthiopia Cancer Society. From a group of 15 founding members, the Society has grown to include more than 350 members and expects to top 500 members soon. "Our membership has to grow even more in order to meet the growing burden of cancer in Ethiopia in a meaningful way," he says.

Wondu left a lucrative position in 2009 with the National Tobacco Enterprise to devote his full attention to the work of MWECS. Under his leadership, the Cancer Society is playing a major role in the development and implementation of the first strategic framework for managing NCDs in Ethiopia. In addition to his role as General Manager with the Cancer Society, Wondu is the point person for the newly formed Ethiopian NCDs Consortium (ENCDC) formed by five NGOs working on NCDs, namely cancer (two organizations), diabetes, kidney and heart.

The long-awaited strategic framework on NCDs has been approved by Ethiopia's Ministry of Health and adopted into the fourth Health Service Development Program (HSDP) and into Ethiopia's five-year Growth and

Transformation Plan (GTP). "This is a major step forward," says Wondu, "and should attract more attention to the ever-increasing problem of NCDs."

Still, MWECS's financial position is tenuous and Wondu's personal sacrifices are significant. For the last six years, the Cancer Society operated out of the family living room with just one permanent employee — a project officer whose salary is partially covered by a consortium of NGOs in Ethiopia. His wife and two children, along with other Society members, are volunteers. Through the generosity of the Society's Board of Directors, Wondu after six years of free service, receives a modest salary but lost all benefits and allowances when he gave up his full-time job to give priority to challenging the growing burden of cancer in Ethiopia.

Recently, Wondu moved the Society's office from his residence to office space in the Getu Commercial Center in Addis Ababa. With a project officer and secretary now on the payroll, "we can challenge cancer in a meaningful way and justify our society's existence."

Managing an NGO with limited resources is particularly challenging, he says. "It is difficult to find employees willing to work for low pay and it is frustrating when one sees that NGOs working on communicable diseases here are well funded." Although Wondu recognizes that tangible progress that has been made in reducing infant and child mortality rates and in controlling major communicable diseases such as HIV/AIDS, tuberculosis and malaria, he points out that Ethiopia is undergoing a rapid economic transformation that is accompanied by changes in the diet and lifestyle of the population and is contributing to the increasing burden of preventable chronic illnesses.

Despite their best efforts - 60 desperately poor children have been supported financially by the Cancer Society - children with treatable cancer continue to die. Wondu was particularly affected by the recent death of a young girl, Beza*, from the north-eastern part of Ethiopia, whose working parents together earn less than $40 USD per month. "We buy some medicines; expensive medicines like L-Asparagines not included, and cover the cost of transportation between villages and the hospital, but due to our weak financial position, we are unable to provide families with shelter. Because of this, they have nowhere to stay between treatments and have no food to eat."

Beauty contestants participated in a walk to promote breast cancer awareness.

At an event commemorating International Breast Cancer Awareness Month in October 2010, Beza appealed to government leaders and the world at large for help. Wondu recalls Beza posing the question "why the place we live determines whether we live" and asking that the world community "please send us medicines about to be expired" so that she might be cured and live again the life of a healthy child.

Wondu wants the world to know the magnitude of the problem in Ethiopia. He also wants the people of Ethiopia to know that most cancers can be prevented, that they can be cured if diagnosed early, and that a patient's quality of life can be improved even if the disease is diagnosed in advanced stage.

International organizations are beginning to take notice. Last July, a delegation led by INCTR's USA President Aziza Shad, a pediatric oncologist at Georgetown University Hospital, visited the Black Lion Hospital, and subsequently helped organize Ethiopia's first International Symposium on Pediatric and Adolescent Oncology in collaboration with the Addis Ababa University, Black Lion Hospital, Georgetown University Hospital and INCTR USA. This represented the first step towards developing a comprehensive pediatric oncology program in Ethiopia, which will be focused on the training of health care professionals to deliver protocol-based treatment for children with curable cancers and ensuring the availability of the necessary drugs and equipment. The program will also include the development of appropriate palliative care and pain management services for pediatric cancer patients. "We look to the support of INCTR and others to help us avert the catastrophe of preventable and treatable cancer deaths," says Wondu. ■

** The patient's name has been changed to protect her identity.*

For more information on MWECS, visit www.mathycancersoc.org

Marcia Landskroener for INCTR

NNCTR/INCTR NEPAL COMPETES TO WIN GLOBALGIVING'S OPEN CHALLENGE

Poverty, gender inequality, lack of education and health services are just a few reasons why very few women have been screened in Nepal. Too often, cancer victims present at a far advanced stage, when it's too late to save their lives. This problem is compounded by geographical isolation in rural areas. This is why the NNCTR/INCTR Nepal plans to screen women for cervical and breast cancer in the Kathmandu Valley and to provide cancer education sessions to their families in early 2011.

The NNCTR team provides education sessions to school children in order to raise awareness about cancer prevention in the Kathmandu valley.

To reach out to rural communities, NNCTR/INCTR Nepal organizes screening camps where results and necessary medications are provided on the spot, and patients with positive screening results are referred for follow-up at no cost. Additionally, participants in the screening camps attend breast self-examination workshops and cancer education sessions.

"I was so happy to find that both the screening and medication were free of cost. I would not have been able to afford or access these services otherwise," said a screening camp participant recently. Since it was founded in 2002, NNCTR/INCTR Nepal has screened 15,460 Nepali women for cervical cancer and 2800 for breast cancer in collaboration with the International Network for Cancer Treatment and Research (INCTR), the Australian Cervical Cancer Foundation (ACCF), PHASE Worldwide and the Australian Embassy through their Direct Aid Program (DAP).

NNCTR/INCTR Nepal was selected by the GlobalGiving Foundation to participate in its Open Challenge, a fundraising opportunity for non-profit organizations that are doing work that has impact around the world. To succeed, NNCTR/INCTR Nepal had to raise $5,000 from at least 50 donors from November 29th to December 22nd, 2010. This target, which is sufficient to enable NNCTR/INCTR Nepal to screen 500 women for the two most common women's cancers in Nepal (breast and cervical cancer), was exceeded, and has led to INCTR earning a permanent spot on GlobalGiving's website, the internationally recognized marketplace for philanthropy. For more information and to make an on-line donation, please visit NNCTR/INCTR Nepal's project web page, http://www.globalgiving.org/projects/screen-nepali-women-for-cervical-and-breast-cancer/ ■

NANAIMO BHAKTAPUR HOSPICE PALLIATIVE CARE TWINNING PROJECT – SITE VISIT, OCTOBER 19TH THROUGH NOVEMBER 11TH, 2010

A palliative care team from Nanaimo, Canada, led by Dr. Robin Love who serves as a consultant to INCTR's PAX program, made their 4th site visit to Bhaktapur Cancer Center (BCC), Nepal

Dr. Robin Love teaches at the bedside with Nepali doctors, and Nepali and Canadian nurses. *Photo Credits: Richard Tran Venetia Mah*.

from mid-October to mid-November in 2010. This visit was made as part of the Partners in Compassion Project – also known as the Nanaimo Bhaktapur Hospice Palliative Care Twinning Project. The primary focus of the trip was to assist in teaching a palliative care course hosted by BCC's Palliative Care Program.

The major purpose of the visit was to conduct a two-week course in palliative care. This course was attended by 47 participants, including 7 physicians and many nurses from the Kathmandu region. The course included a variety of topics - challenges in palliative care, ethics, pain and symptom management, palliation in cancer and non-cancer diseases, psychosocial aspects of care, development of a palliative care service including home care, care of the caregiver, and the roles of surgery, chemotherapy and radiotherapy in palliative care. Practical workshops and bedside clinical teaching were an important part of the course.

A comfortable patient in the palliative care unit at Bhaktapur Cancer Hospital. *Photo Credits: Richard Tran Venetia Mah.*

Separate workshops related to patient handling, transferring and positioning were held – not only during the course given at BCC, but also at four other hospices and cancer care programs. This is for patient comfort but also for teaching the staff safe patient handling to reduce the risk of injury to nurses and family members. It was very well received, and was entertaining as well as useful.

The visiting team spent time working alongside medical and nursing colleagues in the palliative care unit at BCC in order to continue mentoring and teaching at the bedside. Discussions about the development of a palliative home care nursing service that will be part of the BCC program have been held and will continue.

Dr. Robin Love and some of the doctors and nurses from the palliative care program at BCC. ***Photo Credits: Richard Tran Venetia Mah.***

Another new initiative is a research project that explores the impact of the Partners in Compassion project and consists of structured interviews with some of the partners including Nepali physicians, nurses, patients and families, and some partners here in Canada including physicians, nurses, administrators and nursing students. The main objectives of the project are to explore how this partnership has shaped end-of-life care in the host community, to determine whether the goals and vision of this project are being achieved, to document the experiences and outcomes of the friendship built between Nanaimo and Bhaktapur, and to identify the potential needs and barriers that still exist for the dying and their families in accessing quality and compassionate comfort care at BCC. The information obtained will be utilized to develop a tool to increase awareness in the medical and general community of the concept of twinning and its utility in meeting global needs, in particular the development of palliative care internationally. The information will be presented as a documentary film.

The team was encouraged by the progress made in the further development of the Palliative Care program at BCC. The Medical Director, Dr. Sudip Shrestha, remains committed to improvement, and Dr. Chadani Vaidya has been designated as the palliative physician for the unit. Laxmi Shrestha is the Matron of the Hospital and Nursing Leader of the PCU. Her leadership and commitment remain key features of the program. The PCU staff are more comfortable with the use of morphine and other medications and techniques for symptom management. Their role in developing and hosting the two week course helped to increase their sense of identity and responsibility as a "center of excellence" for palliative care in the Kathmandu Valley.

The team looks forward to their next visit in 2011.

The team consisted of :

- Dr. Robin Love, Palliative Physician and INCTR PAX Program Consultant
- Isabel Flood, Palliative Care RN
- Lisa Engel, Occupational Therapist
- Diena Abdurahman, Physiotherapist
- Jennifer Wade, Kinesiologist
- Sue Overton, Home Care Nurse
- Karen Evans, Home Care Nurse
- Dr. Venetia Mah, Family Medicine Resident
- Richard Tran, Photographer and Film-maker. ■

Dr. Robin Love

NEWS

MEETING IN RAMALLAH

On 30th November, a meeting took place in Ramallah with Dr. Moghi, Minister of Health for Palestine, Dr. Michael Silberman of MECC and Dr. Sidnei Epelman, President of INCTR, Brazil, to discuss the development of a program focused on the care of Arab children with cancer in Palestine. ■

4TH MEETING ON CANCER CONTROL IN FRENCH-SPEAKING DEVELOPING COUNTRIES, MONTPELLIER, MARCH 17-18

More than 110 people from 25 different countries, including North and Sub-Saharan African nations, took part in this event organized by the Alliance Mondiale Contre le Cancer (AMCC), INCTR's French Branch. The main theme of this meeting was "Let us not be silent witnesses" facing the growing cancer burden in French-speaking developing countries.

Six workshops enabled participants to share information and experiences regarding telepathology, retinoblastoma, pediatric oncology, radiotherapy, tobacco addiction and cancer, cancer registration, pain management and supportive care. The presence of representatives of INCTR Brazil and Brussels was very much appreciated. The meeting demonstrated AMCC's efforts to strengthen its international relations. ■

TIKUR ANBESSA (BLACK LION) HOSPITAL

Ethiopia is a landlocked East African nation with an estimated land area of 1.1 million square kilometers. It is the third most populous country in Africa with a population of 79 million—of whom 80 percent live in rural areas. While 86% of the population is reported to have access to basic health services, doctors and nurses are in very short supply: the doctor-to-population ratio is, at most, 1:20,000 and the nurse-to-population ratio 1:3,000.

Black Lion Hospital is the largest general public hospital in Addis Ababa.

Women and children comprise nearly three-quarters of the Ethiopian population. Few Ethiopians live to see old age: one in ten children dies before his first birthday. The average life expectancy for women is 53 years.

With more than 70 percent of childhood deaths attributable to communicable diseases and malnutrition, Ethiopia's healthcare resources have been directed primarily to treat and prevent diseases such as malaria and diarrhea. Only recently has the government recognized the growing burden of cancer. The Federal Ministry of Health estimates that there could be more than 150,000 cancer cases in Ethiopia each year, but available data is limited.

As the nation's sole cancer referral center, Black Lion Hospital is treating only about one percent of these patients. Health experts explain that many Ethiopians with cancer never seek medical treatment and, of those who do, they may not be referred to the cancer center in Addis Ababa.

Affiliated with the Addis Ababa University's School of Medicine, Black Lion Hospital is the training center for undergraduate and postgraduate medical students, dentists, nurses, pharmacists, laboratory technicians, and others who shoulder the health problems of the community and the country at large. Postgraduate medical education is also available through the Department of Internal Medicine.

Only in the last few years have non-communicable diseases, including cancer, received attention as public health issues. The Federal Ministry of Health recently created a task force to address the issue of non-communicable diseases. Members of the task force support endeavors that address the control of cancer, including community research, diagnosis, treatment and palliative care. At present, government resources for cancer care are limited to treatment only.

According to data from the hospital's oncology unit, more than 500 adult and pediatric cases with hematologic malignancies are seen in the hematology clinics every year. Many patients with cancer are also seen at the surgical, gastrointestinal and gynecology clinics. The most common adult cancers are cervical, breast, sarcomas, head and neck, and colorectal cancers, while leukemia, lymphoma, retinoblastoma and osteosarcoma constitute the bulk of pediatric cancers.

Black Lion Hospital aspires to become a center of excellence in the diagnosis, treatment and care of patients with cancer. With the support of Ethiopia's governmental institutions, NGOs and international partners, including INCTR, the hospital is hoping to develop a comprehensive cancer care program, including cancer registry, early detection, prevention, standard treatment and palliative care.

As a significant step in that direction, INCTR USA, in collaboration with Georgetown University, is launching a fellowship training program in January 2012 in collaboration with the Black Lion Hospital's Departments of Internal Medicine and Pediatrics. Aziza Shad, Chief of Pediatric Oncology at Georgetown University Hospital, Washington DC, and President of INCTR USA, is spearheading the initiative to improve capacity in pediatric and adolescent oncology in Ethiopia. An oncology nurse training program will run in conjunction with the two-year fellowship program for young doctors chosen by Black Lion Hospital. In addition, training will also be provided in pathology through the INCTR i-Path program in an effort to improve diagnostic services.

Dr. Shad has put together a team of visiting faculty that includes doctors and nurses from Georgetown University as well as experts from several INCTR branches, the University of Rochester, Harvard University, and the Hospital for Sick Children, Canada, among others. Their mission: to train pediatric oncologists, nurses, pathologists and pharmacists, improve survival for curable childhood cancers and introduce palliative care.

"In addition to faculty from Ethiopia, we plan to have visiting faculty on the wards and clinic, providing hands-on teaching," notes Dr. Shad. "We will also institute protocols for treatment and ensure the availability of drugs.

By improving diagnosis, providing training, and improving supportive and palliative care, we hope to make a difference in the survival of children with cancer."

The initiative in Ethiopia began with The 1st Pediatric and Adolescent Oncology Symposium, a three-day training workshop held last October in Addis Ababa. Emphasis was placed on diagnosis and management of common pediatric cancers, supportive care, palliative care and family support.

"We have benefited tremendously from INCTR's visiting experts program," says Dr. Amha Gebremedhin, head of the Department of Internal Medicine, who has since lobbied the hospital to devote a unit to cancer patients that is not in close proximity to infectious patients.

Dr. Amha has achieved good outcomes in the treatment of patients with chronic myeloid leukemia (CML), thanks in part to a relationship forged in 2004 with the Max Foundation. "As a result," he says, "our patients have been enrolled in the Gleevac International Patient Assistance Program (GIPAP). For patients, both adults and children, who have been treated with Imatinib mesylate, their quality of life has normalized and early deaths have been diminished."

INCTR's international team of doctors, working with Dr. Amha and Dr. Damte Shimelis, head of the Department of Pediatrics at Black Lion Hospital, hope to see similar outcomes on the pediatric cancer ward.

"What we are hoping is that after two years there will be a group of four-to-six well-trained pediatric oncologists who can then become trainers themselves," notes Dr. Shad. "In addition, we plan to collect outcome data in order to track survival rates, and hopefully, demonstrate a significant improvement. We will focus on providing patients with curable cancers, such as ALL, lymphoma, Wilms tumor and retinoblastoma, with effective therapy. We will need to ensure there is enough chemotherapy available to see patients through to the end of their treatment and provide family support to reduce the problem of abandonment of therapy, that is all too frequent in low resource settings.

The availability of chemotherapeutic agents is just one of many challenges at this government-supported teaching hospital. The School of Medicine was initially intended for fewer than 50 undergraduate medical students. Today, approximately 1,000 undergraduate students and 300 postgraduate students are educated in these facilities in Ethiopia. With such large numbers of students, and limited resources, there is shortage of space and teaching aids including books and journals, and access to information technology services.

RESOURCES AT BLACK LION HOSPITAL

Total Beds:	600
Beds Devoted to Cancer Care: (at the oncology center)	18
Staff Physicians:	201
Nurses:	627
Dedicated Oncology Nurses:	26
Pathologists:	> 10
Hematologists:	2
Oncologists	
Medical oncologists:	4
Radiotherapists:	4
Pediatric oncologists:	0
Specialized surgical oncologists:	2
Oncologists in Training	
General and Specialist Surgeons:	> 30
CT Scanners:	1
MRI Scanner:	1
Cobalt Radiotherapy units:	2
Linear Accelerator units:	None

PATIENTS SEEN IN 2010

Total patients:	266,975
Total outpatients:	251,560
Adult cancer patients:	> 2,000
Pediatric cancer patients:	> 200

Pediatric oncology nurses on the unit at Tikur Anbessa (Black Lion) Hospital in Addis Ababa, Ethiopia.

By addressing the shortage of medications and meeting the growing demand for oncology-trained doctors and nurses, hospital leaders are optimistic, that with the support of international partners such as INCTR, Black Lion Hospital can become a model cancer center and take the lead in improving Ethiopia's response to its increasing cancer problem. ■

Amha Gebremedhin,
Damte Shimelis,
Tesgaye Aster,
Aziza Shad and
Marcia Landskroener,
Black Lion Hospital, Georgetown University Hospital and INCTR

PROFILE IN CANCER MEDICINE

ADVANCING PEDIATRIC ONCOLOGY IN INDIA WITH ACTIVE RESEARCH FOCUS

Dr. Sameer Bakhshi studied medicine at the Jawaharlal Institute of Post Graduate Medicine and Research (JIPMER), Pondicherry, and undertook his specialist training in Pediatrics at the All India Institute of Medical Sciences (AIIMS), New Delhi, in 1996; both prestigious medical institutions in India. In 1997 he did his residency and fellowship in oncology at the Children's Hospital of Michigan, Wayne State University. After a five-year stay in USA, he returned to India and became a faculty member at Dr. B. R. A. Institute Rotary Cancer Hospital (IRCH), AIIMS, in the Department of Medical Oncology. He has supervised theses for MD, DM (Medical Oncology) and PhD degrees and also coordinates the teaching program leading to a DM Medical Oncology degree at IRCH, AIIMS. He is a Special Invitee of the Medical Oncology Committee of the National Cancer Control Program of India and an expert for developing standard oncology treatment guidelines for the Ministry of Health & Family Welfare in India.

Dr. Bakhshi initiated and developed a Pediatric Oncology program in the in-patient department of Medical Oncology at IRCH, AIIMS, which, over a span of eight years, has become one of the largest referral centers for pediatric cancers in India, with more than 1000 new pediatric cancer cases being registered per year. However, he remains the only consultant in pediatric oncology at IRCH, AIIMS. His vision is to develop state-of-the-art care for this large patient population, as well as a research program which should be focused on local issues. In his words:

Dr. Sameer Bakhshi

"You cannot reduce the patient load in order to be able to provide state-of-the-art care. You have to adjust to the system and develop strategies within the system that provide the best possible patient services. Waiting for a perfect doctor-patient or bed-patient ratio may mean that state-of-the-art care may never come." He has, therefore, formed a team with the pediatric surgeons, orthopedic surgeons, ophthalmologists and radiotherapists to administer care for his patients. He is assisted by DM Medical Oncology residents and research officers for patient care, and data managers for patient tracking. This has been possible because of the support provided by INCTR and the Jiv Daya Foundation.

Dr. Bakhshi paid special attention to the chemotherapy of bone and soft tissue sarcomas after joining IRCH and his group has been instrumental in defining the role of PET-CT and MRI for determining prognosis in osteosarcoma. Further, the group has also shown the utility of VEGF in assessing the persistence of osteosarcoma cells after neo-adjuvant chemotherapy, and the utility of DCE-MRI as a surrogate marker for angiogenesis in osteosarcoma.

Dr. Bakhshi also initiated the Ophthalmic Tumor Clinic at IRCH and has registered more than 700 cases in the last seven years. He has published several research papers in retinoblastoma dealing with issues ranging from patient compliance, a major issue in retinoblastoma treatment in many south-east Asian countries, outcome in locally advanced retinoblastoma and defining the clinical predictors of high-risk histopathology. In view of the high prevalence of advanced retinoblastoma in India, the group has also focused on research pertaining to higher doses of carboplatin in retinoblastoma, and the significance of angiogenesis.

He has a special interest in hematological malignancies and collaborates with INCTR in projects on acute lymphoblastic leukemia aimed at improving long-term survival. He has also initiated laboratory projects in acute myeloid leukemia (AML) on proliferation, apoptosis and mutational analysis, and demonstrated the role of mitochondrial mutations as a prognostic marker in childhood AML, a breakthrough research finding. All this, while managing the enormous patient burden. The pressure on beds has been alleviated by successfully treating many patients with febrile neutropenia as outpatients; similarly, he has also developed consolidation chemotherapy in AML that can be managed in the clinic. Finally, he has performed more than 75 stem cell transplants for various childhood malignancies including autologous and allogenic transplants and has recently initiated cord blood stem cell transplantation at IRCH. ■

Sameer Bakhshi
AIIMS - All India Institute of Medical Sciences, New Delhi, India