N E T W O R K

THE MAGAZINE OF THE INTERNATIONAL NETWORK FOR CANCER TREATMENT AND RESEARCH

INCTR

Volume 8, Number 4, June 2009 — Inside: ARTICLE: Cancer Control Planning: Supplying the Evidence - **8** - REPORTS: Annual Meeting 2009 Report - **11** - Ethical Principles Versus Good Research Practices in Resource-Poor Countries - **17** - NEWS - **19** - PARTNER PROFILE: Healthcare in Kenya; The Role of the Kenya Medical Research Institute - **20** - PROFILE IN CANCER MEDICINE: Music for the Cure - **24**

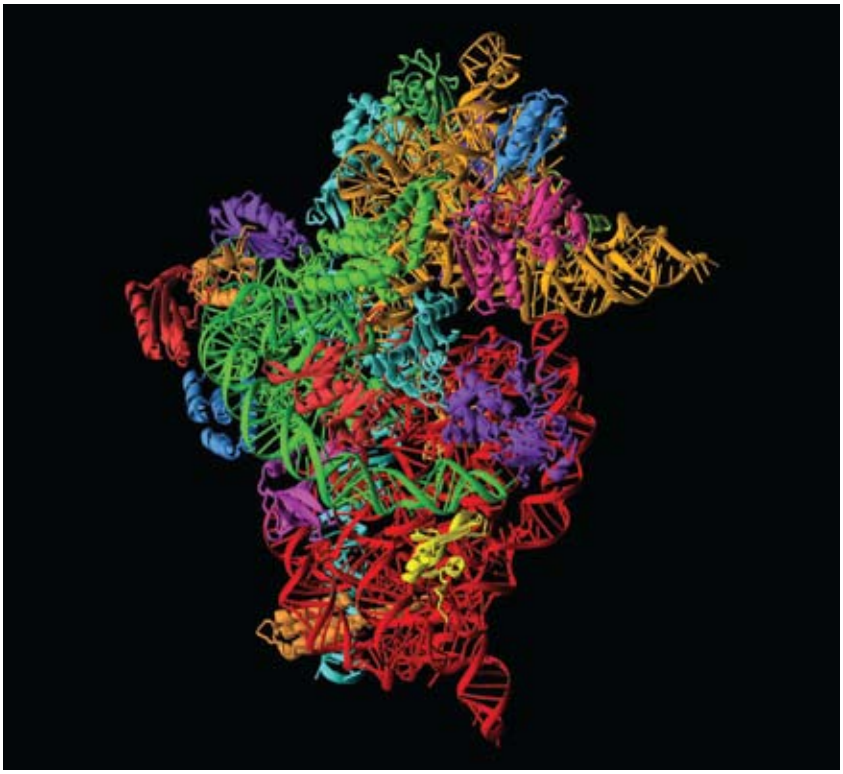
THE PRESIDENT'S MESSAGE

THE CELL

Part 2. Origins

by Ian Magrath

Leeuwenhoek's discovery of tiny *animalcules* visible only with the aid of his microscopes opened up entirely new vistas for scientific speculation and endeavor, although for long the extreme limitations in investigative techniques meant that little more could be done beyond naming those microscopic creatures that were easily recognizable and beginning to probe the microscopic structure of the plants and animals that inhabited the familiar world of the human senses. In the past, the vast lacunae in our understanding of nature had been filled by a host of confabulations implicating creation by design, spontaneous generation, and in the context of disease, evil spirits, internal humors and the like. Now, as suggested by Hook, better microscopes might well provide a means by which *the instruments and contrivances used by nature to bring her designs and ends to pass* might be discovered. And while microscopes of increasingly sophisticated design



Model of the small, 30S subunit of the bacterial ribosome. Ribosomes are responsible for synthesizing the specific protein encoded in the nucleotide sequence of mRNA and hence, of translating information into structure and function. Modern ribosomes contain both RNA and protein, but it is the RNA that is primarily responsible for the catalytic activity (peptidyl transferase) that links amino acids together to form polypeptide chains. Therefore, ribosomes are classified as ribozymes (see text). Their existence would seem essential to the emergence of cells, and the critical role of catalytic RNA would support the existence of a prebiotic RNA world. Photo by V. Ramakrishnan.

led to a corresponding increase of our understanding of the very small – including the fundamental particles of nature themselves - telescopes similarly extended the range of the human senses to the very distant and often very large.

CREATION OF THE CHEMICAL ELEMENTS

Remarkably, these two worlds, the very large and the very small, proved to be more closely integrated than ever suspected, for there is now ample evidence that the massive gravitational force generated by stars, is responsible for creating the atoms that comprise the chemical elements and, consequently, matter and Life. Starting with single protons (hydrogen), thermonuclear fusion, the details of which vary in stars of different masses, gives rise to all of the elements up to nickel (i.e., elements with up to 28 protons). The first step in this process, at least in stars larger than our sun, is the fusion of four hydrogen nuclei (each a single proton) to form helium, in which two of the protons have been converted to neutrons by the weak nuclear force (beta radioactive decay). Since the mass of the newly formed helium nucleus is less than the sum of its four constituent nucleons, the extra mass is converted into electromagnetic radiation and released as starlight (or sunlight). This radiation also creates the pressure that prevents the star from imploding as a result of its own gravitational field. Other elements can be made in a similar way, e.g., carbon via the combination of three helium nuclei, but nuclear fusion cannot give rise to all the elements. Since the nuclei of nickel-56, and iron-56, the latter derived from nickel-56 by radioactive decay, have the highest binding energy of all the elements, the addition of more protons requires energy, and cannot, therefore, be accomplished via nuclear fusion. The heavier elements are formed predominantly in supernovae – the spectacular stellar explosions that occur just once or twice a century in a galaxy the size of ours. Supernovae are of several types only one of which will be described. Type II supernovae occur when a massive star has used up all its hydrogen (which occurs after approximately 90% of its lifespan), and although still able to create energy through helium fusion into carbon, and the successive use of carbon, neon, oxygen and silica as fuel, each new fusion process releases progressively less energy and each new fuel is quickly used up. As iron-56 accumulates in the core, derived from the final phase of silica burning, the star is less and less able to create enough energy to maintain its structure and the core begins to shrink. When fusion abruptly ceases there is a sudden drop in the core pressure (occurring in less than a second), leading to implosion. The core then recoils in a tremendous outburst of energy which blows off the outer layers of the star and transiently emits as much light as an entire galaxy. High energy neutrons produced by the core collapse (as negatively charged electrons and positively charged protons are compressed together) collide with the elements previously made by nuclear fusion, creating the heavier elements by a process of neutron capture and conversion, again via the weak nuclear force, of some of the neutrons into protons. The core remnant may persist as a small neutron star several kilometers across, but in very large stars the end result is a *black hole*. The matter ejected from the supernova is dispersed, and often interacts with interstellar matter in the local region of the universe, creating *nebulae* of sufficient density that the gravitational forces generated can give rise to new stars. Sometimes, when there are high concentrations of the heavier elements, a spinning disc is formed in which the largest concentration of matter is in the center. If large enough, the central portion ignites and a new star is formed, surrounded by a *protoplanetory* disc. The dust and ice-grains (water, essential to life as we know it, is the commonest substance in such discs) orbiting the star may condense into various sized objects,

INCTR

EDITORIAL STAFF
Ian Magrath, Editor
Marcia Landskroener, Managing Editor
Bénédicte Chaidron, Assistant Editor
Sophie Lebedoff, Lay-out

ADDRESS CORRESPONDENCE TO:
INCTR aisbl
Rue Engeland 642
1180 Brussels • Belgium
+32 2 373 93 23 • bene@inctr.be
www.inctr.org

NETWORK: INCTR Magazine
c/o Marcia Landskroener
3817 McGinnes Road
Millington, Maryland 21651 USA
mlandskroener2@washcoll.edu

including asteroids, meteorites and comets that, by accretion, can develop into protoplanets and thence dwarf planets or planets. Such is believed to be the process by which our own solar system formed some 4.5 billion years ago.

THE CRUCIBLE OF LIFE

The young solar system was a tempestuous place, and most of the events that resulted in the formation of the planet Earth took place in the course of tens of millions of years through accretion of smaller masses. During this period a major collision with a body believed to be approximately the size of Mars is believed to have occurred. It both provided additional mass to the Earth and resulted in the formation of the moon, whose gravitational pull causes tides in large bodies of water. It may also have resulted in Earth's axial tilt, responsible for the seasons which, along with the tides, have greatly influenced the diversity of Life. Even after the formation of the solar system, various sized chunks of ice and rock, including meteorites and comets, continued to smash into the inner planets, particularly in a period 3.8 to 4.1 billion years ago referred to as the *Late Heavy Bombardment*. In the case of Earth, some of these objects, especially ice-containing comets, added water to the growing planet – a *sine qua non* for the emergence of carbon-based life. The kinetic energy of these numerous collisions was converted into heat and the hot molten planet evolved structure as the heavier metals, particularly iron, sank down to form the central core. This resulted in the creation of a magnetic field, a factor critical to the subsequent evolution of life on land since it blocks the harmful charged particles that radiate from the sun – the so-called *solar wind* – which had, until then, prevented the formation of a stable atmosphere. The outer layers of the planet (some of which may have come from a surrounding cloud of gaseous silica) solidified as the Earth cooled, but the molten rocks and gas in the deeper layers frequently force their way through weaker points in the Earth's crust as volcanic eruptions that contributed a major part of the early atmosphere, much of it steam, which, as it cooled, rained down on the planet and formed vast seas. Today, 71% of the Earth's surface is still covered by salt water. The composition of the primeval atmosphere remains a matter of controversy, but it is likely that it contained water vapor, ammonia, methane, nitrogen and carbon dioxide – sufficient to create a greenhouse effect and slow the gradual cooling of the planet. One molecule that was fortunately absent was oxygen, for this would certainly have oxidized organic material into carbon dioxide, thus preventing the emergence of Life, although later, oxygen was to play a crucial role in the development of complex life-forms.

It was this hot, watery and violent world that, as hostile as it may seem, provided the necessary conditions for life to evolve.

CARBON

Life, as we know it, is dependent upon the branch of carbon chemistry known as *organic chemistry*, i.e., the chemistry of molecules derived from carbon (C) and hydrogen (H), the simplest of which is methane (CH_4). Carbon, the fourth most abundant molecule in the universe (after hydrogen, helium and oxygen) differs from all other elements in its ability to form long chains of atoms or ring structures that are stable in water, and which provide, as it were, the skeletons of a broad range of molecules that comprise the complex system we call Life. Silica can also form such structures, although only in non-aqueous solvents, such that silica-based life in the universe would seem unlikely. In addition to hydrogen, oxygen, nitrogen and phosphorus many other atoms participate in or project from the carbon skeletons, often in combinations referred to as groups, such as hydroxyl groups, amino groups, or phosphate groups, which are critical to the functional attributes of the organic molecules. Among the vast range of possibilities with respect to organic compounds, however, only a select few were to participate in the creation of Life, which evolved within a billion years of the Earth's formation. Among the great many amino acids possible, for example, all known life-forms encode only 20 in their genes, and all are "left handed" alpha-amino acids, terms which relate to the particular *enantiomer* (mirror image version) and positioning of the amino group in the molecule. Similarly, Life uses only 5 and 6 carbon sugars, which, unlike the amino acids, are nearly always the "right handed" versions of the sugar molecules. The limitation to specific types of molecule may have a deep explanation, but it is also possible that these happened to be the molecules available when life emerged, and that life might well have been built with other molecules (e.g., with right handed amino acids and left handed sugars) had they been in the right place at the right time.

THE PREBIOTIC ERA

For most of human history, Life was believed to consist of some kind of "spirit" or "soul" that animated living creatures (plants and animals). Such a view persists in one form or another in various philosophies, primitive, religious or otherwise, but from a scientific perspective life is a complex, self-organizing, self-replicating and adaptive system that is dependent for its existence upon physico-chemical processes, many of which can be reproduced in the laboratory. On earth, modern molecular evidence strongly suggests that all existing life-forms evolved from a single cell, i.e., Life emerged only once. This is reminiscent of the *singularity* from which the Universe is believed to have originated.

Life's Key Molecules

The molecular systems that comprise life, however, had to be in place before it was possible for cells to evolve. This occurred in the *prebiotic* era, biotic, referring to cellular Life. The key molecules are the nucleic acids, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), which carry the information required for the production of proteins involved in cell structure and the molecular pathways vital to the life, replication and functions of the cell. Perhaps equally important are the molecules (proteins and small RNAs) that regulate the use of the stored information, specifying which genes (informational units), for example, will be expressed and when; and the 20 amino acids which, when bound together in chains, form proteins. Whether polypeptides initially evolved separately from nucleic acids is not known. In either event, molecules with catalytic action (enzymes) that evolved by chance (possibly only once) would have conferred advantages on evolving molecular systems and been retained. This is presumably why the molecules involved in Life's basic processes (metabolism) are remarkably similar in all living organisms. A key molecule found in all cells is adenosine triphosphate, which can store energy and transfer it, as needed, to proteins engaged in specific molecular interactions.

Nucleic acids are comprised of long chains of ring-structured molecules called *nucleotides*, attached to pentose sugar molecules (deoxyribose or ribose). These sugar-nucleotide units (*nucleosides*) can be joined into long chains via phosphate molecules (Figure 1). The five different nucleotides – purines (guanine and adenine, or uracil, in RNA) and pyrimidines (thymine and cytosine) along with pentose sugars must have evolved in the prebiotic era, and polymerized into RNA and DNA.

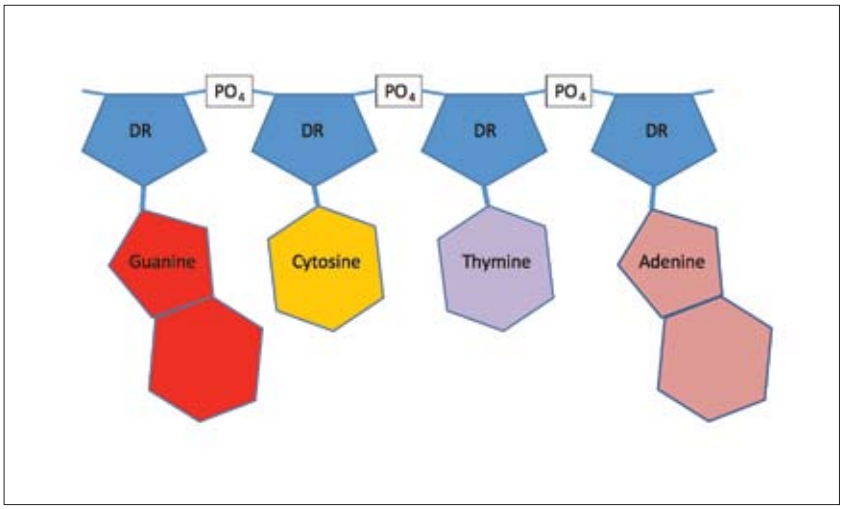


Figure 1. Diagram showing, in simplified form, the structure of a short length of a single DNA strand comprised of nucleosides linked together via the pentose sugar, deoxyribose (DR) by phosphate groups (phosphodiester bonds) (PO_4).

Replication and Translation of Genetic Information

Of profound significance to the existence of Life is the ability of nucleotides to pair with each other in a highly specific way - guanine binds to cytosine and thymine to adenine (or uracil in RNA) - which permits one chain to be used as a template on which to build a complementary chain, or for double stranded forms of DNA and RNA to exist (Figure 2). This is relevant to both the replication of DNA (and RNA) molecules today and to the emergence of self-replicating molecules in the prebiotic era. It also allows the translation of information encoded by genes into protein molecules – which, when organized appropriately, give rise to both the structure and function of cells.

The fact that DNA and RNA use different sugars results in differences in their structure that enables RNA to take on a broader range of func-

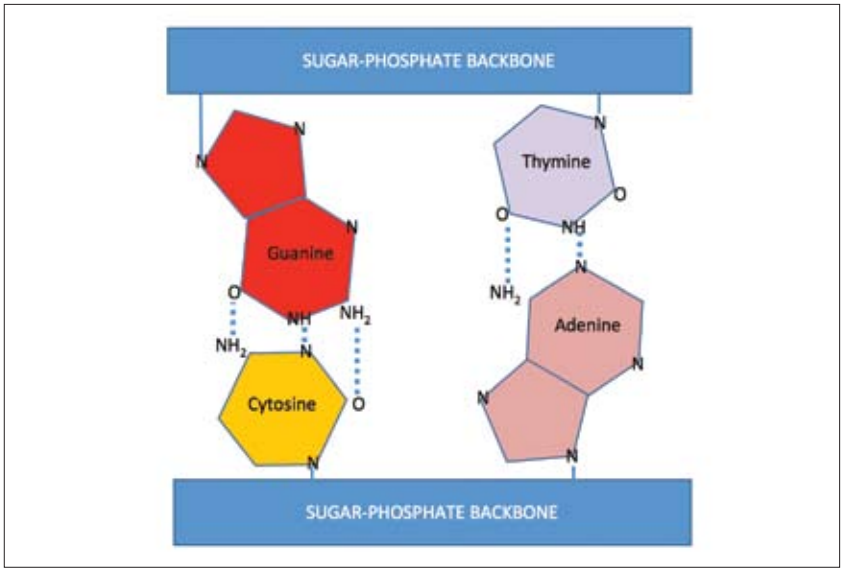


Figure 2. Diagram showing how the nucleotides of DNA undergo "base pairing". Adenine binds to thymine and guanine binds to cytosine via hydrogen bonding, in which a hydrogen atom is "attracted" to certain other atoms such as nitrogen and oxygen (dotted lines).

tional roles than DNA. For example, small non-coding RNA molecules have enzymatic functions that are involved in the regulation of the reading of genetic information (i.e., information encoded in genes, whereby specific nucleotide triplets code for individual amino acids) as well as its translation into proteins. Translation involves the building of a complementary *messenger RNA* (mRNA) on one of the DNA strands (cellular DNA is always double stranded). The information encoded in the mRNA nucleotide sequence is read by a ribosome containing non-coding *ribosomal RNA*, which moves along the mRNA molecule and catalyzes the sequential binding of *transfer RNA* molecules, via their contained RNA triplet *anticodons* complementary to a triplet in the mRNA chain. Each transfer RNA carries a specific amino acid, so that a *polypeptide* (a chain of amino acids, each joined to the next via a *peptide bond*) is built step by step as the ribosome progresses along the mRNA molecule.

An RNA World?

RNA's versatility makes it possible that it provided an intermediate step to the use of proteins as enzymes in the prebiotic era and some postulate the existence of an *RNA world* prior to the evolution of DNA, proteins and cells. Recently, naturally occurring RNA molecules with catalytic activity (*ribozymes*) have been discovered, and ribozymes able to replicate each other in the laboratory have been synthesized. Even modern ribosomes are ribozymes – providing support for an RNA-world. Other small, non-coding RNAs such as *interfering RNAs* and *micro RNAs* have an important role in regulating the expression of genes in all living organisms, and could also be, along, perhaps, with RNA viruses (see below), the remnants of this era. The process whereby RNA might have transferred its contained information to DNA is not difficult to envisage, given the existence of *reverse transcriptase*, a protein used by modern retroviruses to create a DNA copy of their RNA genomes.

Replication Fidelity – Striking a Balance

Double stranded DNA and its contained genes defined by the nucleotide sequence, can be thought of as a kind of zipper. The DNA can be unzipped and a new chain synthesized by base pairing on each side of the zipper (Figure 3), creating a double chain identical to the parental double chain (assuming 100% accuracy). This process led to the accumulation of specific DNA molecules in the (late?) prebiotic era, and provides identical copies for each of the daughter cells during cell division in the biotic era. The process of replication is not, however, perfect, and would be a lot less perfect if the enzymes that catalyze DNA replication (*DNA polymerases*) were not, at least in cells, associated with a proof-reading element that detects copying errors. Repair enzymes then excise incorrectly placed nucleotides (i.e., that do not correspond to the template) and replace them with the correct nucleotide. Changes in the nucleotide sequence (mutations) can also occur as a result of interactions with environmental agents. Mutation, of course, is critical to change, i.e., to evolution, but too high a rate of mutation would hinder the accuracy of self replication, preventing the emergence of stable

molecules with specific functions in the prebiotic era, and hence of Life. Similarly, high enough mutation rates in cellular DNA would lead to cell death. In practice, it seems that the accuracy of replication is similar in all cells (from bacteria to humans) at approximately 1 error per 10^9 to 10^{10} nucleotides. The absolute number of errors made during replication both depends upon and defines the size of the genome. In the prebiotic era the mutation rate, in the absence of proof-reading and repair enzymes, must have been much higher, until, by chance, proteins (or perhaps RNAs) arose that were capable of improving the accuracy of replication, resulting in an increase in the stability of molecules over multiple replication cycles. Mutations, including mutations in repair enzymes, are one of the several types of genetic lesions that contribute to the development of cancer.

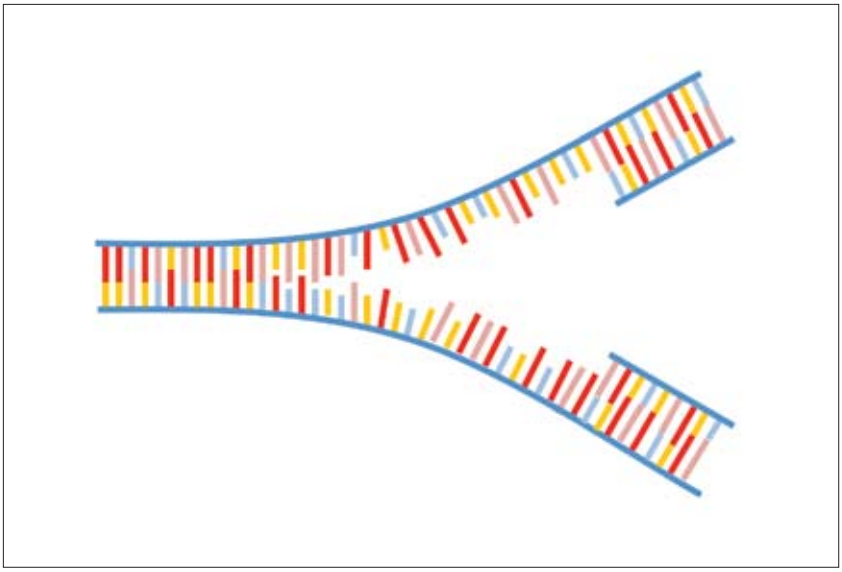


Figure 3. Diagram showing, in simplified form, how DNA is replicated through the uncoiling of its two strands and the use of each as a template on which to build another strand. To the left, the original double strand, to the right, two new double strands. Nucleotides are indicated by long (purine) and short (pyrimidine) lines.

Artificial Cells

The emergence of cells left traces in the fossil record that date to 3.5 to 3.8 billion years ago (e.g., stromatolites containing microorganisms). The prior prebiotic era has left no such traces and therefore, no direct evidence of the nature of the first self-replicating molecules. However, the most basic aspects of cell replication and metabolism are common to all life-forms and probably to molecular systems of the later prebiotic era too. The translation of genes encoded in DNA into mRNA and proteins, for example, must surely have been a prerequisite for the emergence of living cells. If so, it is unlikely that the complex molecular interactions required could occur in a postulated "primeval soup" of dilute organic molecules in the oceans of the young planet. Even if this were the origin of some organic molecules, it would seem likely that the development of complex molecular systems would require close proximity of the component molecules, as might occur in an artificial cell in porous rocks or bubbles trapped in ice. Consistent with this is the discovery of microorganisms known as *endoliths* and *hypoliths*, which occupy microscopic spaces in rocks. Some of these organisms are able to live on traces of iron, potassium or sulphur – also a potential source of energy for prebiotic molecules - and may divide only once a century. Modern *extremophiles* (predominantly Archea and Eubacteria) able to tolerate superheated water or freezing temperatures may have evolved in locations essential to the emergence of Life's key molecules because of the necessity either to prolong the half life of their component units in order that they have enough time to polymerize (cold), or to create complex molecules from simple precursors in the absence of enzymes (heat). Extreme conditions were, in fact, the rule on Earth during the prebiotic era and may have been essential to the synthesis of molecules essential to life.

The origin of such molecules has been intensively studied in the laboratory. In the now classical Miller-Urey experiment, for example, water under an atmosphere of ammonia, methane, hydrogen and water vapor was subjected to electrical discharges, which resulted in the production of a "soup" of organic compounds, including seven of the amino acids present in proteins. Interestingly, some of the key constituents of life have been

synthesized from simple carbon structures such as glyceraldehydes and cyanamide or ammonium cyanide. Adenine, for example, which has a half-life of 17,000 years in freezing water, but just 19 days at 100°C) has been synthesized from hydrocyanic acid (HCN), ironically, a highly toxic molecule to modern organisms dependent upon oxygen to generate energy (ATP). It has also been shown that minerals, such as iron sulphide could catalyze the synthesis and polymerization of organic molecules in the very hot environment of volcanic ocean vents, using volcanic gases such as carbon monoxide, hydrogen sulphide and hydrogen cyanide as raw materials. These and other laboratory experiments demonstrating the synthesis of organic molecules, including nucleotides, sugars and amino acids, from non-organic compounds, do not demonstrate how such molecules evolved, but do provide sufficient information to understand how they might have evolved.

MODERN PREBIOTIC MOLECULES?

In the 17th century some natural philosophers speculated that the *animalcules* discovered by Leeuwenhoek and others might be a link between the living and the dead. While at first sight, such a concept seems alien to our understanding of life and death, these words predate the modern era and were coined in the context of animals (including people) and plants, where alive and dead are distinct states. Leeuwenhoek's animalcules proved not to differ in this regard, but the complex molecules that evolved in the prebiotic era can legitimately be considered intermediate between the mineral, or purely chemical, and living cells. Such molecules, like ancient microorganisms, may well have modern counterparts. The likeliest candidates are viruses, which are, in effect, nucleic acids enclosed in protein (and sometimes lipid) coats, which are entirely dependent upon cells to replicate. Similarly, the replication of prebiotic molecules must also have been subject to the availability of raw materials and energy, which was possibly provided by suitably located artificial cells (e.g., near volcanic ocean vents). And since RNA viral polymerases do not have proof-reading and repair enzymes as part of their replicating machinery, RNA viruses have a much higher rate of copying errors - some 10,000 to a million times higher than in bacteria and probably similar to that of prebiotic molecules prior to the evolution of proof-reading and repair enzymes. The mutation rate imposes an upper limit on the size of genomes since the risk of a copying error arising is in direct proportion to the size of the genome. Once copying became more accurate, larger molecules, perhaps created by combination with smaller molecules, would be stable. Indeed, prebiotic recombination could be reflected in modern *mobile genetic elements (transposons, or jumping genes)*, which may have had a much more important role in the construction of genomes than previously believed. Some prebiotic molecules may have acted quite similarly to viruses, since RNA or DNA protected by adherent protein could have migrated to other locations where it could recombine with other stretches of nucleic acid. For example, among the several kinds of transposons are *retrotransposons* that are transcribed into mRNA then reinserted into the DNA genome with the aid of a *reverse transcriptase* (which also lacks proof-reading properties) that catalyzes the assembly of a DNA copy. Retroviruses are RNA viruses with the same capability and as such represent a class of transposons. Such viruses occasionally "pick up" a cellular gene adjacent to the insertion point and transfer it to another cell, which could have been a means of genetic recombination in the prebiotic era. Today, a similar process has been shown to lead to cancer in animals - it was the discovery of the Rous sarcoma (RSV) virus *oncogene (SRC)* in both normal chicken cells and in RSV that led eventually to a broad understanding of cancer at a molecular genetic level.

How molecular systems of nucleic acids and protein became enclosed in a cell membrane is entirely conjectural, but the propensity for phospholipids in water to form spherical lipid bilayers (the basic element of the cell membrane) when agitated, capable of enclosing admixed molecules, provides at least a crude model for how the formation of the first cell might have happened. While the chance of all necessary ingredients being present at a single location was doubtless extremely low, hence Life's origin in a biotic singularity, the construction of trillions of prebiotic molecules and a time-frame of hundreds of millions of years may well have made the emergence of the cell almost inevitable. ■

CANCER CONTROL PLANNING: SUPPLYING THE EVIDENCE

Most advances in clinical practice are the result of good quality published research. However, over-reliance upon outcomes of clinical studies conducted in high income countries may be inappropriate when developing guidelines or planning cancer control strategies in poorer resourced countries. Guideline developers and cancer control planners need to be able to identify, and have access to reports of good quality research conducted in their own, or similar countries, in order to be in a position to plan and conduct feasible interventions.

Since 2007 INCTR has developed two databases as part of a demonstration project that could lead eventually to a Global Database for Cancer Control in Developing Countries, the construction and analysis of which will provide both negative (relating to poor quality information and gaps in the evidence base) as well as positive (meaningful data that can be used to plan interventions) information. The first database (previously reported in the winter 2007-2008 issue of *Network* [Vol 7 issue 4]) is the result of a collaborative pilot project involving INCTR UK (Mark Lodge, Biying Liu) and NCI Cairo (Prof. Hussein Khaled, Dr Atef Badran, Mrs Howaida Ali Alsayad, Ms Shaymaa Badran). Support was provided by the European School of Oncology, the European Society of Medical Oncology and the Egyptian Foundation for Cancer Research. This project was designed to identify published reports of Egyptian research in five areas of cancer care: breast cancer, bladder cancer, lymphoma, childhood cancers and palliative care. The second database has been created by INCTR UK from studies identified by Mark Lodge, Biying Liu (Oxford UK) and Dr Marilys Corbex (Cairo, Egypt) as a result of a commission from the National Cancer Institute Maryland USA to catalogue published articles of special relevance to breast cancer control in low and middle income (LMI) countries and to summarise the body of research evidence in terms of its scope and quality. Sufficiently high quality material will be used to create systematic reviews capable of being answered by the available evidence.

Both databases have been built using the same basic strategy. Clear Inclusion and exclusion criteria were established: all studies relevant to a particular cancer and either Egypt or LMI countries published between 2000 and 2008 were included; animal studies were excluded. Individual sensitive search strategies were developed for multiple databases (including Medline, Embase, Scopus, Biological Abstracts, Popline) and conference proceedings (ASCO, ESMO, UICC, INCTR and San Antonio Breast Cancer Symposia). Other sources of studies were contacted and invited to contribute. In the Egyptian project great pains were taken to search the contents pages of over forty non-indexed Egyptian journals: a strategy only made possible by the willing collaboration of many senior university librarians across the country. Particular acknowledgement should also be paid to Dr. Don Ekwueme for generously sharing important data from a parallel breast cancer literature search conducted on behalf of the Centers for Disease Control Foundation and Susan G. Komen for the Cure Foundation. The titles and abstracts (where available online) were downloaded or entered by hand into a ProCite 5 database, de-duplicated and coded by area of care (e.g. prevention, detection, diagnosis, treatment etc.).

In the Egyptian project, 1383 studies met the inclusion criteria. The results of the searches are presented in Table 1. (NB: Some articles are necessarily coded more than once; e.g. 'Breast cancer' + 'Palliative care'.)

In the second project, 4871 articles relevant to breast cancer control in LMI countries were identified, including 219 reports of randomized controlled trials (RCTs). Countries producing the most research, collated by WHO Region, and 'Global' reports are presented in Table 2. (NB: Since reports of multicentre studies will be represented more than once if they involved collaboration across WHO Regional boundaries the figures presented in Table 2 will not total to 4871 (100%).)

Both literature searches demonstrate that a simple search on Medline or even two databases is insufficient

	Database searches	Non-indexed studies	Total
Breast	215	217	432
Bladder cancer	262	157	419
Lymphoma	99	234	333
Childhood cancer	73	105	178
Palliative Care	54	30	84

Table 1. INCTR/ESO Egypt study: Indexed and non-indexed studies identified through electronic (database searches) and manual searches (non-indexed studies).

WHO Region	No. of Studies (%)	Leading countries (n)
Africa	230 (5%)	South Africa (80)
Americas	726 (15%)	Brazil (330)
South East Asia	569 (12%)	India (451)
Europe	1465 (30%)	Turkey (674)
Eastern Mediterranean	590 (12%)	Egypt (190)
Western Pacific	1230 (24%)	Mainland China (777)
'Global'	91 (2%)	USA (46)

Table 2. Breast cancer in LMI countries: No. of publications and "leading" countries arranged by WHO Region.

to identify all studies relevant to LMI countries and that establishing a comprehensive evidence base currently requires multiple strategies. Of the 1383 studies identified in the Egyptian project 675 (49%) were identified by electronic searches of four databases and 708 (51%) were only identifiable by searching the content pages and local online citations of Egyptian journals. Of the 4871 breast cancer studies identified only 2499 (51%) were indexed on Medline; 1096 (22%) were available on Embase only; 702 (15%) were not found on either database but were retrieved from non-indexed conference proceedings. (These latter percentages would undoubtedly have been lower if hand searches of un-indexed journals published in low or middle income countries for breast cancer articles had been undertaken.)

Details of the studies identified by the ESO/INCTR Pilot Study will be accessible next year on the University of Cairo website (http://www.cu.edu.eg). Bibliographic citations of the breast cancer articles will be made accessible through the new Web-based *BHGI/INCTR Breast Cancer Control Library* being developed in collaboration with INCTR by Breast Health Global Initiative (BHGI) staff at the Fred Hutchinson Cancer Research Centre, Seattle WA USA.

Bibliographic databases of published studies on their own will be of limited use to decision makers: their most important function is to pull together the raw material from which evidence-based cancer control strategies may be developed. Faced with such a large body of evidence, there is a clear need for taxonomic surveys to arrange and synthesise the data into useful packages, quality assessment of, for example level 1 evidence (randomized controlled clinical trials) and systematic reviews of high quality information in order to facilitate cancer control planning and research agenda-setting in poorer resourced countries.

In the high income countries the technological advances in information management of the last thirty years, coupled with the growing awareness of the dangers arising from methodological bias in the reporting and use of research outcomes, have transformed how research agendas have been developed. In particular the attention paid by Governmental decision-makers (e.g. the UK Department of Health) to the importance of evidence from research syntheses stems in part from the recognition that advances in information technology (IT) now allow us access to more scientific evidence than ever before both through increasingly comprehensive data bases and also through linkages that permit the researcher to progress along a specific desired path in collecting all relevant material. Several major projects, such as the US National Cancer Institute's caBIG and the UK National Cancer Research Institute's ONIX permit simultaneous searching of multiple, integrated data bases containing different but complementary information, such as molecular profiling and clinical characteristics, and subsequent analysis pertinent to a specific question raised by a researcher uninvolved with the data collection.

"All existing sources of evidence, especially systematic reviews, must be considered carefully before undertaking research. Research which duplicates other work unnecessarily, or which is not of sufficient quality to contribute something useful to existing knowledge, is unethical."

Research Governance Framework for Health and Social Care
Department of Health 2nd ed.
April 2005 2.3.1

The model established by Cochrane systematic reviews – that each review should conclude with a brief summary of the review's implications for clinical practice and future research – has become accepted as a methodological benchmark. The contribution of properly conducted research syntheses to improvements in clinical treatment is universally acknowledged with systematic reviews and meta-analyses now occupying the apex of most research hierarchy pyramids (sometimes vying for top position with large randomised trials). The equally valuable role systematic reviews have to play in determining

research agendas is less widely recognised. This role (as outlined in the five research functions of systematic reviews listed in Box 2) can be summarised as helping facilitate the preparation of high quality study protocols for ethical review and protecting patients from recruitment into badly designed or unnecessary studies.

Five Research Functions of Systematic Reviews:

1. Identify all relevant published studies
2. Provide methodologically transparent summaries/syntheses of the scope, outcomes and quality of published research
3. Prevent wasteful duplication of research effort and resources
4. Identify areas where new or better research is needed
5. Identify methodological challenges previously encountered by authors

Table 3. Five Research Functions of Systematic Reviews.

Whereas the original data INCTR has identified comes from studies conducted in LMI countries, expertise in preparing systematic literature review and meta-analysis still resides mostly in high income countries. Out of the 4871 published articles identified in the INCTR Breast cancer literature search only 29 systematic reviews and meta-analyses (<0.6%) were identified. Therefore, in parallel with improving access to published reports of research studies, capacity in research synthesis expertise needs to be built in low and middle income countries.

Ad hoc introductory programs are useful in raising awareness but can be expensive and have not been shown to be very productive in terms of published output. The best way to build capacity is to ensure that knowledge of systematic review methodology - how systematic reviews are prepared and what their limitations are - becomes an integral part of the postgraduate medical training (PGMT) curriculum. Universities and other providers of PGMT have a responsibility to require that future generations of health care professionals are fluent in the fundamentals of evidence-based practice. However, they may also need to build their own bibliographies, since it is clear that the well-known data bases fail to incorporate evidence from a large number of journals. Indeed, as countries increase their research outputs (to say nothing of practice guidelines and information for the public) individual data bases may not be able to handle the deluge of data, such that simultaneous searching of multiple data bases scattered around the world will be required, along with applications that permit rapid manipulation of both bibliographic and other forms of data. The integration of hospital based data, bearing in mind issues of confidentiality, may be a future step in a holistic approach to data gathering and use. Such comprehensive approaches will require national health systems, international collaboration and the development of robust interfaces to ensure interoperability. Indeed, such approaches will permit the use of a considerable amount of data collected outside the research arena, which is presently largely inaccessible and therefore wasted, to be used to the benefit of populations and patients.

Five conclusions may be drawn from the progress of the Global database project so far:

1. Research articles originating from low or middle income countries are under-represented in the more accessible indexed databases.

2. Searching one or even two reputable databases is insufficient to identify all relevant studies on an issue.

3. The development of guidelines and national cancer control plans can be facilitated through building an accessible and maintained database of relevant research literature.

4. More systematic reviews of reports of studies conducted in low and middle income countries are needed, but will only be possible after all data is catalogued, made widely accessible, and assessed for quality.

5. Postgraduate medical training curricula should include an appreciation of systematic review methodology in order to encourage the development of evidence-based clinical practice and research.

Much of the published research, albeit markedly less in quantity, conducted in low and middle income countries remains less accessible than that conducted in high income countries and consequently unread. We can use existing technology, combined with growing expertise in systematic reviews, to provide a clearer picture of the scope, quality and outcomes of studies conducted in poorer resourced settings and to benefit from the lessons they bear. ■

Mark Lodge
INCTR UK
Oxford, UK

ANNUAL MEETING 2009 REPORT

INCTR's Annual Meeting 2009 was held from 22nd–24th, March in Antalya, Turkey. The Annual Meeting is unique in having, as its entire focus, cancer in developing countries. It is generally held in a developing country, and a high proportion of its speakers come from developing countries. This creates a sense of "ownership" which is vital to the active participation of health professionals from such countries in collaborative INCTR projects. The purpose of the Annual Meeting is to bring together INCTR members from all over the world to be updated on INCTR programs and projects, to comment and exchange views relating to INCTR activities, to have the opportunity to participate in educational sessions devoted to various aspects of cancer control in developing countries and to consolidate the spirit of friendship and collaboration that is central to INCTR's mission. Some 182 participants from 41 countries attended the 2009 meeting.

INCTR AWARDS

At each of its Annual Meetings, INCTR gives two awards to individuals who have made outstanding contribution to cancer treatment or research in one or more developing countries. These awards are given in part to recognize the achievements of the recipients, and, since each awardee gives a presentation on his or her work, in part to inspire others to greater efforts by demonstrating that much can be achieved even when resources are limited. The Nazli Gad-El-Mawla award is given for outstanding contributions to cancer control by an individual from a resource-poor country.

INCTR Awardees, Dr Masera (left) and Dr Ngoma (right). Dr Cavdar (local host) is on the extreme right.

The 2009 award was made to Dr. Twalib Ngoma, a radiation oncologist from Dar es Salam, Tanzania. Dr Ngoma is the Executive Director of the Ocean Road Cancer Institute in Dar es Salam, an institution that he persuaded the government to establish by an act of Parliament in 1996. He is the former President of AORTIC (African Organization for research and Training in Cancer), in which capacity he dedicated himself to putting cancer firmly on the priority list of African health ministers. In Tanzania, Dr Ngoma is the Secretary for the National Cancer Strategy Steering Committee that is responsible for the development and implementation of the Tanzanian cancer control strategy. In this respect, he acts as advisor for cancer to the Ministry of Health and Social Welfare. He is also the Team leader for palliative care for cancer and HIV/AIDs patients in Tanzania. Dr Ngoma serves as the Head of the Tanzanian office of INCTR and participates in several INCTR research projects.

The Paul P. Carbone award is given for outstanding contributions to oncology or cancer research by an individual from a resource-rich country. The 2009 award was made to Dr. Giuseppe Masera. Dr Masera is Director of the Pediatric Clinic of San Gerardo Hospital, Monza (Milan), Italy, a large (900 beds) teaching hospital affiliated to the School of Medicine of the University of Milan-Bicocca, where he is also a Professor of Clinical Pediatrics. Dr Masera was one of the founders of the Italian Association of Pediatric Hematology and Oncology (AIEOP). After being appointed full Professor of clinical Pediatrics in 1984 he expanded his interests to include collaborations with international institutions. In 1986, Dr Masera developed a collaboration with "La Mascota" hospital that resulted in the establishment of a new unit for pediatric hematology/oncology in Nicaragua's capital, Managua. He also promoted a twinning project between La Mascota and the Pediatric Hematology/ Oncology Department in Monza.

NETWORK

Audience during the Opening Ceremony, 22nd March.

Subsequently, in 1996, he created the Monza International School of Pediatric Hematology/Oncology (MISPHO) in order to promote the training and continuing education of specialists in pediatric hematology/oncology in 15 Latin American countries. Dr. Masera also worked with St Jude Children's Research hospital in support of the development or a pediatric oncology collaborative group involving six countries in Central America (AHOPCA).

INCTR REPORTS

Reports were given by the President, and by members of INCTR's Special Panel, Clinical Research, Education and Palliative Care programs relating to ongoing and proposed projects. These reports are available on INCTR's portal: http://inctr.ctisinc.com:9000/sites/InCTR/Education/Annual%20Meeting%202007/Forms/AllItems.aspx

KEY NOTE LECTURES

Keynote lectures are given by distinguished scientists, physicians or others involved in cancer control to provide broad overviews of topics relevant to other elements of the meeting. This year Dr. Stuart Bell, from the National Cancer Research Institute UK Informatics Initiative, spoke on *Building an International Online Cancer Research Community*, Dr. Kathleen Foley, from the Open Society Institute, USA, spoke on *Improving Palliative Care at a Global Level*, Dr. Fikri Icli, Ankara University, Turkey, spoke on *Prevention of Smoking: the Role of the Health Provider* and Salih Emri, Hacette University, Turkey, spoke on *Mesothelioma in Turkey; An Environmental Hazard.*

PROFFERED PAPERS AND POSTERS

Each annual meeting provides opportunities for participants to present their own work. As an added incentive, a prize is given for the best posters in adult and pediatric oncology. This year, there were eight oral presentations of participants' own work and over 87 posters displayed throughout the course of the meeting. These provided focal points for much lively discussion.

This year's awardees for "Best Pediatric Poster" were Drs. Al-Hahad S., Al-Jadiry M. and Al-Khafagi M. from the Children's Welfare Teaching Hospital, Irak, for their group's work on *Prevalence of Hepatitis in Pediatric Malignancy at a Children's Welfare Teaching Hospital*. Awardees for "Best Adult Poster" were Drs. Dey S., Pandey R., Gupta P., Biswas S., Roy P., Gharami F.H., Koner S. Mukherkjee A. from Netaji Subhash Chandra Bose Cancer Research Institute, India, for their work on *Efficacy of i.v. Zoledronic Acid Compared to i.v. Ibandronic Acid in patients with Bone Metastases – a Study from Eastern India.*

This year, for the third time, an additional five people were selected by a special panel (led by Dr. Ama Rohatiner), on the basis of posters they had co-authored, to participate in a 5 day *Workshop on Scientific Writing* to be conducted by Elizabeth Heseltine, who has for long edited the monograph series on carcinogenic risk of the International Agency for Research on Cancer. Those selected were: Dr N. Anwar from Shaukat Khanum Memorial Cancer Hospital

Dr Muhammad Umar Khan, laureate of INCTR's Workshop on Scientific Writing.

& Research Center in Pakistan, Dr. R. Anorlu from the College of Medicine, University of Lagos in Nigeria, Dr. M. Al-Jadiry from Children Welfare Teaching Hospital – Medical City in Irak, Dr J. Iqbal from Jinnah Hospital and Allama Iqbal Medical College in Pakistan and Dr. M. Umar Khan from Shaukat Khanum Memorial Cancer Hospital and Research Center in Pakistan. The aim of this workshop is to assist in the development of a draft manuscript into a paper of sufficient quality to be submitted to a national or international journal. To date, seven of the 10 papers that were included in the prior two workshops have been published.

As with prior Scientific Writing Workshops, financially support was provided by the Office of International Affairs of the National Cancer Institute.

CONFERENCE THEMES AND WORKSHOPS

The main conference themes for the 2009 meeting, entitled INCTR's Strategies for Cancer Control in Developing Countries were *Education for Cancer Professionals, Pediatric Cancers, Oral and Gastroinstestinal Cancers* and *AIDS-related malignancies*. Two simultaneous workshops were held on *Breast Cancer Control* and *Lymphoma Pathology in Developing Countries.*

PANEL DISCUSSION

Consensus discussions are held in order to develop specific recommendations or draw conclusions on the selected topics. This year a consensus discussion was held on Ethical Issues in Research in the Developing Countries (see report on page 17).

MEET THE EXPERT SESSIONS

Early morning "Meet the Expert Sessions" were attended by a large number of early-birds. In each session, one or two experts led the discussion, which, for the most part, engendered lively audience participation. The wide ranging topics included: *Supportive Care in Patients Undergoing Therapy, Hospital Versus Home-Based Palliative Care, Cancer Registration, Developing Sustainable Programs in Cancer Therapy, Lymphomas in Developing Countries, The Physicians' Role in Nursing Education, Wilms' Tumor and Pediatric Nasopharyngeal Cancer, Psychosocial Aspects of Pediatric Oncology, Empowering Women Financially and Educationally, and The Development of Partnerships.*

Dr Joe Harford (OIA) discusses cancer registration at an Early Bird Session.

COMMITTEES, STRATEGY GROUPS, BOARDS AND FORUMS

A number of committee and board meetings took place in the course of the meetings including an *Office and Branch Meeting*, in which ongoing activities, accounts, fund raising and communications throughout the network were discussed; an informal meeting of the *Special Panel of the Advisory Board*, the role of which includes selecting the future venues for the Annual Meeting, selecting INCTR Awardees and providing advice on INCTR programs; and a *Members Forum*, in which INCTR members have an opportunity to comment on any aspect of INCTR's work and to suggest new areas of endeavor with respect to INCTR's overall programs, projects, structure, and management. Associate members are also be able to nominate two members of the governing council.

An expanded Annual General Meeting and Offices/Branches meeting will be held in Brussels on March 26th-27th, 2010 on the tenth anniversary of INCTR's establishment in the Belgian Capital.

SIDE MEETINGS

Various "side" meetings took place in breaks or in the evenings during the three day period of the main meeting. Among them were a dis-

THE NAZLI GAD-EL-MAWLA AWARD LECTURE

TWALIB A. NGOMA, OCEAN ROAD CANCER INSTITUTE (ORCI), DAR ES SALAAM, TANZANIA

I consider it a great honor to be the recipient of the 2009 **Nazli Gad El-Mawla Award** and appreciate the opportunity to share my experiences with all of you. The main purpose of my lecture is to show that even when resources are very limited, with good planning and prioritization a few things can be done, and done well. But firstly, I would like to give special thanks to the many individuals who have contributed to what I am about to share with you, including my parents, my family, teachers, mentors, colleagues, international collaborators and the almighty God for giving me life, strength and the realization that the universe is like a great echo chamber which will sooner or later send back to you what you transmitted. I have learned that if you love humankind, the love will be reflected back to you. If you sow anger and hatred, you'll reap anger and hatred and if you think mainly of yourself, people will never be drawn to you. Whereas if you put others first and yourself last, every one will be your friend. In this lecture I will attempt to highlight my 30 years of work and contribution to cancer control in Tanzania specifically and Africa in general. It is my hope that I can convey a picture of the enormous needs and consequent gaps in cancer control in Africa and that all of you in your various capacities will be motivated to do what you can to help address the existing problems.

The defining moment in my career was in 1975 when, as a third year medical student, a visiting professor in radiotherapy from Howard University, in Washington DC, caught my imagination. Prof. Ulrich

Konrad Henschke was a remarkable man in his early sixties with an infectious enthusiasm. He gave us a memorable lecture on radiotherapy and cancer that inspired me to devote my own career to radiation oncology.

CONTRIBUTIONS TO CANCER CONTROL

I would list the following as my main contributions to cancer control in Tanzania: raising the visibility of cancer as a health problem in Tanzania; persuading the government to establish ORCI by an act of parliament; expanding and developing ORCI into a regional comprehensive cancer center; establishing an INCTR office in Tanzania; promoting the development of palliative care; instituting cervical cancer screening; improving the treatment (as part of an INCTR collaborative program) and access to care (supported by a My Child Matters award), of children with Burkitt lymphoma; making Tanzania a PACT model demonstration site; ensuring that oncology and palliative care training programs are accepted and approved in local universities; instituting telemedicine services; steering the National Cancer Control Strategy and Action Plan; and assisting in the establishment of other cancer centers.

BURKITT'S LYMPHOMA: WHAT WE CAN DO, AND WELL

Burkitts Lymphoma was initially described by a surgeon, Dennis Burkitt, in Uganda, in 1958 and is the commonest childhood cancer in Tanzania. Burkitt lymphoma is a potentially curable lymphoma using simple chemotherapy alone and we have done all we can to increase awareness of this and to encourage appropriate management and research. We have also developed Burkitt Lymphoma National Treatment guidelines.

CHALLENGES AND INTERVENTIONS

When I was in medical school I was taught that cancer is rare in Africa. Now GLOBOCAN data show that over half of the global cancer burden occurs in developing countries. The growing cancer burden in developing countries must be addressed but goals need to be realistic and achievable and prevention must be at the core. Limited resources and competing health priorities allowing, all possible steps must be taken to prevent avoidable cancers, to treat curable cancers and to provide palliation and supportive care to those patients who need it. The experience with Burkitt lymphoma in Tanzania has proved that even in low resource countries, with good planning and funding it is possible to give good quality treatment to more children and improve survival. And if we can treat Burkitt lymphoma well, we can also do well in a few other cancers. ■

THE PAUL P. CARBONE AWARD LECTURE FOR INTERNATIONAL ONCOLOGY

GIUSEPPE MASERA, UNIVERSITY OF MILANO-BICOCCA, S.GERARDO HOSPITAL, MONZA, ITALY

Every year about 200,000 new cases of childhood cancer are diagnosed worldwide, some 85% of whom live in low and middle income countries (LMI) – a figure that is projected to increase to over 90% in the next 15-20 years. When adequately treated, childhood cancer has a high cure rate (overall 5-year survival is 75-80%), but unfortunately, most children in the world receive poor or no therapy. While survival rates have constantly increased in economically advanced countries since the 1960s this has not been the case in countries with limited resources, creating a progressively increasing "mortality gap" that will be difficult to eliminate. As countries develop and infectious diseases are increasingly well controlled, non-communicable diseases (including cancer) take on increasing importance. Because of the young median age of their populations childhood cancer accounts for a increasing fraction of all cancer in LMI. Together, these observations provide ample justification for directing more resources into pediatric cancer in developing countries.

Our own experience with Nicaragua began in 1986 when we replied to a request from Dr. Fernando Silva, a Pediatrician-Poet, who was the Director of the "La Mascota Hospital" in Managua. This led to the development of a collaborative program with the following goals:

- To develop a well-equipped Pediatric Cancer Unit (PCU) at La Mascota Hospital, and twinned with the University of Monza, and an outreach program to peripheral hospitals in Nicaragua.
- To improve survival in children with cancer by providing the best possible (in the local context) standardized treatment at

no cost and associated with financial support for needy families.
- To provide continuing education for health professionals.
- To develop financial support from diverse sources to ensure sustainability.
- To create a "therapeutic alliance" among health professionals and parents/volunteers, in order to sensitize health authorities and mobilize resources.
- To reduce refusal and abandonment of therapy, a significant problem in Managua, by developing a psychosocial program and a "long-distance adoption" program.
- To promote formal research projects in order to encourage a scientific approach and ensure continuous progress.

The success of this program, in the early 1990's, led to a new idea: the extension of this approach to other Latin American countries through the establishment of other twinning programs. The Monza International School for Pediatric Hematology/Oncology (MISPHO) was created and, since 1996, meetings for discussions and training have been organized with the participation of about 40 pediatric-oncologists from 15 countries (Bolivia, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, Peru, Dominican Republic, Uruguay, and Venezuela). Additional twinning programs were established between Honduras, El Salvador and Guatemala with St. Jude; Paraguay with Modena and Madrid; Colombia with Boston; and the Dominican Republic with the University of Colorado College of Medicine, (Aurora, USA).

In 1998 the "Asociacion de Hemato-Oncologia Pediatrica de Centro America" (AHOPCA), was created, which included all the Central American countries and the Dominican Republic and collaborated with the International Out-reach Program of St. Jude, the Pediatric Oncology Group of Ontario (POGO) and MISPHO.

After more than 20 years the "La Mascota Program" has achieved the following:

- a well functioning Pediatric Hemato-Oncology Unit that has treated about 2,700 children with an overall survival rate of approximately 60%
- excellent facilities, including 32 patient rooms, an outpatient clinic, an operating room for minor procedures and day surgery, a hematology laboratory and a hostel for patient families with 18 rooms and 2 play-rooms.
- the involvement of Nicaraguan civil society through the Parents' Association (MAPANICA) and volunteers (CONANCA).

The La Mascota Program demonstrates that a global, long-term twinning program is feasible, rewarding, and able to create new opportunities and new collaborations.

Consequently, we believe that "an attempt to reduce the gap in mortality from childhood cancer between developed and less developed countries should become an integral part of the care and research activities of hemato-oncological departments in developed countries and is not simply an exercise in solidarity". ■

cussion about the development of a new INCTR Pathology Program, a meeting to discuss the treatment of acute lymphoblastic leukemia in India, a meeting of Indian pediatric oncologists, a meeting to discuss the on-going project on the treatment of Burkitt Lymphoma (HIV-related or not) in Africa, supported by the NCI Office of HIV and AIDS Malignancies, several meetings of the palliative care group focused on the several ongoing projects in Nepal, India, Brazil and Tanzania and a Fund-raising Committee Meeting.

The Gala Dinner.

PUBLICITY

Several press conferences took place with journalists from Turkish Newspapers; interviews relating to cancer in developing countries in general, and Turkey in particular, were conducted by our Turkish hosts for Broadcast on Turkish television.

CONFERENCE EVALUATION

Between 87% and 92% of attendees who completed the evaluation form rated the meeting very good or excellent with regard to fulfillment of expectations re: learning outcomes, satisfaction with the content and quality of the education sessions and enhancement of the sense of an INCTR community.

CME ACCREDITATION

The INCTR Annual Meeting 2009 was approved by the Accreditation Council of Oncology in Europe (ACOE). The 8th INCTR conference has been granted European endorsement by the UEMS and awarded 15 European Continuing Medical Education Credits (ECMEC) credits. The ECMEC has been recognized within those European States which have agreed to participate in this European system and by the American Medical Association (AMA). ■

INCTR would like to thank the following organizations for their support of the INCTR Meeting 2009

ETHICAL PRINCIPLES VERSUS GOOD RESEARCH PRACTICES IN RESOURCE-POOR COUNTRIES

The INCTR Annual Meeting has become a much anticipated forum for the entire INCTR community and supporters to discuss, not only the challenges and advances in cancer treatment and research in developing countries, but also to explore some of the larger issues that surround the work of clinicians and researchers. Over the past few meetings, relying on topics arising during its meetings and review of ongoing INCTR research projects, the INCTR Ethical Review Committee has prepared a panel discussion on topics pertaining to ethics in clinical research that have recently been vigorously debated, particularly in Europe and the USA, with the goal of discussing their relevance to, and potential impact on, research in developing countries.

Two important events in research ethics and good practices preceded the Ethics Panel Discussion in Antalya. The first was the October 2008 revision of the *Declaration of Helsinki* (DoH)[1] by the World Medical Association (WMA). The second was the recent publication in the national Official Journal on 23 December 2008 by the Turkish Government of the *Regulation on Clinical Trials*, which entered into force in January 2009, only a few months prior to the commencement of the INCTR Annual Meeting.

Both of these events are highly significant for cancer researchers in developing countries. The revision of the DoH followed years of debate regarding the fundamental ethical tenets for biomedical research, with a particular focus on the poorer, less developed areas of the world. The newly revised 'basic principles' have the potential to impact directly on what is 'acceptable and not acceptable' in designing and implementing the oncology research INCTR carries out in some of the most challenged and challenging areas of the world.

The new Turkish *Regulation on Clinical Trials* provided a concrete example on 'home territory' regarding how a country is able to develop through regulation to improve the possibilities and framework for research. Building on its earlier 1993 Regulation on Investigational Drugs (Ðlac Arastırmaları Hakkında Yonetmelik) and 1995 Good Clinical Practice Guidelines, Turkey took deliberate steps at the end of 2008 and the beginning of 2009 to bring its legislation in line with the EU Directive on Implementing Good Clinical Practice (2001/20/EC)[2] of 4 April 2001 as well as the subsequent EU [Commission] Directive 2005/28/EC on Clinical Trials[3].

These two developments, one global and one national, provided a strong background for the panel and the audience, which included many who have conducted research in countries with limited resources, to debate ethical principles and their applicability to current research practices. The discussion moved between principles, regulations, and practices, exploring their inter-relationship, mutual support, and sometimes potential contradictions.

The session opened with two questions posed by Francis P. Crawley, Chairman of the INCTR Ethical Review Committee:

1. What does research ethics bring to clinical trials in oncology globally?
2. Does the revised DoH contribute to the needs of researchers in developing countries?

In order to understand better the role of research ethics in developing country research, the background to the WMA's development of the DoH was sketched between its first agreement in 1964 and the recent controversies leading to the 2008 revision. The history of the DoH provides a nearly unique insight into how research ethics developed, tensions between what is considered acceptable or not acceptable in experimenting on persons, and complicated relations between social and political interests that impact on society's views on ethical principles.

The discussion highlighted the central role of the individual in research ethics, as stated in paragraph 8 of the DoH: 'In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.' This legitimate concern for the well-being of the individual is challenged at times, particularly in developing countries. The tension is reflected later in DoH's paragraph 21: 'Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.' INCTR scientists and professionals seemed able to find many concerns between this interest of promoting the health of their individual patients and finding new cancer treatments and interventions for advancing improved care, especially for the poorer and more vulnerable among our global populations. Risks and burdens, as well as the importance of the research objectives, need to be evaluated by both the research subjects and investigators. Persons living in different cultural contexts, or with different levels of education, may have different needs and expec-

tations regarding their participation in health research. Decision-making on the ethical acceptability of the design and performance of a research protocol needs to be carried out locally according to the national ethical review structures with input from Community Advisory Boards, patient organizations, and those involved with the provision of healthcare.

Further impact on decision-making in research ethics brought about by revisions made by the DoH included:

- a highlighting of the need to further protect vulnerable individuals, communities, and populations in research;
- the requirement to register publicly all clinical trials;
- the ongoing sensitivity around the use of control arms, particularly placebos, in research; and
- the need to ensure that research participants (communities and individuals) may share in all benefits of the research as well as to describe in the protocol provisions for post-trial access to interventions used in the research.

All of these topics resonated well with the INCTR research community.

Professor Tezer Kutluk of Hacettepe University and a member of the Board of the International Union Against Cancer (UICC) provided a cutting edge presentation on 'Ethical Principles in Oncology Research in Turkey'[4]. He focused on the long history of the regulation of investigational medicines in Turkey, highlighting Turkey's many contributions to the international discussion, as well as to the developments leading to the publication of the recent *Regulation on Clinical Trials*.

Professor Kutluk emphasized the idea that the central principles in medical ethics should be held internationally. He outlined the evolution of medical ethics in Turkey, which he suggested began formally in 1960 with the first regulation on investigational drugs in Turkey. This was then followed in 1982 with the introduction in the Turkish Constitution of the need for consent in human experimentation. A new law on investigational drugs was introduced in 1993. In 1995 Turkey adapted the ICH Good Clinical Practice Guidelines as part of its own requirements[5]. These changes helped to guide clinical trials in Turkey between 1993 and end 2008.

The December 2008 *Regulation on Clinical Trials* brought significant changes to the research landscape in Turkey. One major change was the dissolving of Local Ethics Committees to be replaced by a network of Regional Ethics Committees. In addition, the Central Ethics Committee will be replaced by an 'Advisory Board for Clinical Trials'. Another major change was the introduction by the Ministry of Health of Good Clinical Practice training programs, now mandatory for members of ethics committees. In accordance with the new *Regulation*, the Ministry of Health is also drawing up clear guidelines on the ethical conduct of 'non-commercial' clinical trials.

Professor Ahmet Demirkazik of Ankara University and the INCTR provided a presentation on 'Ethical Practices in Oncology Research in Turkey'[6]. He emphasised the key role of clinical trials for developing new oncology interventions in Turkey, reiterating the importance of the December 2008 *Regulation on Clinical Trials*. Professor Demirkazik stressed the point that much was new in the *Regulation* (some of which is in conflict with previously existing regulations or practice), the value of which would only be ascertained with experience.

A major challenge in oncology research in Turkey had to do with delays in receiving final ethical review clearance for clinical trials. Under the 'old' system, local ethics committees had to transfer their decisions to the Central Ethics Committee. The 'new' system was still not in place, but it was hoped that implementation would be accelerated. It was felt that remaining conflicts with existing regulations put too much of a burden on clinical trial investigators while not providing them with the financial or administrative room to address their challenges. Clinical trial insurance, for example, remained a major hurdle for oncologists wanting to initiate their own clinical trials. In addition, the hospital administration retained the major control over the project budget and its expenditures. This meant that investigators were often underfunded and understaffed, including insufficient clinical trial staff (site coordinators, study nurses, data managers and pharmacists).

The experience of Turkey in developing a Good Clinical Practice and ethical review framework for clinical trials was well appreciated by the INCTR community. For many in the audience both the advances as well as the ongoing frustrations seemed to ring close to home.

During the open discussion with the audience, a number of issues were brought into the panel discussion reflecting current concerns by INCTR researchers as they address the ethical challenges in research within their resource-poor countries. Points raised during the discussion included the following:

- The ongoing challenge at the need for the approval of clinical trials against the deficit of ethics committee personnel to review applications, particularly in developing countries. There remain significant challenges in

training members of ethics committees and in ensuring their appropriate composition. Some participants felt that a patient representative should be included in all ethics committees reviewing research.

- Equipping resource-poor settings for research is a major challenge that is under-addressed in international regulations and the international discussion on research ethics. Reference was made to the capacity-building activities carried out by the INCTR and the GCPA, sometimes in cooperation, in Africa, Asia, Latin America, and Eastern Europe.
- The problem of incentives for clinical trial participation (particularly cash incentives) was raised, as well as the unethical influence this has on both the researcher and the patient/clinical trial subject. It was felt that at times the use of undue incentives might also bear on participants' expectations for access to trial benefits.
- Cancer screening was highlighted as an area of particular concern for the INCTR community, especially the difficulty of providing information leading to voluntary rather than coercive testing.
- The DoH requirement that in clinical trials any new intervention should be compared to best current proven intervention was discussed in depth. Unlike some other branches of medicine (where 'best' may indeed mean 'best'), it was felt that 'best current proven' in the context of medical oncology should mean best available in the local setting. Insisting on best (and often highly toxic) internationally available interventions may either prohibit research in developing countries or risk patient/subject lives where support (such as blood products or ICU facilities) is not locally available.
- Access to clinical trials was highlighted and discussed. Members of the audience felt that most patients are in favour of research and see it as a means of accessing treatment. At the same time, members felt that this access was not a patient's right. Currently including overseas or resource-poor sites in multi-centre trials is often too expensive in terms of set-up and monitoring. Local capacity must be strengthened and improved before progress in this area can be made. For resource-poor countries, the development of research for oncology is considered a good and even a necessity. Clinical trials are a key way to improve health care in oncology and meet patient needs for healthcare.
- The participants stressed the overriding paramount importance of giving attention to local populations and their needs when conducting scientifically and ethically sound clinical trials in oncology in developing countries.

The Ethics Panel Discussion brought the INCTR experts two important avenues for viewing their ethical challenges in clinical trials: the global discussion on research ethics in the DoH and the national approach to resolving Good Clinical Practice exemplified by the Turkish *Regulation on Clinical Trials*. At the end of the session, the participants generally agreed on the need to work together in research ethics within the INCTR in order to improve their research and eventually develop new cancer interventions for some of the world's poorest peoples. ■

References available on www.inctr.org/newsletter

Sabine Perrier-Bonnet, Alliance Mondiale Contre le Cancer AMCC/INCTR, France - Patricia Scanlan, Ocean Road Cancer Institute & INCTR, Tanzania - Francis P. Crawley, Good Clinical Practice Alliance, Europe & INCTR Ethical Review Committee, Belgium

EXPERT VISIT TO EAST AFRICA

INCTR, with the support of the NCI Office of HIV and AIDS Malignancies, is working to establish improved pathological diagnosis in the context of its study of HIV+ and HIV- Burkitt lymphoma in equatorial Africa. In this context, a team of 5 pathologists visited four participating centers in East Africa between 7th and 12th June to assess available equipment and techniques and to assess the accuracy of diagnosis. A major problem in resource-poor countries is the lack of modern diagnostic reagents. INCTR will assist in making modern diagnostic techniques available in these centers and also plans to introduce a telepathology program built on iPath, a web-based application enabling case reviews, consultation and education. ■

INCTR PAX TEAM VISIT TO NEPAL

Nepal was the first country to participate in INCTR's palliative care program, and services continue to grow and develop in a number of institutions, both within and outside the greater Kathmandu area. This visit, which took place between March 25th and April 3rd, focused on the establishment of a training program at the Nepal Institute of Health Sciences, increased networking between sites providing palliative care services, the establishment of a Nepal Hospice Palliative Care Association, and the identification of potential "physician champions" to help lead palliative care initiatives in Nepal. More information is available in a report available on INCTR's portal (http://inctr.ctisinc.com:9000/sites/InCTR/Palliative/default.aspx). ■

HEALTHCARE IN KENYA; THE ROLE OF THE KENYA MEDICAL RESEARCH INSTITUTE

Kenya, a former British colony, which was named after the second highest mountain in Africa, gained its independence in 1963. It has a population of approximately 38 million. Kenya spent 4.6% of its Gross Domestic Product (GDP) on healthcare in 2006. This was well below the high-income countries' average of 11.2% for the same period. Total government health spending was US$ 14 per capita at average exchange rate in 2006 which compares with the high income countries average of US$ 2470. Life-expectancy for women was 51 years and 50 years for men in 2006. This is expected to decrease due to the rising incidence and prevalence of HIV/AIDS. The child mortality rate was 78 per 1,000 live births. The under-financing of the health sector has reduced its ability to ensure an adequate level of healthcare for the population. Thus, the provision of health and medical care services in Kenya is partly dependent on donors.

CANCER IN KENYA

In 2004, the mortality rate for cancer was 129 per 100,000 people which is similar to high income countries although Kenya has a much lower incidence rate. Cervical cancer is the most common cancer in women especially in the rural areas. Data from Nairobi Cancer Registry, located in an urban setting show that breast cancer is the most common cancer in women closely followed by cervical cancer. Cancer of the oesophagus is the most common cancer in men.

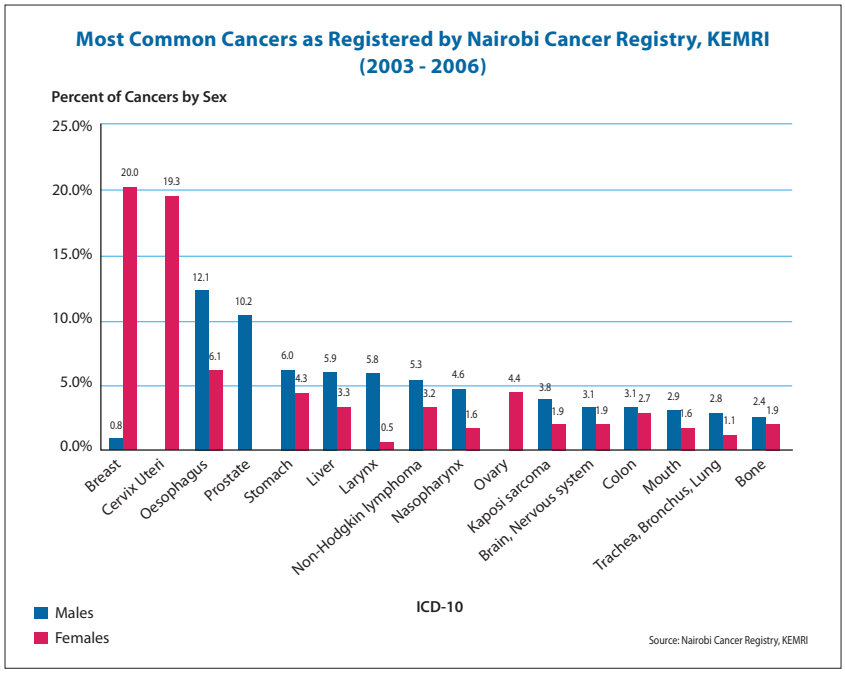


Figure 1. Frequency of the most common cancers in Kenya.

Over 90% of all cancers present late, in clinical stages III and IV. Against this background, there are only two public radiotherapy centers in Kenya some eight medical and radiation oncologists and 14 palliative care specialists.

HISTORY OF KENYA MEDICAL RESEARCH INSTITUTE

The Kenya Medical Research Institute (KEMRI) is a state corporation established through the Science and Technology Act (Amendment) of 1979, as the national body responsible for carrying out health research in Kenya. KEMRI has grown from its humble beginning 27 years ago into a regional leader in human health research. The Institute currently ranks as one of the leading centers of excellence in health research both in Africa as well as globally. KEMRI has been mandated to:

- Conduct research in human health.
- Co-operate with other organizations and institutions of higher education in training programs and in research relevant to health care in Kenya.
- Disseminate and translate research findings for evidence-based policy formulation and implementation.
- Co-operate with the Ministry of health, which is presently responsible for medical research, the National Council for Science and Technology and the Medical Science Advisory Research Committee on matters pertaining to research policies and priorities.
- Undertake any or all actions that are believed necessary, desirable or expedient in order to carry out its functions.

RESEARCH PROGRAM COMMITTEES

There are four Research Program Committees which are essentially

coordinating committees with the mandate to oversee all the research activities that are being carried out in the Institute with a view to providing advice and direction for national development. Each research Program Committee is composed of a multidiscplinary group of experts from KEMRI, the universities and the relevant Ministries and Government Agencies.

Infectious Diseases Control Research Program Committee

This program aims at the reduction of the disease burden due to infectious agents and in particular due to HIV/AIDS and related infections. It focuses on research in opportunistic infections, tuberculosis, sexually transmitted infections, viral hepatitis, acute respiratory infections, drugs development and management. The program mainly focuses on epidemiology, immunology, molecular biology, virology, microbiology, prevention and control of infectious diseases.

Parasitic Diseases Research Program Committee

This program aims at the reduction of disease burden due to parasitic infections and particularly due to malaria, schistosomiasis, leishminaasis, filariasis and intestinal parasites. The program concentrates on epidemiology, parasitology, immunology, molecular biology, pathophysiology, vector biology and the control of parasitic diseases, including drug management and the development of vaccines.

Epidemiology, Public Health and Health Systems Research Program Committee

This program is mandated to define and investigate the incidence and prevalence of diseases and health issues of major public health importance and to develop strategies for promotion of better health. The scope of its activities includes health systems research, public health education, applied human nutrition, maternal and child health, reproductive health and population studies, behavioral studies and environmental and occupational health.

Figure 2. Picture of a KEMRI training centre.

Biotechnology and Non-Communicable Diseases Research Program Committee

The focus of this program is the development and promotion of modern molecular biological techniques for the production of pharmaceuticals and biologicals and for other applications relevant to the promotion of health. The program also focuses on non-communicable diseases including oncology, cardiovascular and renal diseases. Two conferences organized by this committee are scheduled to take place in Kenya in 2010. One is focused on biotechnology. The other is the 1st National Conference on Non-Communicable Diseases.

KEMRI CENTERS

KEMRI has been divided into several centers, each having its own mandates and activities. These include:

- Center for Biotechnology Research and Development (CBRD)
- Center for Clinical Research (CCR)
- Center for Geographic Medicine Research-Coast (CGMR-C)
- Center for Global Health Research (CGHR)
- Center for Infectious and Parasitic Diseases Control Research (CIPDCR)
- Center for Microbiology Research (CMR)
- Center for Public Health Research (CPHR)
- Center for Respiratory Diseases Research (CRDR)
- Center for Traditional Medicine and Drug Research (CTMDR)
- Center for Virus Research (CVR)
- The Eastern and Southern Africa Center of International Parasite Control (ESACIPAC)

- KEMRI Graduate School of Health Sciences
- Health Safety and Environment
- Production centre

The Centre for Clinical Research has various mandates, one of which is research in non-communicable diseases including cancer. This falls under a unit referred to as the *Pathology and Oncology Research Unit*.

PATHOLOGY AND ONCOLOGY RESEARCH UNIT (PORU)

PORU has been mandated to undertake research on cancer and other non-communicable diseases. Among the members of staff of this unit are a pathologist, one oncologist, an ear, nose and throat surgeon, a head and neck surgeon, public health personnel and laboratory technologists. A number of research activities on cancer have been undertaken through this unit. The ongoing activities are:

1. Nairobi Cancer Registry

This is a population-based registry covering the population of Nairobi and its environs – approximately 3.5 million people. The registry was established in 2001 with support from the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO). One of the biggest challenges of the registry is financial resources given that it is entirely dependent upon donor funding with no support from the government. This year the registry received financial support from the International Network for Cancer Treatment and Research (INCTR) to re-start the data collection for the period 2005/2006. The objectives of the registry include:

- To establish and maintain, a population based cancer registry for the Nairobi metropolitan region.
- To provide reliable cancer data to the Ministry of Health and other health-care providers and educators for the purpose of planning service delivery.
- To make cancer data available for research in epidemiological studies, clinical management, prevention and other related program.
- To liaise with other local and international cancer organizations on cancer research, prevention, control and surveillance.
- To develop a National Cancer Registry through the establishment of regional registries.
- To advocate for policy frameworks that provide support for and contribute to effective cancer control and prevention programs.

2. My Child Matters program

The My Child Matters project was initiated in the year 2007 with the aid of a grant provided by sanofi-aventis and administered by the International Union against Cancer (UICC). The broad aim of the program is to increase the access to care of patients with Burkitt lymphoma, the commonest childhood cancer in Kenya. The project includes the assessment of the level of knowledge about the disease and identification of potential risk factors among the communities living in Nyanza and Western Provinces of Kenya. A major goal is to educate communities and especially health professionals about the disease in order to ensure that patients receive treatment at the earliest point in the natural history of this rapidly progressive lymphoma. The project objectives are:

- To register cases of Burkitt lymphoma in health-care facilities in Nyanza & Western provinces.
- To identify, if possible, familial and environmental factors associated with the occurrence of Burkitt lymphoma among communities in Nyanza & Western provinces.

Figure 3. Participants in a training session given by the My Child Matters team.

Figure 4. Educating the rural public about Burkitt lymphoma.

- To assess existing level of knowledge of Burkitt lymphoma among patients, their families, neighbours and communities by administering a questionnaire.
- To educate patients, families, their neighbours, communities and health care workers to recognize Burkitt lymphoma.
- To assess changes in health seeking behavior and referral patterns among these communities.
- Through these efforts, to improve the outcome of Burkitt lymphoma treatment in health care facilities.

3. Histology Laboratory

This laboratory falls under the PORU unit and provides histopathology (including immunohistochemistry) and cytopathology services. Various projects besides routine pathology services to the public are served by the histology laboratory. Currently they include research on Hepatitis B, nasopharyngeal cancer and Epstein Barr Virus, Burkitt lymphoma, other lymphomas, cervical cancer, breast cancer and prostate cancer.

AFFILIATION WITH INTERNATIONAL ORGANIZATIONS

International Network for Cancer Treatment and Research (INCTR)

INCTR provides mentorship and support to the My Child Matters project on Burkitt lymphoma in Western and Nyanza provinces. Dr Ian Magrath, President of INCTR visited the rural areas where this study is being undertaken. INCTR has also provided funding for the Nairobi Cancer Registry, which had ceased data collection due to lack of funding. Data collection was re-initiated in June 2008.

UICC and Sanofi-Aventis

These two organizations support the My Child Matters project described above.

Other organizations that have supported the cancer registry in the past include: World Health Organization, International Agency for Research on Cancer and National Cancer Institute, USA, which supported training of cancer registrars in 2002.

Future Plans

It is envisaged that the research programs at KEMRI will continue to emphasize applied research likely to accrue rapid benefits to the public. Our unit (PORU) is dedicated to research and information dissemination in cancer and other non-communicable diseases. The Unit welcomes the participation of additional international networks which will help to expand the number of collaborative programs. Funding and technical support from both local and international collaborators will continue to be pivotal in meeting KEMRI's objectives in the coming years. ■

Anne Rugutt-Korir, Geoffrey Mutuma, Samuel Gathere, Alice Musibi
Kenya Medical Research Institute (KEMRI)
Nairobi, Kenya

PROFILE IN CANCER MEDICINE

MUSIC FOR THE CURE

Sidnei Epelman, the Director of INCTR Brasil, was brought up in São Paulo, where he has also spent most of his professional career as a pediatric oncologist. Trained in medicine at the University of Mogi das Cruzes, situated in greater São Paulo, he undertook his residency training in the pediatric department of the A. C. Camargo Hospital, a well known cancer hospital in São Paulo, after which he gained his specialist qualification in pediatric oncology. But in spite of his love of the teeming metropolis, home to some 20 million people, Dr Epelman's perspective is decidedly global. In 1985 a scholarship from the World Health Organization enabled him to spend training periods in three major institutions in the USA and he subsequently collaborated in a scientific study with the US National Cancer Institute (NCI), which he visited for a period of additional training in 1990-1. All this was directed towards his main goal in life: "I consider it a privilege to ensure that disadvantaged children with cancer have the same chance of being cured as children from families able to afford the best care" says Dr Epelman. And since 80% of children with cancer live in developing countries – including, of course, Brazil – this implies both national and global approaches. Dr Epelman achieves this through his activities with two non-profit organizations, TUCCA and INCTR.

In 2001 he became the Chairman of TUCCA, a Brazilian organization dedicated to the treatment of children with cancer. Dr Epelman, and his wife Claudia, who provides psychological support to the children and their

Dr. Sidnei Epelman

families, have proved to be enormously successful at fund raising. Taking advantage of a Brazilian government program that through tax benefits to donors is designed to promote more cultural events, the Epelmans were able to team up with Brazilian musicians and initiate a series of benefit concerts, often featuring the best known international soloists. The proceeds from the sales of ticket support the care of children with cancer treated at the Santa Marcelina Hospital, a large general hospital administered by nuns that serves a population of some four million people in one of the poorer areas of São Paulo, and where Dr Epelman is currently head of the department of pediatric oncology. That he chooses to work in this area is illustrative of his desire to bring better care to the disadvantaged. "It poses many challenges," he says, "but my approach is to persevere, and that way, we often succeed against the odds." Already, significant improvements to the facilities have been made. Just a few years ago, a new day clinic funded by TUCCA, was opened. Unexpectedly, the clinic houses a well equipped kitchen where a famous Brazilian chef devotes time every week to giving cooking lessons to the patients' mothers, who learn how to create nutritious, tasty meals with the most basic ingredients.

Dr Epelman has been involved in INCTR since its inception and created the Brazilian branch a decade ago. He has played a leading role in the retinoblastoma strategy group, and undertook a major campaign to create awareness of the early signs of this disease which is curable if detected early. One approach was to make a video demonstrating the major early sign of retinoblastoma. Translated into many languages, it is freely available via the Web. With INCTR's PAX team, a new palliative care program linked to community health centers was established last year at Santa Marcelina and Dr Epelman's team, working with INCTR's Clinical Trials Office, recently initiated a program for the accreditation of Brazilian centers as competent in the management of clinical trials. This program is likely to have an immediate effect on the quality of care. Dr Epelman also hopes to develop programs for Portuguese-speaking countries in Africa and for Palestinian children. "The majority of children with cancer in the world do not have access to effective care. Working through TUCCA, INCTR and other partners, we can change this, but not without significant financial support." What better way to raise the necessary funds, while bringing pleasure into the lives of many, than by harnessing the healing powers of music! ■