N E T W O R K

THE NEWSLETTER OF THE INTERNATIONAL NETWORK FOR CANCER TREATMENT AND RESEARCH

INCTR

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THE PRESIDENT'S MESSAGE

PATHWAYS TO CANCER

Part 2. The Lives of Cell

by Ian Magrath

The ability of lenses to magnify has been known since at least the 5th century B.C.E., as attested to by Aristophanes' reference to a burning glass in his play *The Cloud*. But it was not until the early 17th century that the simple notion of magnifying an already magnified image was conceived and multiple lenses were combined in a single instrument. Thus were born, almost simultaneously, the telescope and the microscope, which extended human vision to both the very far and the very small, thereby provoking a host of new ideas about the natural world in which we live and the universe beyond. The telescope, in the capable hands of Galileo, allowed confirmation of Copernicus' heliocentric theory of the solar system and eventually, after some four centuries of development, has penetrated the outer reaches of the visible universe, enabling astronomers to see galaxies as they were when the universe was young. The microscope led imme-

The Tarantula nebula, a neighbor of our galaxy, showing a cluster of massive stars (Hodge 31, bottom right), several of which have erupted into supernovae. The material spewed across vast distances of space has compressed the nebula gas into sheets and filaments (top left) and spawned new stars (center). Image from the Hubble telescope; credit: the Hubble Heritage Team; Aura/STScI/NASA.

diately to the discovery of micro-organisms, spermatazoa and blood cells by Leeuwenhoek, and to the confirmation of the "germ" theory of disease. Better instruments enabled Robert Brown, in 1833, to discover cell nuclei in plants, and led, a few years later, to the independent theories of Schleiden and Schwann, who proposed that animals and plants are made of up of cells and their products (e.g., wood, shell and bone). Schleiden and Schwann both proposed that each individual cell had the potential to give rise to an entire organism - a theory which was confirmed in 1997 when Wilmut and colleagues reported that a sheep, Dolly, had been cloned by inserting the nucleus of an adult mammary gland cell into an enucleated ovum. More sophisticated microscopes and their descendants, using sub-atomic particles instead of light, led to the visualization of molecules and atoms and eventually to an ability to create

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

ADDRESS CORRESPONDENCE TO:
INCTR at the Institut Pasteur
Rue Engeland 642
1180 Brussels • Belgium
+32 2 373 93 23 • bene@inctr.be
www.inctr.org *or to*

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

and track (in *cloud* chambers) whole families of new subatomic particles. Physicists had finally achieved, in a manner of speaking, the alchemists' dream of transforming base metal into gold, an accomplishment aided greatly by the insights of a particularly extraordinary alchemist, Isaac Newton, who showed, perhaps more than any other, that unraveling the secrets of the *alma mundi* (the soul of the world) was tantamount to revealing those of the *alma universalis* (the universal soul).

It was also in the 5th century B.C.E. that the Greek philosopher, Democritus, building on the ideas of his teacher, Leucippus, proposed that matter is not infinitely divisible, but made up of elementary particles that he called *atomos*. Democritis postulated the existence of a "void" or vacuum between the material atoms, and suggested that objects are perceptible through "emanations" (*eidola*), leading to awareness and thereby, thought. These ideas, although entirely speculative, were embryonic forms of modern scientific concepts of the vacuum of space, electromagnetic radiation (the visible wavelengths of which we call light), and the role of both eye and brain in vision, although we still have little understanding of the physical basis of consciousness. Modern atomic theory was developed in the context of chemical reactions by John Dalton in the early 19th century, but it was another hundred years before Rutherford was able to provide the first scientific evidence that atoms consist of a tiny nucleus surrounded by electrons. While the idea that matter is not infinitely divisible was hotly contested (e.g., by Aristotle), nobody, until Max Planck, at the dawn of the 20th century, ever conceived that energy too, is not infinitely divisible, but rather, is comprised of individual packets of energy, or *quanta*. This counter-intuitive notion was the key to the conceptual leaps in the understanding of both matter and energy, which, as shown by Einstein's equations and subsequent experimental evidence, are inter-convertible and therefore different forms of the same thing. In the last 100 years, progress in the physical sciences has contributed greatly to the biological sciences by providing new instruments with which to probe and analyze the complex molecular interactions that govern the lives of cells in health and disease. Such instruments, along with novel biochemical techniques, have made possible the essentially final mapping of the human genome (published within the last few months), an achievement comparable in its significance to the complete mapping of the world, but achieved, from start to finish, in a tiny fraction of the time. This momentous step will help speed up the process of understanding how the approximately 25,000 genes revealed by the map (arranged along two intertwined strands of deoxyribonucleic acid, or DNA, some two meters in length and miraculously packaged into the nuclei of cells invisible to the human eye) direct the development of a human being from a fertilized ovum; regulate the interactions of the estimated 10^{14} cells in the microenvironments (tissues and organs) that comprise the human body; and govern the behavior of people living in the macroenvironments that exist on Earth.

E UNIBUS PLURUM

Taoists believe that the world of *ten thousand things* we inhabit evolved

from an ultimate single reality (*the Tao*, equivalent to *Brahman*, in Hindu, or *the void* in Buddist philosophies) which continues to permeate and energize the entire web of differentiated being we experience today. This perspective is similar to that of modern cosmologists, who continue to seek a unified field theory in which the four fundamental forces of nature and the numerous sub-atomic particles currently recognized, existed originally as a single force immanent in the high energy universe that came into being immediately after the *big bang*. Neither physicists nor Taoists deny the present existence of a multiplicity of things, but rather recognize their interrelatedness, and their emergence or differentiation from the original unity. This evolutionary process appears to have been both self-realizing and self-organizing and also exquisitely dependent, with respect to the structure of the universe, the chemical characteristics of the elements and the emergence of life on earth, on the values of the fundamental *constants* of nature, such as the relative masses of protons and electrons and the relative strengths of the four fundamental forces.

THE CREATION OF ELEMENTS

There is general agreement among cosmologists that immediately (i.e., prior to 10^{-35} seconds) after the big bang, the universe was extremely hot - above 10^{28} degrees Kelvin! Extremely rapid cooling, due to the massive expansion caused by the big bang and subsequent *inflation*, led to the differentiation of primordial energy into a plasma of *quarks* and *gluons*, which existed for perhaps 10 microseconds after the big bang. After 10 milliseconds, the temperature would have dropped to 100 billion degrees, leading to the emergence of high energy particles, including *electrons and baryons* (protons and neutrons), the latter comprised of quark triplets bound together by the *strong nuclear force* mediated by gluons. In the next three minutes or so, further cooling (to about a billion degrees) permitted protons and neutrons to combine to form the nuclei of the lighter elements, but some three hundred thousand years would pass before the temperature dropped sufficiently (to perhaps three thousand degrees) to permit electrons, under the influence of the *electromagnetic* force carried by *photons*, to stably associate with nuclei to form neutral atoms.

Galaxies and stars probably began to form a few hundred million years after the big bang, as a consequence of minute differences in the distribution of energy (quantum fluctuations), prior to its condensation into matter. Over time, in regions of sufficient density, the predominant element, hydrogen, began to aggregate under the influence of gravity. In large enough aggregations, destined to become stars, the gravitational force was sufficient to cause hydrogen nuclei (protons) to fuse, forming helium nuclei (with the aid of the *weak nuclear force*) and releasing electromagnetic energy, including light, in the process. In more massive stars, then and now, more powerful gravitational fields drive the *hydrogen cycle* more rapidly, converting all of the hydrogen to helium after only a few hundred million years. At very high temperatures, carbon-12 can be formed via fusion of thee helium-4 nuclei and energy produced by a *carbon fusion cycle*. Elements beyond carbon (i.e., of higher atomic weight) can also be made by successive nuclear fusions, but fusion releases energy only up to the formation of iron-56. Building elements of higher atomic weight *requires* energy. Thus, as iron accumulates energy production is sharply cut back, gravity is unopposed by the energy pressure, and gravitational collapse occurs, causing electrons to fuse to protons in the star's core, and the formation of a massive nucleus composed almost exclusively of neutrons. If this process is sufficiently rapid the result is a cataclysmic thermonuclear explosion, or *supernova*, in which the mantle of the star and its contained elements are expelled into space, leaving behind the dense core as a *neutron star*. Elements of higher atomic weight than iron-56 are probably produced in supernovae when existing elements capture high energy neutrons and convert some into protons via the weak nuclear force. Hydrogen is also recreated in supernovae, via fission of elements made in the course of millions of years, and from this, new stars can form, but the stellar dust is now also rich in carbon, oxygen and nitrogen and may even contain carbohydrates and amino acids - the building blocks of proteins. Matter of this kind, containing the full range of elements, may form solar systems, in which the central region of the aggregated matter forms a star, and outer regions condense into various satellites, including planets. Our own solar system was formed in this way some 5 billion years ago.

RECOMBINATION AND THE EVOLUTION OF COMPLEXITY

The successive stages of differentiation that have occurred since the big bang permit corresponding increases in complexity, not only through the emergence of new entities, but through their recombination. Thus, each atom is comprised of only three

types of subatomic particle (up and down quarks, and electrons), but combinations of protons and neutrons form the atomic nuclei of the 92 naturally occurring elements. These, in turn, combine, according to their chemical properties, (determined by the number of protons in the nucleus, which is identical to the number of surrounding electrons), to create an enormous number of different molecules. Among the elements, none has as broad a spectrum of compounds as carbon, which accounts for approximately 75% of the 7 million known chemical compounds, and although, today, many carbon compounds can be synthesized, the bulk of them are associated with living organisms - hence carbon chemistry is known as organic chemistry. The ability of carbon to combine with itself and produce a variety of rings, chains and branched molecule, accounts for its broad range of compounds and also creates the possibility of storing large quantities of information within the molecules - in DNA, for example. Here, the sequence of four organic *bases* arranged along its length determines the sequence of amino acids in proteins made according to the DNA blueprint. The latter also contains various "punctuation marks" which signify the beginnings and ends of polypeptide chains, and sequences involved in the regulation of the *expression* of the gene (i.e., translation of the encoded information into a protein). Proteins are organized into interdigitating molecular pathways, which are ultimately responsible for the wide range of structures and functions that comprise living systems.

THE EMERGENCE OF CELLS

In the case of the planet Earth, as with the universe as a whole, the early conditions were very different from those that exist today. As the planet cooled, a tempestuous climate resulted in the generation of a variety of organic molecules, some of which must have had the ability to self-replicate. Whether carbon compounds present in interstellar dust were important to this process is unknown. Nor is it clear how self-replicating *pre-biotic* molecules evolved into primitive life forms within a mere half a billion years or so after the formation of the planet. Life, as we know it, first appears in the fossil record in the context of another self-realizing and self-organizing system - the cell. Cells are characterized by a lipid membrane which separates internal from external cellular environments and provides protection for the cell's molecularly coded information (DNA) as well as the protein products made in the cell's synthetic machinery. Some proteins (called *receptors*) are expressed in the cell membrane where they can detect molecules in the external world and respond by initiating pre-programmed reactions. Other membrane or secreted molecules can influence the behavior of other cells through binding to their receptors. Finally, cells are able to replicate themselves and their contained information.

Cancer develops in a stepwise process through the accumulation of multiple mutations associated with successive increments in "invasiveness" or malignant potential. The earlier in this process that interventions are made, the more successful they are likely to be.

The earliest microfossils, dating to almost 3.5 billion years ago, already demonstrate the existence of single-celled organisms called *prokaryotes*, i.e., consisting of a simple cell type in which the single loop of DNA is not enclosed within a cell nucleus. Many species of *Archaea*, one of the two prokaryotic *domains*, are able to survive in extreme conditions, e.g., boiling water and acid environments. Some use hydrogen gas or sulfur as their energy source. They and their predecessors were capable of flourishing in the harsh environments of the kind which must have abounded on the young planet at a time when its atmosphere consisted of methane and ammonia, but no oxygen. The other group of prokaryotes, *Eubacteria,* also evolved into species able to survive in a broad range of environments by developing relevant metabolic processes. The *cyanobacteria*, for example, are able to use sunlight as a source of energy, trapping it in pigments such as rhodopsin and chlorophyll, and using it to convert carbon dioxide and water into glucose, with release of oxygen. In the course of a further half billion years such *photosynthetic* bacteria began to create the atomospheric oxygen essential to the evolution of plants and animals. But oxygen is highly reactive and capable of damaging DNA – a problem overcome when some bacteria began to use oxygen as an energy source. These *aerobic* bacteria collaborated with other "single celled" organisms (probably Archeans), in some cases living within cells larger than themselves (so called *endosymbiosis*) in a mutually beneficial relationship. Photosynthetic bacteria also shared their metabolic skills through endosymbiosis, and the permanent fusion of prokaryotes is the probable origin

of both mitochondria and chloroplasts, responsible for aerobic respiration and photosynthesis respectively, in the more complex *eukaryotic* cells which evolved some two billion years ago. The first such cells - algae and protozoans - were also "single celled" organisms, but much larger than prokaryotes. Retaining the most basic genes (e.g., for protein production), which had evolved in prokaryotes, eukaryotic cells expanded the genetic repertoire, and enclosed the now much longer DNA strands in a second, protective nuclear membrane, coiling them up into multiple chromosomes which allow the DNA to be packaged in the smallest possible volume while ensuring efficient replication and, in multicellular organisms, differential gene expression. Eukaryotic cells also contain a number of cell *organelles*, e.g., membrane structures involved in manufacturing proteins via RNA intermediates, and a *cytoskeleton* that gives shape to cells and allows movement.

Multicellular plants and animals doubtless evolved (perhaps a billion years ago) from variable aggregations of identical single cells (colonies) which permanently fused, allowing cells to become specialized, via differentiation, creating tissues and organs, and in the process, *organisms* able to function as individuals. Cell specialization inevitably resulted in restrictions on the right of abode of cells in each tissue (microenvironment), and also meant that replication of the entire organism had to be concentrated in special cells (germ cells) that retained totipotentiality. Thereafter, evolution would require the death of individual organisms. Moreover, horizontal exchange of genetic material, possible in prokaryotic cells, even of different species, is essentially prohibited in eukaryotic cells (except by viruses). In multicellular organisms, however, cooperative genetic exchange can occur within a single species via the process of sexual reproduction (requiring germ cell fusion) - and a new form of cooperation is possible; the association of individuals in communities, which may include specialized members.

GENERATION OF BIODIVERSITY

Ultimately, the potential for variability in cell types resides in the informational content of DNA. While it may be surprising that a human *genome* consists of only some 25,000 genes, the degree of possible complexity is enormously increased by the fact that various modules or *domains* of proteins are able to assume three-dimensional shapes that enable them to complex with and often modify other proteins (enzymatic activity), such that the *proteome*, or total protein expression pattern, is much larger than would be predicted by the size of the genome. This is further amplified by the differential expression of genes in different cellular contexts (including during the process of differentiation), resulting in enormous numbers of expression patterns in different cells, and in the same cell in different circumstances. The evolutionary process has been driven by modification of the genetic

GENETIC PATHWAYS TO CANCER

Pathway Involved	Consequence of Abnormality	Examples of Genes Involved
DNA protection	Increased rate of mutation	CYPp450, GSTM1
DNA repair	Persistence of mutations	MMR, NER, BER
Genome stability	Gross chromosomal alterations	BRCA1, BLM, ATM
Apoptosis in presence of damaged DNA	Survival of cells with gross DNA damage	PARP, p53, p73, MDM
Cell cycle (DNA replication)	Inappropriate cell division	Rb, p16, CDK4, cyclin D1
Differentiation	Differentiation block	Notch, STATS
Apoptosis and differentiation	Prolonged lifespan	BCL2, BAX, APAF1
Receptor-induced apoptosis	Failure to activate apoptotic pathways when stimulated to do so	FAS, TRAIL, TNFα
Growth factor	Proliferation	SIS, KIT, FGF
Receptor for growth factor	Proliferation with or without a signal	HER2/NEU, FMS
Signal Transduction	Proliferation in absence of signal	PI3K, APC, SMADS
Master control gene	Altered regulation of many genes	MYC, NFKB
Production of enzymes able to cleave basement membranes	Inappropriate ability to enter and leave blood vessels, i.e., to migrate	HGF, MET, MMPs
Production of factors that stimulate endothelial cells	Formation of new blood vessels able to supply cancer cells	HIF1,VGEF, PDGF
Cell senescence genes	Allows cell to survive longer	Telomerase

Table 1. Multiple pathways must be affected to cause cancer. Some genes (referred to as *tumor suppressor genes*) are inactivated e.g., DNA repair genes. Others (referred to as *oncogenes*) – e.g., those involved in cell division, are over- or inappropriately expressed. Sometimes, pathways active during embryogenesis, e.g., those related to cell migration, are reactivated. Genetic changes in cancer cells can also provide tumor markers or tumor-specific (or relatively specific) therapeutic targets, which are beginning to be exploited.

information, both by small progressive changes in sequence and by duplication of entire genes and re-use of modular elements in new contexts. Clearly, the permissible degree of genetic change must be finely tuned in order that new species emerge in the context of different or changing environments, while ensuring that existing species have stability within biological time-frames. This has led to the evolution of multiple mechanisms to protect the integrity of the information encoded in DNA, including protection against chemical damage as well as repair mechanisms for damaged DNA, or errors that occur during DNA replication. As a last resort, cells with irreparable damage are eliminated through the activation of molecular pathways that lead to cell death (hence the term *programmed cell death, or apoptosis*). Apoptosis is also essential for "fine tuning" structural relationships during embryological development and cell differentiation that occurs throughout life. In some circumstances, it can be activated via receptors in the cell membrane. Interestingly, some of the apoptotic pathways involve mitochondria, derived from the original endosymbiotic prokaryotes.

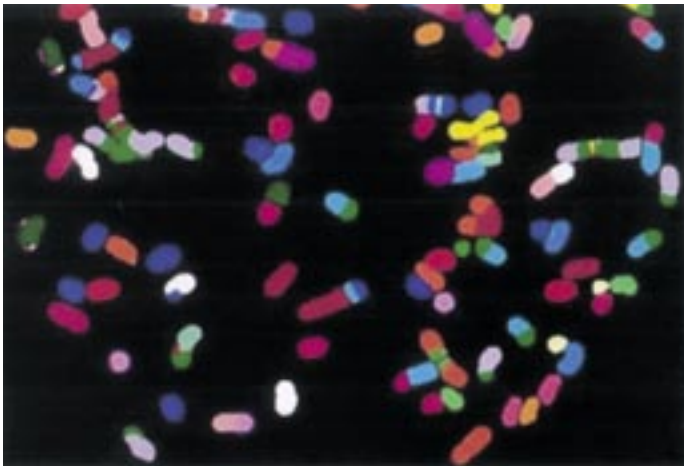


Figure 1. Chromosomes from a cell line derived from prostate cancer, demonstrated by spectral karyotyping, a technique in which chromosome-specific probes are used and the data analyzed by computer, which assigns each chromosome a single color. SKY readily detects the extensive exchanges (translocations) among chromosomes that have occurred as a result of genetic mutations causing *genomic instability*. Reproduced by courtesy of Meena Augustus, Ph.D., Avalon Pharmaceuticals Inc., Germantown, MD, USA.

CANCER CELLS

Invasive cancer is a disease process that, to a degree, may be seen as a negative consequence of the evolutionary need for information resident in DNA to undergo change and thus to allow for Darwinian ecological adaptation and the evolution of species. In multicellular organisms, genetic changes (mutations) must occur in germ cells if they are to influence the characteristics of the offspring. In cancer, however, the genetic changes occur in somatic cells. Not all such changes lead to cancer. Some may be inconsequential, others may lead to the death of the cell, e.g, via apoptosis. The most dangerous are those which impair the efficiency of pathways that normally protect the integrity of DNA (including apoptotic pathways) such that genetic changes are more likely to occur, or persist. Some of the genetic changes must also lead to relevant alterations in cell behavior, including inappropriate cell proliferation and prolonged lifespan. Altered proliferation can be associated with mutations in growth factors, their receptors, the molecular pathways that *transduce* the signals from receptors, or the *cell cycle* genes and their inhibitors, that regulate the actual process of cell division. Altered proliferation and lifespan are frequently coupled to a failure to differentiate with retention of self-renewal properties, leading to abnormal accumulation of the genetically modified cells and their progeny. Cancer cells may also develop the ability to cross barriers that obstruct normal cells, e.g., through the inappropriate expression of particular enzymes, and to survive in microenvironments hostile to their normal counterpart cells; the ability to enter blood vessels, travel to other sites and proliferate there are the hallmarks of *metastasis*. In order to grow above a minimal size, however, and hence to be harmful, most cancer cells need to coerce nearby cells to cooperate with them in providing their essential needs, and in particular to create new blood vessels (*angiogenesis*) that can bring them essential nutrients and oxygen.

Modifications of so many pathways (Table 1) do not occur all at once. Cancer develops in a stepwise process through the accumulation of multiple mutations. Some cells are partially *transformed* and may, in certain circumstances, be detected as abnormal cellular accumulations, e.g., polyps, or so-called *carcinoma-in-situ*, in their tissue of origin. Not all of these pre-malignant lesions develop the necessary genetic changes to become invasive cancers within the lifetime of the individual. Other cancers may be detected prior to deactivation of molecular pathways that would prevent them from spreading beyond their tissue or organ of origin (so called "early stage" cancers). It is clear why early detection is critically

important. More advanced cancers are much more difficult to treat both because they are more widespread, and also because the multiple genetic changes required to permit them to spread, after which local therapy is ineffective, also make them more resistant to chemotherapy.

The malignant behavior of cancer cells arises from their ability to grossly disrupt the organization of their tissue or organ of origin, and/or to illegitimately invade other tissues with impunity where they compete with the rightful occupants. Negative effects may be due to pure physical encroachment (sometimes leading to compression of vital structures) as cancer cells continue to accumulate, or to the indirect effects of the biochemical products of cancer cells on normal cells - either at a local level, or at the level of the whole patient.

Genetic changes leading to cancer may involve modifications in the base sequence of specific genes or in their regulatory elements, alterations in gene expression caused by changes in chromosomal proteins or chemical changes (e.g., methylation) in DNA, by amplification or deletion of regions of DNA, or by gross structural changes in chromosomes, such as *translocations* (Figure 1). Ultimately, all such changes result in an intrinsically altered pattern of gene expression (Figure 2) and/or protein function (some genes being over expressed or inappropriately expressed, others under expressed, or inactivated), as well as the failure to create appropriate expression patterns in response to external stimuli, particularly those associated with cell proliferation, differentiation and survival. Gross structural changes in DNA may lead to the creation of a new *fusion* gene through the interchange of pieces of chromosomes in which the chromosomal breakpoints are within the involved gene sequences. Sometimes, the equivalent of a genetic change may be provided by a viral gene. Rarely, mutation in the germline (usually in genes involved in maintaining the integrity of the genome) may predispose family members, from then on, to cancer.

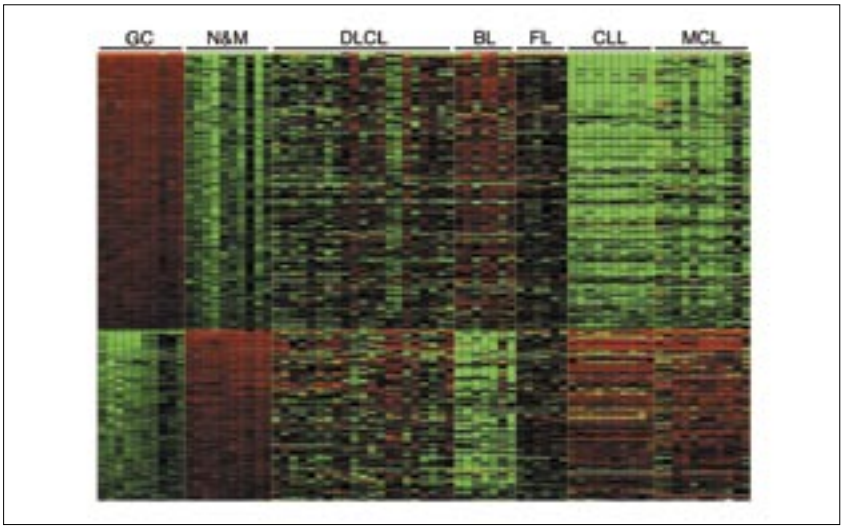


Figure 2. Profiling techniques enable the expression of large numbers of genes to be examined simultaneously. Here, each row represents a different gene, and each column, messenger RNA (corresponding to the expressed genes) extracted from a sample of a specific normal or tumor cell type (e.g., GC = germinal center cells, BL = Burkitt's lymphoma). The degree of expression of each gene is represented by a color (red, highest, green, lowest). Reproduced by courtesy of U. Klein and R. Dalla-Favera, Columbia University, New York.

A WORK IN PROGRES?

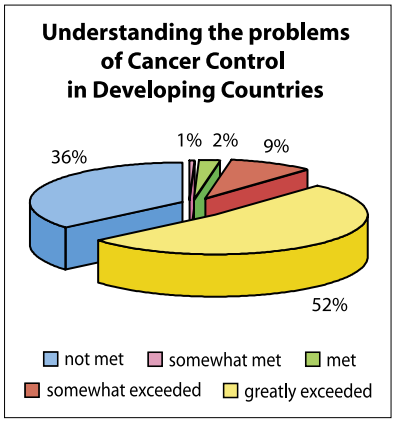
Life evolved only after billions of years of preparation in a vast universe consisting of hundreds of billions of galaxies each containing hundreds of billions of stars. Here, the chemical elements were built, step by step, permitting the formation of at least one planet in which conditions were appropriate for the creation of the complex molecules that regulate the lives of cells. Billions of years of subsequent evolution, involving an enormous degree of cooperation, led eventually to brain cells that were able to unravel the remarkable history of the universe and to learn that cancer is a process in which the information stored in cells is corrupted, such that the normal regulatory systems have gone awry and cells function selfishly rather than to the benefit of the individual. Perhaps the accumulation and use of human knowledge will prove to be a continuation of the process of self-realization that began some 15 billion years ago, leading to a reduction in human inequities, environmental damage and other ills of the world (including diseases, such as cancer). Alternatively, through too great an emphasis on competition and conquest rather than cooperation and compassion (a kind of cancer community?) progress in understanding may simply herald a cataclysmic end - to human history, at least. One or other of these alternatives is likely to prevail before the end of the present century. ■

NETWORK

INCTR'S ANNUAL MEETING

INCTR's Annual Meeting has become an important event which serves to bring together INCTR Associate Members from many different countries to strengthen international collaboration in all aspects of cancer treatment and research, to report progress that has been made in INCTR projects in the last year and to identify focal points for discussion that may lead to the development of new projects. While it is essential that key figures in cancer treatment and research are involved in these discussions, it is essential, in the interests of ensuring long term viability of programs, that young health professionals participate. Professional education - including continuing education - underlies much of the meeting content, and although primacy is given to an exchange of views among health professionals from a variety of backgrounds, didactic elements are included in order to provide a foundation on which discussion can be based.

It must be recognized that cancer control, although founded on the same basic principles throughout the world, must contend with even greater obstacles in developing countries than those present in more affluent nations - obstacles that ultimately arise from the economic difficulties faced by the populations susceptible to cancer, and the paucity of resources available to study predisposing factors, and to determine the best approaches, in the local settings, to prevention, early detection and treatment. For these reasons, essential research relevant to cancer control in developing countries must, in part or in whole, be conducted in those countries themselves, where the pattern of cancer may be regionally unique, where the lifestyles, nutritional status and co-morbidities of potential and actual victims of cancer differ so profoundly, and where the availability or access to treatment may be poor or even absent. It will be essential to improve and supplement available resources - human and institutional - for the control of



cancer and also to involve the entire family and local community in the process -particularly since success, to a large degree, is dependent upon the avoidance of cancer, or its detection at the earliest possible stage of its evolution - before it has become a true "invasive" cancer. Diagnosing cancer earlier is a critical factor in reducing mortality rates and this will require knowledge of the symptoms and signs of cancer (among health professionals and the population at large), and in those cases where it is known to be beneficial, screening of asymptomatic populations. Demonstrating success is essential to generating a lower threshold for diagnosing cancer, and a political will to grapple with the problem.

INCTR's annual meeting is unique in having, as its entire focus, the problems encountered in developing countries, and in bringing together experts both from within those countries and from affluent nations to discuss possible approaches, as well as the evaluation of such approaches, to the control of cancer; a problem that is becoming more and more immediate as communicable diseases are overcome, and populations age and adopt the bad habits of affluent societies, particularly smoking.

In addition to the INCTR Award Lectures and oral presentations of participants own work, this year's meeting featured a series of presentations on cancers that are particularly frequent in Africa and the Middle East, but also in many other countries in less developed world regions, and several discussions pertaining to more general issues of cancer

control, including ethics and palliative care. A plenary session in which INCTR members presented their own work was held, and posters were left up for viewing throughout the meeting. As usual, the "ever increasing" role of technology in helping to control cancer in developing countries was discussed. This year, there was a particular focus on information technology (IT) and the development of INCTR's IT program.

SOME OF THE ADDITIONAL MEETINGS IN CAIRO

• *A meeting of the Breast Cancer Strategy Group* took place, in which decisions re: data collection for the retrospective breast cancer survey were made and members were asked to review the first draft of the new protocol for the treatment of locally advanced breast cancer. It was also decided to send two persons to attend the conference organized by the Breast Health Global Initiative to be held in Bethesda early in 2005.

• *The Middle East Cancer Consortium* met and decided to pursue the development of a uniform data collection system to be used by all participating centers, at least with respect to presenting features and disease characteristics.

• *An update of the phase II study in Burkitt's lymphoma,* recently commenced in sub-Saharan Africa was provided and problems being encountered discussed.

• *A Lymphoma Strategy Group Meeting* took place to discuss initiating a study in diffuse large B cell lymphoma treatment, using standard "CHOP" therapy as well as Rituximab.

• *The Special Panel of the Advisory Board* met to finalize the list of nominees for INCTR Awards in 2005 and the rules to be applied to eligibility. A proposal to award a third prize to a deserving organization was made but no decision taken. Members also discussed the Annual Meeting 2005 and decided that the 2006 (or possibly early 2007) meeting should be held preferably in Brazil, but otherwise, in Brussels.

• *The Tissue Banking Committee* met again to discuss the importance of a high quality tissue bank under INCTR auspices and to develop a questionnaire to determine the needs, experience, regulatory issues etc. faced by collaborating centers who might potentially participate in its development. It was also decided to hold training courses in tissue banking.

• *Meeting of INCTR Offices and Branches.* A closed session of INCTR offices and branches was held at which each branch presented a report, and its priorities for the coming year. There was general endorsement of the draft INCTR Charter, which outlines the guidelines and policies of the entire INCTR network.

• *A Meeting of the Education Committee was held* to discuss priorities for the next year, as well as collaboration with the NCI Office of International Affairs.

• *Three members of INCTR's palliative care team provided informal training* in palliative care for 15 persons from the African continent, India and France.

• *An educational session on how to write an abstract* was given by Dr. Rohatiner, who organizes the proffered papers session.

THANK YOU TO SPONSORS

INCTR would like to thank the following companies for their sponsorship of AM 2004: Agfa, Lilly, Schering, Astra Zeneca Oncology, Sanofi-Synthelabo, Roche Oncology, Pierre Fabre Oncology, Janssen Cilag and Lipomed. ■

MEETING EVALUATION

QUESTIONS	VERY GOOD	EXCELLENT
Understanding of the epidemiology and management of selected cancers in developing countries: head and neck, bladder, retinoblastoma, osteosarcoma, cervical cancer.	33%	27%
Overall rating for the quality of the education offered at this Annual Meeting?	32%	37%
Was the information useful and relevant to your work and practice techniques?	30%	49%
Did you feel that the presented information was well balanced and supported with adequate evidence?	23%	53%
Did the program allow adequate time for discussion and questions?	32%	38%
How would you rate session 3A and B "Proffered Papers"?	25%	40%
Should the Annual Meeting include a poster session?	-	93%
How would you rate the management of this meeting?	23%	72%
How would rate the pre-conference registration service?	22%	74%

NETWORK

AWARDS INFORMATION

INCTR gives two annual awards to individuals who have made outstanding contributions to cancer treatment or research in one or more developing countries. The purpose of these awards is not simply to recognize and honor the recipients, although this is certainly an important element, but also to show, by their example, that much can be accomplished even when resources are limited. It is hoped that their work and philosophy brought through the award lectures to a broader audience than would otherwise be the case will inspire others to greater efforts.

Each of the awards is named after a distinguished oncologist. They began their careers when there was so little knowledge about the causes of cancer that people could only live in fear that they would one day be a victim. The diagnosis was usually hidden from those unfortunate enough to develop cancer, because so little could be done for them. It is thanks to the resolution and fortitude of Dr. Nazli Gad-el-Mawla, Dr. Paul P. Carbone, and others like them, who worked through a time when cancer specialists were often accused of prolonging the misery of cancer patients rather than helping them, that today, at least in the wealthier nations, more than half of those who develop cancer can be cured. Both Dr. Nazli and Dr. Carbone were responsible for training numerous young people, and so leave us a precious legacy through which their work will be continued.

The Nazli Gad-el-Mawla Award is made for outstanding contributions to cancer control by an individual from a country with limited resources. Nazli Gad-el-Mawla was a pioneer Egyptian oncologist, who, as a member of a small group of oncologists working at the National Cancer Institute in Cairo in the 1960s and 70s, helped to build the institute into one of the premier cancer centers in the Middle East. She founded the Department of Medical Oncology in 1970 and, as part of it, developed a strong pediatric oncology program. She is known particularly for her work in the chemotherapy of cancer of the bilharzial bladder, which accounts for some 25% of all cancer in Egypt, and in hematological malignancies. She was highly respected both by her colleagues in Egypt and also by the international community of oncologists in which she became increasingly active throughout her career.

The 2004 Award recipient is Dr. Mahmoud M. Mahfouz: M. Mahfouz is Professor of Oncology and Ex-chairman (1968-83) of Kasr El-Aini Oncology and Nuclear Medicine Center, Cairo University (NEMROCK), Egypt, which has been a wellspring of oncology centers throughout Egypt. Since 1951, Prof. Mahfouz has been involved in education and training in radiation and medical oncology in various Egyptian universities as well as other countries (Sudan, Ethiopia, Saudi Arabia, Iraq, the Emirates and Malaysia). He has supervised more than 185 postgraduates for their MD and Masters degrees in oncology in Egypt. Prof. Mahfouz has made major contributions to education and health care in Egypt through his leadership and participation in governing bodies and committees of various Egyptian universities. He was Egyptian Minister of Health from Jan '72 to Sept '74 (during the October War), Member and Chairman of Education, Scientific Research and Youth Committee of the Senate (Shuraa Assembly), 1982-2002, member of the Presidential Advisory Board, Medical Advisor to the Ministry

Dr. Mahmoud Mahfouz receiving the Nazli-Gad-El Mawla Award.

of Scientific Research, President of the Egyptian Society of Radiology and Nuclear Medicine (1982-1985), President of the Radiation Technology Council of the Egyptian Academy of Scientific Research and Technology, and Vice President of the Medical and Drug Research Council of the Egyptian Academy of Scientific Research and Technology. Prof. Mahfouz has also undertaken leadership roles in various international organizations involved with health, science and education, including the Egyptian African Society, the International Organizations of Medical Parliamentarians, the International Physicians for Prevention of Nuclear War (IPPNW) and the Pugwash Movement of Science and International Affairs (the organization being winner of the Nobel Peace Prize in 1985). He has served or acted as consultant to various UN committees and organizations, including the UN Scientific Committee on the Effects of Atomic Radiation, 1961-1966, WHO Technical Committee on Cancer and Radiation, the International Atomic Energy Agency (IAEA) Division of Human Sciences (Medical Research) and the East Mediterranean Regional Office of WHO (EMRO). He has been the recipient of numerous honors and awards, including the El-Gomhoria State Merit (1974), Egypt, Chevalier of the Legion D'Honneur (1982), France, the Art and Science Order (1992), Egypt, the State Merit Prize for Biological Sciences (1992), Egypt and the Mubarak State Prize (2003), Egypt.

The Paul P. Carbone Award in International Oncology is made for outstanding contributions to oncology or cancer research by an individual from a resource-rich country. Paul P. Carbone was a pioneer American oncologist, who, as the Associate Director for the Clinical Oncology Program at the National Cancer Institute, Bethesda, played a critical role in the development of cancer chemotherapy. Subsequently, he continued his work as the Director of the Cancer Center at the University of Madison, Wisconsin. From the beginning he recognized not only the needs of patients in developing countries, but also the contribution that scientific research conducted in such countries could and should make to the global efforts against cancer. Dr. Carbone's family has established the Paul P. Carbone MD Foundation for "the support of scientific, educational, and charitable endeavors that reflect Dr. Carbone's practice of the art and science of oncology and his lifelong dedication to teaching and mentoring."

The 2004 Award recipient is Dr. Franco Cavalli. Dr. Cavalli has been Head, since 1978, of the Division of Oncology at the Ospedale San Giovanni, Bellinzona (Switzerland) and is a former President of the Swiss League Against Cancer and of the Swiss Institute for Cancer Research. Early in his career, Dr. Cavalli learned of the health problems in Nicaragua. He subsequently visited the country and created an association called "Medical Help for Nicaragua," later called "Association for Medical Help to "Central America". This association was officially recognized and financially supported by the Swiss government. In 1987, he started a program to develop a pediatric hemato-oncology program at the only children's hospital,"La Mascota," in Managua, Nicaragua, which included the building of new wing, where the newly created division for hemato-oncology was established. Staff training and medical and technical assistance were also provided. In 1988 he launched "Nora Astorga," a project devoted to the early diagnosis of cervical cancer. It also provided funds to build a radiotherapy center which is now functioning very well. Cytologists, nurses and health workers were trained, as well as a gynecological oncologist. Nora Astorga undertook a study, with the Nicaraguan government, for the early detection of cervical cancer in a region in Nicaragua with a population of 100,000 people, half living in the city and half being rural workers (campesiños). Following this pilot study in 1991-1992, plans were developed to move to a national screening program for cervical cancer through the Nicaraguan government. The experience in Nicaragua has provided an example for other poor Central American countries such as El Salvador and Guatemala. Dr. Cavalli has adopted four children from Nicaragua and Colombia - another example of his commitment to people in need. ■

Dr. Franco Cavalli receiving the Paul P. Carbone Award.

NETWORK

M. Mahfouz, MB. ChB, DMRE (Cairo), FRCR (London)
Professor of Oncology and Ex-chairman of Kasr El-Aini Oncology and Nuclear Medicine Center, Cairo University

HEALTH PROMOTION: A HUMAN RESPONSIBILITY

Since the creation of life, the maintenance and sustenance of health has been one of the primary tasks of all bio-systems. Thus, health promotion is an integrated and instinctive psychosomatic biological process.

It is worthy of recapitulation that God the Almighty has granted the right to life to all the unicellular and multi-cellular organisms that exist on earth. It is, therefore, the responsibility of all living creatures to sustain this gift. In the case of mankind, this responsibility is exercised through the use of knowledge - acquired through careful observation and used to aid adaptation to differing climates and cultures. Such knowledge has for long been stored and accumulated as memories and in the written word and today, vast quantities can be made available through electronic storage devices. Knowledge is transmitted through education and training to present and future generations. In this address, I will consider 5 main topics.

1. The role of biology in the emergence of civilization.
2. Knowledge accumulation and the evolution of civilization.
3. The importance of the physical development and education of children and their mothers.
4. Healthy behavior.
5. Responsible policies for health maintenance and environment control.

The available historical and anthropological evidence shows the importance of ancient Egyptians to the development of civilization as we know it. They benefited from optimal meteorological conditions and, for the most part, an abundance of food and water, and were among the earliest peoples to develop systems of agriculture and writing.

Since ancient times there has been an enormous degree of human migration – peaceful and otherwise, and genetic mixing. This has resulted in constant technology transfer and progressive accumulation of knowledge and its innovative use. Unfortunately, most developing countries are suffering from overpopulation associated with slow economic growth, thus drastically restricting their ability to keep up with the soaring cost of medical care. In the context of strategies for health maintenance, or control, including cancer control, special importance must be given to the following principles:

1. The eradication of illiteracy and the education of females, especially in the child bearing age (15-45 years).
2. The safe physical and psychological development of the nervous system.
3. The prevention of disease and the early detection of health problems at community, population and individual levels.
4. The promotion of health awareness among all peoples.
5. The adoption of strategies to protect the environment.
6. The inclusion of new knowledge from an understanding of the molecular basis of disease into educational programs for medical, paramedical and veterinary professionals.

In particularly poor populations, the individual has much less control over factors which affect his or her health. To improve this situation, it will be important to promote the participation of individuals and families, as well as community leaders, in health promotion strategies. Communication will need to be improved through using the most effective channels, such as religious advisors and relevant media, including radio, television and video films that can be shown in community centers. While the cooperation of the corporate world would greatly help, effective strategies must involve governments and intergovernmental cooperation. In this respect, the World Health Organization (WHO) has a vital role to play, and we welcome the new Resolution on Cancer Prevention and Control approved by the Executive Board of the WHO, for adoption at the next World Health Assembly. Equally important are plans to develop a Global Cancer Control Strategy and a Report on Global Cancer Control - projects that will be supported by Cancer Technical Groups and a WHO Cancer Network of Partners. Organizations such as INCTR will have an important role to play in these new and exciting developments.

F. CAVALLI, MD, FRCP
DIRECTOR ONCOLOGY INSTITUTE OF SOUTHERN SWITZERLAND (IOSI), BELLINZONA, CH

CANCER IN THE DEVELOPING WORLD: CAN THE DISASTER BE AVOIDED ?

All experts agree: in the next 20 years the number of cancer patients in the developing world is going to increase exponentially. It has been calculated that in 2020 there will be 10 million deaths because of cancer, of which 7.5 million will be in the developing world. Currently, the world is ill-prepared to deal with this situation and we could soon have a repetition of the disaster which much of the developing world is today witnessing with AIDS.

In fact, most of the problems faced in developing countries are similar for both diseases: a rapid increase of the number of patients, a lack of sufficient resources to tackle the problems and soaring costs of care - treatment is generally devised with only the economic situation in the developed world in mind.

Moreover, the evolution of the global economic situation is very uncertain; the opinions of experts are at best controversial. The disaster could be even worse than is presently expected by most people if the next twenty years continue on the same track as the last two decades, in which worldwide poverty has not decreased and the economic differences between developed and developing worlds have markedly increased.

But current developments in the fight against AIDS could give us some hints on how to deal with the cancer problem. I feel that

the following measures could be among the most important ones:

• Today many NGO's and professional societies are becoming increasingly interested in "doing something for cancer in the developing world", but there is a tragic lack of coordination. Most probably, UICC would be best placed to provide a forum for achieving the necessary coordination to guarantee the rational use of resources.

• Different models for supporting the development of cancer care and above all, cancer control in countries with limited resources, should be devised. The overall goal should be to have a national cancer control plan in each country. But in the developing world the problems of lack of resources, poverty and illiteracy are obstacles to success, and different approaches may be necessary than those used in affluent countries.

• In this context, technology transfer must always take into account the local situation. This can be effectively achieved, e.g. via the so-called "twinning method," which we have extensively used in our Central American projects (Lancet 1998; 352:1923-1926; Ann Oncol 1993; 4:37-40) Any attempt to enforce the use of inappropriate and expensive western technology should be avoided, while know-how should be continuously adapted through discussions which take the local situation into consideration.

• Strong political pressure must be mounted at all levels: from national governments to the World Bank and from G8 countries to the UN. But governments cannot succeed alone. Cooperation with major philanthropic organisations (e.g. Bill and Melinda Gates Foundation) must be actively sought.

• Political and social pressure should be brought to bear on pharmaceutical companies in order to move towards more equitable drug development policies, i.e., paying more attention to the circumstances and resources of developing countries.

ATTENDEES' COMMENTS ON THE AM 2004

Congratulations to the Organizing Committee.

This kind of meeting helps me to improve my clinical practice.

Strict adherence to time should be an absolute must.

A list of experienced pediatric oncologists in each country could be prepared with the help of INCTR branches and the Central Office could invite these experts to send their CV's.

INCTR has made important progress towards achieving its objectives.

More sessions on laboratory research should be included in the conference.

More separate sessions for the nurses should be included in the annual meeting.

This year the meeting was very impressive.

Panel discussions on new developments or controversial protocols would be useful.

INCTR should include surviving patient groups in the meeting as physicians can learn a lot from their experiences.

Thanks for the great efforts to help Iraqi Doctors to attend the meeting.

We would like the meeting to continue to be held annually, preferably in 3rd world countries like Egypt.

Could INCTR campaign for legislation to ban smoking in public places in Egypt ?

It might have been better if more papers were presented orally "rather" than as posters.

This conference has permitted good interactions and exchanges between the participants.

I would have liked to hear more about how other developing countries are coping with specific aspects of cancer control.

I would like INCTR to dedicate more emphasis to supportive and palliative care during the annual meeting.

Poster presentations in the conference could usefully be divided into different categories.

It is a very good idea to hold INCTR meetings in different places in developing countries.

The size of the meeting is perfect to allow attendees to get almost 95 % of the information - which is not possible in bigger conferences.

HIGH-DOSE TREATMENT AND HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN DEVELOPING COUNTRIES

The use of high-dose treatment (HDT) with autologous or allogeneic haematopoietic stem cell support was discussed at the Annual Meeting of the INCTR, focusing on the specific problems surrounding the use of both treatment modalities in the developing country setting. Ama Rohatiner (St. Bartholomew's Hospital, London) and Aziza Shad (Georgetown University, Washington DC) introduced the subject as treatment for adults and children respectively.

The terminology can be confusing; the differences between the two treatment approaches are critical, relating not only to the source of stem cells, but also reflecting differences in the indications for each type of treatment, training needs of medical and nursing staff, facilities required and, not least, the cost.

HDT refers to the use of gram doses of chemotherapy, supported by autologous peripheral blood progenitor cells (PBPC), bone marrow suppression being the dose limiting toxicity. In contrast, haematopoietic stem cell transplantation involves the use of a myeloablative (or non-myeloablative) conditioning regimen, followed by infusion of bone marrow or PBPC from an HLA identical sibling donor (or HLA identical, unrelated or 'volunteer' donor). An allograft can be regarded as the ultimate form of immunotherapy, relying as much on the immunologically mediated 'graft-versus-tumour' effect as on the efficacy of the myeloablative regimen.

HDT + AUTOLOGOUS HAEMATOPOIETIC STEM CELL SUPPORT

A treatment modality used predominantly in adults, this is now regarded as 'standard of care' in some countries for younger, newly diagnosed patients in second complete (or partial) remission of diffuse large B-cell lymphoma, selected patients with recurrent Hodgkin Lymphoma and younger newly diagnosed patients with myeloma, following initial combination chemotherapy. Its role in other haematological malignancies remains experimental.

The use of PBPC has replaced autologous bone marrow, blood count recovery being significantly faster, making the treatment safer and cheaper. Whilst specific expertise (and equipment) are required to enable PBPC to be collected and cryopreserved, departments experienced in the management of patients with acute leukaemia should be well able to look after such patients.

ALLOGRAFTING

Allogeneic bone marrow transplantation should only carried out at specialised centres. The indications are: consolidation of first remission in 'high-risk' AML, consolidation of 2nd remission of AML and ALL and as treatment for younger patients with chronic myeloid leukaemia and aplastic anaemia. The problems occur in the post-transplant period, the so-called 'first 100 days', relating to the management of acute graft-versus-host disease (GVHD) and cytomegalovirus (CMV) infection and subsequently, complications of chronic GVHD. One of the difficulties in the developing country setting is the need for close follow-up afterwards, some centres admitting patients for the entire 3 months with obvious implications for cost (both financial and 'human').

Professor Zeba Aziz (Jinnah Hospital, Lahore) supported the development of HDT, as therapy for selected younger patients with lymphoma. She stressed the importance of being realistic with regard to selection of patients for whom such treatment would be given with curative intent. Dr. Suresh Advani (Jaslock Hospital, Mumbai) agreed and went on to discuss the importance of having referral centres for children and young adults with acute leukaemia for whom an allograft would be the only curative therapy when conventional chemotherapy had failed. Dr. Mahmoud Al-Jurf (King Faisal Hospital and Research Centre, Riyadh) pointed out that whilst in the West only 1 in 4 patients would be expected to have an HLA identical sibling donor, in developing countries the chances are higher, since families are generally larger. He focussed on the use of allografting for severe aplastic anaemia and CML, alluding to the special issues of performing allografts in the Middle East, namely, the high incidence of seropositivity for CMV and Hepatitis B infection, also noting the incidence of TB in endemic areas. Dr. Hossam Kamel (NCI, Cairo) described the situation in Egypt as a model for the development of allografting in a resource-poor country, but alluded to the difficulties of trying to reconcile 'what is possible' with 'what is available'. He described the specific problems of allografting in Egypt where there is high incidence of Hepatitis B and C infection and the endemic problem of schistosomiasis, which can result in 'silent' peripheral fibrosis of the liver and subsequent fatal veno-occlusive disease.

The discussion centred on the justification for and logistics of developing expensive treatments applicable to few patients, as compared to measures for the prevention and early diagnosis of common cancers. The latter public health priorities are hard to reconcile with what are perceived to be the competing needs of relatively small numbers of patients who nonetheless have potentially curable illnesses. It is now possible to define who should (and who should not) have HDT or an allograft and, in the developing country setting the question of selection of patients is crucial.

A Victorian medicine made from bone marrow.

Although no formal consensus was sought, there appeared to be agreement that where well trained staff and the necessary infrastructure are in place, HDT or allografts should be offered to appropriate candidates who fulfill predetermined criteria for patient selection. However, careful consideration would need to be given to the priority of such programs in the overall context of cancer control, or in the programs of individual institutions, particularly if publicly funded. Ideally, service provision should be on a regional basis to avoid unnecessary duplication. ■

Ama Rohatiner, Director of INCTR UK Office.

EDUARDO CAZAP ESPOUSES GLOBAL VIEW OF CANCER

SLACOM

Sociedad Latinoamericana y del Caribe de Oncologia Médica
Latin American and Caribbean Society of Medical Oncology

More than 550 million people inhabit Latin America and the Caribbean — countries with a widely disparate range of resources for cancer care. Countries such as Mexico, Argentina, Chile, Brazil and Peru have modern cancer centers, well-trained health professionals and access to radiotherapy. Other countries — in the Caribbean, Ecuador, Bolivia and elsewhere — have limited resources. Vastly different incidence rates of individual cancers are also evident. The high incidence of gallbladder cancer in Chile is unheard of in Costa Rica. The cervical cancer so rampant in the Caribbean is rare in urban areas of Argentina, where, instead, breast cancer is epidemic. Less than an hour away, Argentina's poorest patients arrive at the National Cancer Institute, predominantly with head and neck, cervical and lung cancers. And there are tremendous gaps in medical qualifications and the capacity for clinical and basic research. Countries like Argentina have a strong tradition in clinical cancer research, with several cancer institutes offering certification programs for medical oncology. In other Latin American countries, general surgeons provide cancer treatment and perform chemotherapy without the benefit of specialized training.

"The common denominator throughout Latin America and the Caribbean is the lack of support from governments for cancer plans, cancer registries, and cancer activities," says Eduardo Cazap. Based on the recognition of the vast differences that exist between rich and poor countries, and the similarities we share with countries in Europe, we decided two years ago that we needed a regional organization to address these disparities. Cazap brought together leading oncologists from Mexico, Peru, Chile, Uruguay and Brazil to form the Sociedad Latinoamericana y del Caribe de Oncologia Médica. SLACOM's mission is to access the educational, treatment and clinical research needs of the region, and to develop better cancer management programs through collaborative initiatives.

Eduardo Cazap espouses a global view of cancer.

"It is difficult for one organization to solve all the problems and to have sufficient resources and reach to manage the cancer situation," admits Cazap, "so we have asked two leading oncology organizations in the world — the European Society of Medical Oncology and the American Society of Clinical Oncology — for endorsement and support of our project. We believe the best way to solve problems in the developing world is to bring together different organization from different regions." With the support of the European Society for Medical Oncology (ESMO), for which Cazap represented Argentina and Latin America from 1997 to 2003, SLACOM is working with specialists from Europe to develop guidelines for diagnosis and management and recommendations relating to the early detection of cancer to be used in Latin America.

Other organizations that could be helpful to SLACOM, he says, are UICC and the American Cancer Society. "If the effort of six or seven important organizations in the world could be coordinated, we could improve our ability to make a difference," Cazap says. "INCTR is one of the groups that can be a player in this effort. My vision is similar to Ian Magrath's — a global vision of cancer treatment and research, understood from the perspective of developing nations."

A challenge for SLACOM is to find the intersection between those people with deep knowledge of the problem, and organizations that have the resources to help.

"We want to improve collaboration not only within our region, but throughout the world," Cazap says. "Sometimes the situation is a lack of education, or of a cultural or social framework that makes for effective treatment. Our primary objective is to develop a strong organization to improve the quality of care in the region, and to improve the education of specialists, as well as general physicians and the general population. The International Union Against Cancer (UICC) and the American Cancer Society have already demonstrated that if the developing world makes better use of readily available information and technology, cancer curability improves significantly." ■

E. Cazap provided the information for this article, which was prepared by M. Landskroener for INCTR.

TRAINING OF ONCOLOGISTS FROM KABUL

A discussion was held with members of the Office of International Affairs, NCI, Bethesda, INCTR staff, and Drs. Kamal and Malik from Afghanistan (Kabul) to discuss progress and future goals for training selected persons from Kabul in regional cancer centers in order improve cancer services (presently essentially non-existent) in Kabul. A plan was made to train a medical doctor in General Oncology at the Tata Memorial Hospital. This one year training has already commenced. In addition, a laboratory technician from Kabul has already received 3-months training at the Shaukat Khanum Hospital at the beginning of 2005. ■

ESMO SESSION ON STRATEGIES FOR CONTROLLING CANCER IN DEVELOPING COUNTRIES

On November 2nd, the European Society for Medical Oncology included a session on cancer control in developing countries, in which INCTR was invited to participate. There were a number of good presentations and a discussion session, but perhaps the most important aspect of this meeting was the fact that major professional societies are becoming interested in the plight of cancer patients in developing countries. This augers well for future collaborations. ■

ONCOLOGY NURSE TRAINING COURSE IN BURKINA FASO

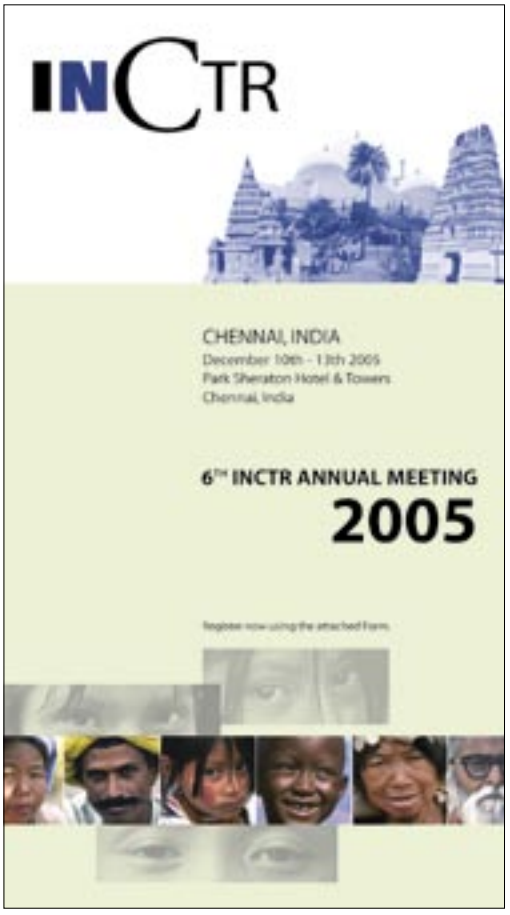
Sabine Perrier-Bonnet held a further training course for oncology nurses between 6th November and 14th November. The course was taken by 55 doctors and nurses and included didactic training, practical demonstrations (prescription of chemotherapy and side effects, psychological support and pain control related to palliative care), and many other discussions. Further courses of this kind are planned to take place in the course of the next year. ■

DATA MANAGEMENT COURSE RELATING TO INCTR'S ALL PROTOCOL IN INDIA

A training course was held between 11th and 20th November for 5 data managers, one each from the centers participating in INCTR's new treatment protocol for acute lymphoblastic leukemia (ALL), which has recently been initiated. The course covered both basic aspects of Good Clinical Practice, as well as specific issues pertaining to the data management and quality assurance of the INCTR study. The course was well received, and similar courses will be held for data managers from new participating centers, whilst videoconferencing will be added in the course of the next year to data monitoring visits already underway. ■

PLANNING INITIATED FOR A TRAINING COURSE IN PCR TECHNIQUES

A small group met on 25th and 26th November to have preliminary discussions on holding a training course in polymerase chain techniques (PCR), including realtime PCR. The purpose of this would be to demonstrate and standardize PCR techniques presently being used in INCTR collaborating units, as well as to provide theoretical information and practical experience regarding the use of such techniques. This course will probably take place in cooperation with the Insitut Pasteur, Brussels, and Imperial College, London, as well as with members of INCTR's translational research program. Please contact INCTR for more information, or to express an interest in this course. ■



INCTR 6th Annual Meeting, will include its standard components (keynote lectures, reports from INCTR Programs, educational/scientific sessions, workshops and role of technology) and will have a particular focus, this year, on important cancers in Asia. Deadline for Abstracts is August 1st, 2005. More information is available at www.inctr.org

NETWORK

CANCER IN INDIA

A decade ago, infection was the most prominent cause of morbidity and mortality in India. With the recent positive change in the economic status and technological advances in our country, there has been an appreciable upgrade in the literacy level. Consequently, health awareness has risen even in the most peripheral regions of India.

Due to its vast size and large population, health care delivery is of variable quality, but is available throughout the country via the central government, state governments and the private sector.

There has been a prominent shift of focus of attention from infection to cancer over the last decade. In today's India, cancer is an increasingly important health problem. The incidence is steadily rising due to improvement in lifestyle but because of increased cancer awareness, cancer is being diagnosed much earlier. Today we have infrastructure addressing all aspects of cancer control, including prevention, early detection, diagnosis and treatment. Again both government and private hospitals cater to cancer-related needs. Nevertheless, cancer treatment is still conducted in tertiary referral centers, usually located in the metropolitan cities where chemotherapy, radiotherapy and surgery are all readily available under the same roof.

India has a population of more than 1000 million which leads to more than 800,000 new cases of cancer being detected per year. According to the National Cancer Registry Program, lung cancer is the commonest cancer in men. Lung is a leading site of cancer in women as well, although cancer of the cervix and breast are the commonest cancers in women.

Cancer in India is unique from the perspective that it usually presents in a clinically advanced stage in a very high percentages of cases - about 75-80%. There are also some unique aspects of cancer epidemiology in India. For example, tongue cancer in males from Bhopal, and gall-bladder cancer in Delhi have among the highest incidence rates in the world.

Survival rates in most cancers are today comparable with the western world, but vary from center to center within India. Five year survival rates are 40-60% for breast cancer in females and 40-50% for cervical cancer.

Bone marrow transplantation today has become an easily available form of potentially curative treatment. It is being offered by four leading centers in India namely Jaslok Hospital and Research Center, Tata Memorial Hospital, Mumbai, CMC Vellore, AIIMS Delhi and the Apollo Hospital in Chennai. A bone marrow donor registry program has been recently initiated. India has also entered the world of targeted therapy, which is in the limelight in the treatment of cancer worldwide. We have a national surveillance program for the early detection and prevention of cervical and breast cancer and educational programs for breast self examination, and the dangers of tobacco, which are promoted at a national level.

Cancer diagnosis and treatment is expensive all over the world. The same applies for India. For western countries, the cost of cancer treatment is met by medical insurance companies which is not the case for the bulk of Indians. While some of our patients have private medical insurance and state-run mediclaim policies, the bulk of the cost of treatment is borne by the patient himself. There are, however, a number of societies providing financial help for patients seeking cancer treatment, including cancer support groups.

Fortunately today, due to the privatization of pharmaceutical companies, many chemotherapy molecules, including many targetted drugs are being indigenously produced. Both trademarked as well as indigenously manufactured drugs are readily available, the latter being much less expensive.

JASLOK HOSPITAL AND RESEARCH CENTRE: OUR ROLE IN CANCER TREATMENT

Our hospital, Jaslok Hospital and Research Center, a public charitable

Jaslok Hospital and Research Centre.

trust hospital, was established in July 1973. Today, it is a 377-bedded hospital which includes 230 paying, 51 free and 96 subsidized beds. It is a tertiary referral center and a mul-

tidisciplinary, multi-faculty hospital and is recognized by the Medical Council of India for the training of post-graduates for the diplomas of the National Boards in internal medicine, pediatrics, neurology, medical oncology, general surgery, nephrology, radiation therapy and interventional cardiology.

Thawing of peripheral blood stem cell.

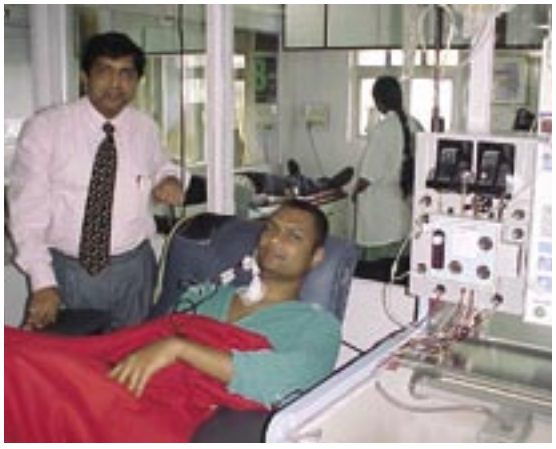
The Medical Oncology Department and Bone Marrow Transplant Unit at our hospital is headed by Dr. S.H. Advani and was first established in 1985. Today it includes 8 medical oncologists, 12 cancer surgeons, chemotherapy nurses, research fellows, a research nurse and a data manager. We have an out-patient department, chemotherapy daycare (six beds) and in-patients distributed throughout the hospital. A bone marrow transplant unit (two beds) performs two transplants a month. We are supported by a blood bank which includes a cell separator and cryopreservation facility. Our infrastructure is complete, with state-of-the-art hematology, histopathology, microbiology, cytogenetics and molecular medicine labs and also an electron microscopy department. We have our own radiotherapy department, which has a linear accelerator and a cobalt radiotherapy unit. We have a "superspeciality" post-graduate training program for trainees in our department registered for the qualification of Diplomat of the National Board in Medical Oncology.

Chemotherapy nurses are well trained in the administration of chemotherapy and also run an intravenous indwelling catheter care clinic. We have an Imaging department, which includes MRI, CT scan and PET scan, all of which contribute greatly to the management of patients. There is a strong interest in research projects and currently our unit is actively involved in multiple phase II and phase III international multicentric clinical trials. In the future we plan to study familial and hereditary patterns of cancer.

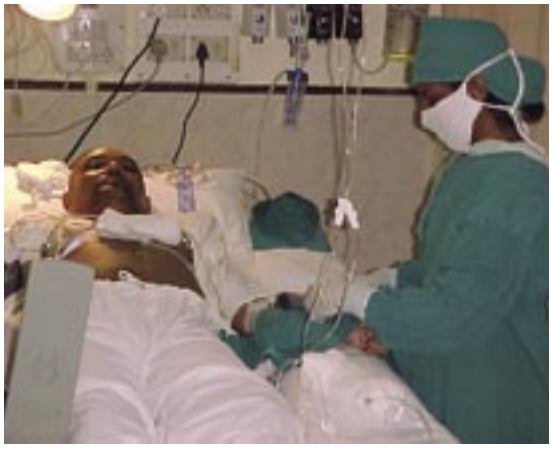
We also have several cancer support groups—including social workers, V-care and Make-A-Wish Foundation—that make an important contribution to the overall care of our patients.

On an average we see 50 adult and five pediatric patients in the out-patient department in a day, of which four or five are new. At any one time there are approximately 150 in-patients. In our bone marrow transplant unit we have so far performed 12 allogenic and 38 autologous bone marrow transplants in a variety of diseases. Our unit caters to patients coming from various parts of the country and also from even more distant neighboring countries, including Pakistan, Bangladesh, Nepal, Kenya, Nigeria and other south Asian countries.

We have a fully equipped data management system with an experienced staff, six computers dedicated to oncology clinical trials. Our data manager participated in a training program at the INCTR office in Belgium. We have good access to the Internet as well as our own website: http://www.jaslokhospital.net. ■



Peripheral blood stem cell collection.



Peripheral blood stem cell infusion.

Contributed by Suresh Advani, Department of Medical Oncology, Jaslok Hospital, Mumbai, India.

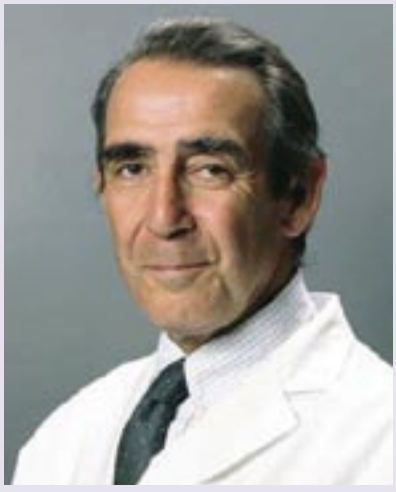
PROFILES IN CANCER MEDICINE

PHYSICIAN PROFILE: MAJOR ADVANCES IN THE TREATMENT OF HEMATOLOGIC NEOPLASMS

A hematologist who has followed in his father's footsteps, Santiago Pavlovsky understands that in the battle against cancer, clinical research is paramount. Named Doctor of the Year 2000 by Argentina's National Ministry of Health, Dr. Pavlovsky has served since 1989 as Medical Director of FUNDALEU, the foundation devoted to fighting leukemia and operating within the Angela Ocampo Hospital and Clinical Research Center. This center, recognized for its high level of medical care, participates in national and international protocols, the data from which forms part of Argentina's national registry and supports the work of two medical groups he established as a young physician — GATLA and GATHEM — both dedicated to the development of clinical research programs in hematological malignancies in Latin America.

"My father was one of the most outstanding hematologists of his time," says Dr. Pavlovsky. Alfredo Pavlovsky, a first-generation son of a Russian immigrant, founded the International Society of Hematology two years after World War II. In 1956, he established the Leukemia Foundation in Argentina where Santiago Pavlovsky is now director.

"During my childhood I was able to meet most of the pioneers in hematology from around the world," Dr. Pavlovsky recalls. "In my father's time, and when I graduated in medicine, hematological malignancies were incurable. The best you could do was to establish a diagnosis. There was very little chemotherapy available. Today, these diseases are highly curable. In four decades, we've gone from a no cure rate to a 75% cure rate in acute lymphoblastic leukemia, a 90% cure rate in Hodgkin's lymphoma and childhood non-Hodgkin's lymphoma, and a 50% cure rate in adults. I'm pretty optimistic about the future."



Dr. Santiago Pavlovsky.

Dr. Pavlovsky attended the University of Buenos Aires, earning his medical degree in 1964 and his doctorate in 1968. He completed post-graduate studies in hematology in Paris before returning home to launch the onco-hematology department at the Instituto de Investigaciones Hematologicas (IIH). As he sought to better understand advances being made in onco-hematology, and to share his own research efforts, he pursued several study-travel opportunities, including those with the International Agency for Cancer Research, the International Union Against Cancer and the Programa de Intercambio de Hematologos Latinoamericanos.

Throughout his 40 years in cancer medicine, Dr. Pavlovsky has witnessed not only the development of new drugs, but better combinations of new drugs and the establishment of national and international protocols. "Now we can very quickly finish a protocol, learn about the results, and then establish a new protocol that improves the outcome," he says. "This experience has been the same in most countries in the world."

Dr. Pavlovsky predicts that, more and more, hematological disorders will be treated with specific drugs that target the molecular disorder of the disease, and avoid the side affects of toxicity. Doctors today are using targeted treatment for chronic myeloid leukemia in place of bone marrow transplantation. "The drug, Gleevec, is given by mouth with excellent tolerance, and the response is fantastic," Dr. Pavlovsky remarks. "This is the most outstanding advancement in the field, and a good example of what we can expect in the future. Instead of a cocktail of toxic chemotherapy, we can have a single drug attacking a cancer on the molecular level."

Of all his accomplishments, Dr. Pavlovsky takes the greatest satisfaction in having organized cooperative trials and improved the level of care in Argentina and throughout Latin America, by establishing protocols that treat all hematological patients in the same way. "The improvement of survival and cure rates was the same all around the country," he says.

In the case of Hodgkin's lymphoma, Pavlovsky conducted a landmark study in 1978 demonstrating that long-term survival rates were quite good when chemotherapy alone was used to treat patients in early stages of the disease, compared to chemotherapy plus radiotherapy.

His work generated great international respect. In 1983, Dr. Pavlovsky was nominated Cancer Advisor of the Pan American Health Organization and coordinator of the Collaborative Cancer Treatment Research Program, a project sponsored by NCI and the Pan American Health Organization, with the aim of supporting clinical research projects and disseminating cancer information throughout Latin America. Among his many international medical committee assignments, he served as a consultant to WHO's Cancer Program in Developing Countries, as a member of the International Blood and Marrow Transplantation Registry, as founding member of Global Organization Against Leukemia, and as a member of the Advisory Board of INCTR and as chairman of the International Affairs Committee of ASCO. ■

Marcia Landskroener for INCTR