

NETWORK

THE NEWSLETTER OF THE INTERNATIONAL NETWORK FOR CANCER TREATMENT AND RESEARCH

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THE PRESIDENT'S MESSAGE

THE COMMUNITY AND CANCER

Part 1. Cooperation and Competition
by Ian Magrath

How selfish soever man may be supposed, there are evidently some principles in his nature, which interest him in the fortunes of others, and render their happiness necessary to him, though he derives nothing from it, except the pleasure of seeing it. Adam Smith. The Theory of Moral Sentiments.

A brief survey of the events that have occurred in the 15 billion years or that the universe has existed gives the impression of an inevitable progression towards the emergence of life, and ultimately of intelligent life. The sense of inevitability arises, in part, from the particular values of the physical constants - values that have permitted the creation of atoms and molecules of continuously increasing complexity since hydrogen emerged at the time of the big-bang. Statistical considerations also favor inevitability, since even if the formation of planets able to support life were an exceed-



Example of a fossil of an Ediacaran animal from the Precambrian era. This has been named Dickinsonia costata. Its relationship with modern animals is speculative; it has been variously considered an annelid worm, or a cnidarian (a group including jellyfish, corals and sea anemones). Reproduced with kind permission of: C Richard Paselk, HSU Natural History Museum.

ingly unlikely event, the passage of billions of years and the creation of trillions of planetary systems in the hundreds of billions of galaxies known to exist would seem to guarantee the creation of life and the

eventual development of rational thought at least once in the universe, and possibly innumerable times. Inevitability may, of course, be an illusion, arising from our particular vantage point as recently evolved

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intelligent beings - prior evolutionary steps, of necessity, lead to Homo sapiens. But whether the evolution of intelligence was inevitable or not, our perspective is unavoidably anthropocentric and presumes, at least in non-scientific circles, that Homo sapiens is the culmination of the evolutionary process. The corresponding social implications have been dire, for such a view fosters the idea that nature exists purely to be gainfully exploited, justifying the mutilation and pollution of the very source of our being. Ancient ecosystems such as tropical rain forests - vast repositories of information and products of great potential value (see Table) that have barely begun to be categorized - have already been decimated. Apart from the effect on biodiversity, the loss of trees (at the rate of 25 million acres a year) reduces the consumption of carbon dioxide by photosynthesis, contributing significantly to global warming.

INCTR

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Within human society a parallel trend exists whereby the few rich and powerful assume their interests to be paramount, while the voices of the numerous poor are scarcely heard. Hobsbawm, in *The Age of Extremes* speaks of the social changes in the 1960s as being "best understood as the triumph of the individual over society, or rather, the breaking of the threads which in the past had woven human beings into social textures." This comment goes a long way towards explaining the root cause of the present enormous inequality in the world, which further exacerbates social tensions. While poverty is a major cause of malnutrition and ill-health as well as poor access to health care in the developing countries, over-consumption in the high-income countries, particularly in the USA and UK, has created an epidemic of obesity, diabetes, and associated diseases, including various cancers. The role of tobacco in the causation of many diseases, including cancer, has been known for decades, but governments have failed to address the problem with any real enthusiasm, largely due to commercial interests, or increasingly, in developing countries, because of an urgent need of money. The Global Tobacco Framework is a major achievement, but why did it take so long to accomplish, and will a majority of member states heed its exhortations? The wealth of nations consists of three components - material, cultural and biological. At the present time, it would seem, the latter two are being sacrificed in favor of the former, while the distribution of material wealth is grossly uneven. The value of reason, it would seem, depends upon the uses to which it is put.

THE RECORD OF REASON

Homo sapiens is one of the most recent species to emerge and, at least in terms of his faculty for rational thought and tool making, would appear to be the most complex animal ever to have evolved. But complexity does not necessarily equate with success and on its present record, rational thought is unlikely to greatly benefit life on Earth. Even from the perspective of mankind alone, the remarkable technological progress of recent years has failed to prevent the lives of at least half, and probably the majority of humans on the planet, from continuing to meet Thomas Hobbes's description, in 1651, of being "solitary, poor, nasty, brutish and short." It is of some interest, even if tongue-in-cheek, to compare the contributions to life of our distant ancestors, the prokaryotes, with our own. In the course of some three billion years these simple cells created the basic metabolic pathways used by all life forms, an oxygen-containing atmosphere and eukaryotic cells, all essential to the emergence of multicellular organisms. This led to the explosion of animal biodiversity in the Cambrian period, beginning just over 500 million years ago, and the colonization of the land by animals and plants. In contrast, human activities have, in the space of a perhaps a few thousand years and with dramatic acceleration in the last fifty, destroyed large swathes of primordial forest, created massive pollution, and initiated the sixth major extinction of species that has occurred since the Cambrian explosion. Human activities are also bringing about significant climate change, which threatens to create a major global catastrophe. Intelligence, it would

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PRODUCT	PURPOSE	ORIGIN
Digitalis	Cardiostimulant	Digitalis purpurea (foxglove)
Atropine	Anticholinergic	Atropa belladonna (deadly nightshade)
Camptothecin	Anti-cancer	Camptotheca acuminata
L-dopa	Anti-parkinsonism	Mucuna species (e.g., velvetbean)
Ephedrine	Sympathomimetic	Ephedra sinica
Etoposide	Anti-cancer	Podophyllum peltata (mayapple)
Irinotecan	Anti-cancer	Camptotheca acuminata
Morphine	Analgesic	Papava somnifera (poppy)
Pilocarpine	Sympathomimetic	Pilocarpus jaborandi (Indian hemp)
Taxol	Anti-cancer	Taxus brevifolia (Pacific yew)
Teniposide	Anti-cancer	Podophyllum peltatum (mayapple)
Topotecan	Anti-cancer	Camptotheca acuminata
Tubocurarine	Muscle relaxant	Chondodendrum tomentosum
Vinblastine	Anti-cancer	Cantharanthus roseus (periwinkle)
Vincristine	Anti-cancer	Cantharanthus roseus (periwinkle)
Cyclosporine	Immunosuppressive	Hypocladium inflatum
Tacrolimus	Immunosuppressive	Tolyplocadium inflatum
Lovostatin	Cholesterol lowering	Monascus purpuris (red yeast rice)
Penicillin	Antibiotic	Penicillin notatum
Amimnoglycosides	Antibiotics	Streptomyces species
Beta-lactams	Antibiotics	Streptomyces species
Fluoroquinolones	Antibiotics	Streptomyces species
Bleomycin	Anti-cancer	Streptomyces verticillis

Table: Some Medicinal Products Derived from Plants, Fungi and Bacteria.

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seem, has yet to overcome instinctive behavior; indeed, its preponderant use, at least, in political arenas, would appear to be the justification of behavior that evolved in the context of survival in the prehistoric era, and which has become horribly distorted by the very success of humans in terms of population growth and the development of ever more effective tools and weapons. As the human population continues to expand, accompanied by an increasing demand for energy and food, it is imperative that people see themselves not as distinct from the planetary ecosystem, but as part of it, and with a unique and unprecedented responsibility towards it that stems directly from their ability to appreciate its magical beauty, its complex interrelationships, its miraculous mechanisms and its profound mystery.

OEKOS

The sense of unity with respect to the ecosystem (Greek, *oekos* = house) we are part of probably existed in prehistoric human communities to a much greater extent than it does today. Yet scientific evidence points strongly towards a singular origin of the trinity of energy, matter and life. The long journey from the perfect point, that was the beginning of the universe, to the human brain has occurred in a series of steps, each dependent on the one before. Sometimes, dramatic changes have occurred in minuscule fractions of a second (e.g., the events that occurred immediately after the big bang, relating to the primordial energy fields and particles) while others have taken billions of years of preparation (e.g., the creation of the 92 elements in massive stars). The

shallow seas that filled much of the surface of the planet Earth, as soon as it had cooled sufficiently, must have provided an appropriate environment for the emergence of life, for fossilized stromalites, the remains of huge mattresses (*Greek, stroma*) of prokaryotic cells, date back to less than a billion years after the formation of Earth. Similar domed structures containing living microorganisms continue to form today. The fact that all living organisms, including humans, use the same molecular information systems and basic metabolic pathways confirms life's unique origin - the biological equivalent of the cosmic singularity. If there were once other life forms, they have certainly left no trace.

This puts a very different gloss on what we, from our individualistic viewpoints, see as competition - a lesson translatable from ecology to economics. Prior to multicellular organisms, individual cells generally had an extremely transient existence, dividing over and over again to give rise to vast clones of cells. Here, the species (a much less well defined concept in prokaryotes) is automatically conceived of as the biological entity rather than the individual cell. Darwin's theory of "survival of the fittest," refers to a process whereby a species becomes increasingly adapted to survival in a particular ecological niche through *natural selection* of the most appropriate genetic traits from among the wide range expressed in the individuals of the species. Over time, the higher reproductive rate of the "fittest" individuals ensures that they come to predominate in the population. Horizontal transfer of genes in prokaryotes, which even occurs between species, permitted

this process to be greatly speeded up. Darwin, of course, was unaware of the existence of microorganisms, and his theory was derived from the study of animals and plants, where natural selection is not only a process of adaptation to a particular habitat, and to dispersal to other habitats (adaptive radiation), but also has much to do with the establishment of a harmonious relationship among the various species (i.e., reproductively isolated populations) living in a particular habitat. Such a balance, although it involves predation, can be seen primarily as a cooperative process that ensures maximal use of available resources through maximization of biodiversity, a process in which prokaryotes continue to play a vital role. In more complex species remarkable degrees of specialization occur, but species also share each other's captured energy as well as essential molecules. These intimate forms of cooperation in multicellular organisms are not dissimilar, in principle, to gene transfer in prokaryotes. In stable ecosystems both the number of species and the numbers of individuals in each species remains within defined limits over relatively long periods of time, varying according to the size of the habitat.

TERRESTRIAL COLONIZATION - A JOINT VENTURE

Animals and plants emerged on Earth in the course of the last billion years. This new phase of evolution was eventually to lead to the remarkable ability of life to contemplate itself. The best preserved of the earliest animal fossils (all marine) were discovered in the Ediacara Hills of Australia by a geologist, Reginald Spriggs, in 1946. The classification of

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the Ediacaran animals, which lived between some 540 and 650 million years ago, is difficult, and while some resemble modern phyla, such as the annelid worms, arthropods of various kinds (insects and crustaceans), or corals, others may belong to phyla long since extinct. The colonization of the land by animals, plants and fungi probably began somewhat more than 400 million years ago. One element vital for plant evolution, among many others, was the creation of soil. This was provided by decaying organic matter (courtesy of prokaryotes), mixed with rock particles and tilled by the earliest animals, such as those resembling annelid worms and insects. Similar organisms continue to perform this important task today. More complex terrestrial plants and animals also had to await both the development of the more efficient energy generation of aerobic respiration, and also sufficiently high atmospheric oxygen levels. The presence of an ozone layer, also dependent upon high atmospheric oxygen concentrations, was necessary to protect against harsh ultraviolet light. Unfortunately, the fruits of billions of years of photosynthesis can be destroyed in a few decades, an event which would have a profound effect on a broad range of terrestrial life forms. Even the present degree of depletion, caused by atmospheric pollution by humans, has led to an increase in the incidence of a common skin cancer - melanoma - as well as other skin and eye diseases. Increased UV radiation is also likely to decrease populations of marine organisms, including phytoplankton, which will have a corresponding effect on fish, with negative effects on the human food chain.

Ultimate success in terms of the invasion of land was dependent upon many other forms of close cooperation, which also persist to the present day. Of particular importance was the symbiotic relationship between plants and fungi, which first occurred in the form of lichens, most probably one of the earliest terrestrial immigrants. Heinrich Anton de Barry, who coined the word *symbiosis* in 1866 showed that lichens are not single organisms, but result from the close cooperation between autotrophs (organisms able to trap energy from the sun or inorganic materials) and heterotrophs (life forms that feed on other life forms). Since fungi are able to absorb large quantities of water and to extract minerals from particles of rock, they can protect the sensitive algae from dessication and provide them with minerals in return for a share in the carbohydrates produced by the algae (during photosynthesis). Lichens remain among the first organisms to colonize forbidding environments such as deserts, but as fungi and plants evolved, the symbiotic relationship between them also developed. Today, mycorrhizal fungi are closely associated with the roots of nearly all plants, continuing to assist in the absorption of minerals and water and uniting with them in a vast cooperative, if underground, network. Some relationships are not precisely balanced, and sometimes fungi kill the trees they would otherwise succor. Life, like human society, is, however, a work in progress, and parasites, who generally take more than they give, abound at all levels. They even have their own parasites (hyperparasites).

Prokaryotes continue to be vital to the survival of more complex

organisms on land. Nitrogen fixing bacteria live in rhizobial nodules on the roots of some plants, giving them access to this abundant atmospheric element, which is essential to the synthesis of a number of vital molecules, including amino acids, the building blocks of proteins. A particularly important collaboration is that between flowering plants (*angiosperms*) and insects, birds and mammals. Such plants (which include many trees) like other life forms, provide an immense variety of habitats and food for animals - conveniently signposted by the brilliant colors of flowers, or the smell of fruits. Insects, in return, intercede in the process of plant reproduction (pollination) and to a lesser extent, dispersal, while birds and animals have a major role in spreading seeds, either through ingestion, or carriage on some part of their body. This willingness to "pay" as it were, a price in energy for the benefit of the species is not limited to plants. Animals prey upon each other, creating balanced relationships which permit the species of both predator and prey to survive. Disturbance of this balance, which may have taken millions of years to establish, via the introduction of alien species or the removal of a particular predator - both of which are often the result of human colonization, can result in multiple extinctions and a marked reduction in biodiversity.

LAMBORNELLA CLARKI

A remarkable demonstration of the cooperative nature of predation is found in the relationship between the single-celled ciliate, *Lambornella clarki*, and the mosquito, *Aedes sierrensis*. *Lambornella* lives in rain-filled tree holes in the western United

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States, where the mosquito lays its eggs. Both ciliates and mosquito larvae are able to prey on bacteria in the water, but the mosquito larvae also feed on *Lambornella*, if present. In this case chemicals released by the larvae trigger a morphological change in *Lambornella* (similar to that occurring in other Tetrahymena ciliates), such that it can penetrate the tissues and feed on the flesh of some of the mosquito larvae. Infested larvae are still able to develop into adults, in which the parasitic ciliates preferentially migrate to the ovaries, rendering the mosquito sterile and also triggering hyperactive egg-laying behavior. The mosquito, loaded with ciliates, flies to other holes, and, in the process of trying to lay eggs, or through dying on the surface of the water, deposits *Lambornella* into the water, thus ensuring its dispersal.

The story does not end there. The female of *Aedes sierrensis* feeds avidly on the blood of large mammals, including humans and is the vector of the parasitic microfilarial worm which causes heart worm disease in dogs. It is also capable of transmitting Western Equine Encephalitis virus to people and horses. There are many variations on this dance of nature. Some Tetrahymena are exclusively free-living; others are exclusively parasitic, e.g., on fish, or, in the case of *Plasmodium* species, which cause malaria, on humans. In this case *Anopheline* mosquitoes rather than *Aedes* play a critical role in the dispersal of the ciliate. Malaria kills over a million people each year, and may be a factor in the high incidence of a common childhood cancer in equatorial Africa - Burkitt lymphoma. From the biological perspective, human infectious and parasitic diseases represent a means

of maintaining the human population size within the limits specified by the natural ecosystem. People, of course, see things differently, and the present population explosion occurring in developing countries is, in large part, a consequence of the conquest of infectious diseases and the development of much more efficient methods of food production. Reason alone might suggest

**"It is the highest
impertinence and
presumption, in kings
and ministers to
pretend to watch over the
economy of private people,
and to restrain
their expense...
They are themselves always,
and without exception,
the greatest spendthrifts
in the society."**

**Adam Smith.
*The Wealth of Nations.***

that the substitution of birth control for the regulation of the population size through disease would help to reduce the ecological damage presently caused by humans, but the issue is complicated by the need for education, by cost, even if small, and by cultural and religious ideologies.

CONFLICT

Conflict can be seen as a quite different phenomenon from predation, relating more to competition for females within a species (e.g., rutting deer), or dispersal through the establishment and protection of

distinct territories occupied by one or a group of animals. Rarely does conflict of this kind result in death. Territorialism, whether involving competition for physical (relevant to food and energy supplies) or ideological space, is also the ultimate cause of human conflict, but in people, the development of more effective weapons and strategies has led to a significant and ever increasing toll on life as well as a markedly higher rate of disruption and physical displacement of communities. Rational thought, in other words appears to enhance rather than diminish conflict. Life's survival strategy - biodiversity - has been robust enough to overcome 5 catastrophic extinctions since the emergence of animals and plants. It will probably survive the sixth, a child of rational thought, but whether through the use of reason, or the extinction of intelligent beings, remains to be seen.

ECOLOGY

Human beings, in spite of their modern sense of being apart from nature, represent a generalist species - i.e., one whose strategy is to be reasonably well adapted to a range of habitats rather than highly adapted to a single habitat. Whilst highly adapted species compete more successfully in their particular niche, they also are at higher risk of extinction. Many feather mites, for example, live on particular feathers of particular birds, and their survival depends entirely upon that of their host. Organisms able to survive in more than one habitat, particularly if widely dispersed, are more likely to survive natural changes in climate or local ecosystems. Modern humans, although descended from arboreal apes, have colonized a large number

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of widely dispersed habitats - not through the slow process of structural and behavioral changes on which adaptive radiation depends (although genetic differences do play a role in human adaptation to some environments), but as a consequence of their omnivorous diet, their tool making skills, their ability to effectively communicate through language and their intelligence. Thus, the species can accumulate collective knowledge and undertake knowledge-based collective action that enhances survival and the quality of life. Knowledge, however, is "context sensitive" and may not always be transferable to different environments and circumstances.

ECONOMY

In the year that the 13 colonies of the United States of America declared their independence from the British Crown (1776) Adam Smith's book, *An Enquiry into the Nature and Causes of the Wealth of Nations*, was published. Smith, who is often referred to as the father of economics, was successively professor of logic and of moral philosophy at the University of Glasgow before leaving academic life. His writings encompass a broad range of subjects, particularly morality and ethics and he was particularly recognized for his teachings on communication and the importance of *sympathy* between speaker and listener. This concept spills over into a broader principle encompassing the interactions of societies. In the opening sentences of *The Wealth of Nations*, Smith pointed out the importance of the division of labor - which is the community equivalent of biodiversity. We must be prepared to contribute to society in

order to gain something in return. In biological systems, as in human interactions, the contribution can extend to life itself, in which case, the individual surrenders all benefits in favor of the community as a whole. Adams pointed out that societies cannot run on benevolence alone, but he also believed that a system built on greed and selfishness is morally flawed and that an economy without ethics and compassion will be destructive for both individuals and society. In contrast, rewards are found in justice and benevolence. Smith's well known metaphor of the invisible hand derived ultimately from the nature of human relationships and, for that matter, of all relationships in which there are communities of living organisms. Where the efforts of individuals are responsible and relate to the needs of the society, society as a whole benefits, but any major departure from this rule will, as Smith observed, result in disaster. Thus, ultimately, the preservation of the community takes precedence over the well-being of individuals.

Ironically, Smith is often quoted in support of a modern notion that profit is the sole purpose of business - leading to the conclusion that commerce has no need to reflect the needs of society. Such forms of business may be characterized, at best, as social parasitism, at worst, criminal. Health care is a special case since health can be impaired by many commercial products (as well as the manufacturing process itself) while other products are important to its maintenance. The delivery of effective health care is fundamentally related to the well being of the community and must,

therefore, in some way, be regulated at a community level. The free-market model of price determined by demand is seen in this, as in many other contexts, to be naive and unworkable at the level of the patient, since the quality of care requires expert assessment, which the consumer is rarely in a position to undertake. Smith's emphasis on the need for compassion applies particularly to the provision of health care, but unfortunately, economic considerations affecting only a small sector of society often take precedence.

A vital question for our times is how to ensure that the ever-increasing knowledge-base can be integrated and used to develop strategies that are ethical, egalitarian, culturally sensitive, lead to respect for and care of the environment and its contained ecosystems, and are based on effective cooperation among macro and micro communities. Any answer to this question must address approaches to diluting nationalistic impulses directed towards dominance and curbing irresponsible or actually harmful business practices. Competition should be used, in analogy with natural selection, to improve the quality of products rather than to maintain, too often through veiled or overt threats, the present unequal distribution of material wealth. International governmental and non-governmental, non-profit organizations (often referred to as *Civil Society*) will have a particularly important role to play in moving towards this goal which must be achieved if a variety of human ills, including conflict, poverty and disease, are to be overcome. ■

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FIRST INCTR MULTIDISCIPLINARY CONFERENCE MANAGEMENT OF A PATIENT WITH HODGKIN LYMPHOMA WITH MEDIASTINAL INVOLVEMENT PRESENTED AT THE INCTR ANNUAL MEETING, 2004

INTRODUCTION

DR. AZIZA SHAD: Multidisciplinary conferences are a standard feature of patient management in major cancer centers. The aim of such meetings, in which a team of medical experts discusses the optimal management of a particular patient, is to confirm the diagnosis, ascribe stage, where appropriate, review all investigations and reach a consensus on the best possible treatment for the patient. Thus, multidisciplinary conferences may be held to discuss newly diagnosed cases, relapsed cases, or any patient in which a therapeutic decision needs to be made. In addition, such conferences foster good relationships among the members of the medical team, and an educational experience for all.

PARTICIPANTS

Session Chair: Dr. Aziza Shad, Pediatric Oncologist, Lombardi Cancer Center, Washington DC, USA.

Moderators: Dr. Corina Gonzalez, Pediatric Oncologist, Lombardi Cancer Center, Washington DC, USA, and Dr. Henning Bredenfeld, Medical Oncologist, University of Cologne, Germany.

Participants: Prof. Nadia Mokhtar, Pathologist, NCI Cairo, Egypt; Dr. Ali Khan, Radiologist, North Manchester General Hospital, UK; Prof. Mahmoud El-Gantiry, Radiation Oncologist, NCI Cairo, Egypt, and the audience of the 2004 annual INCTR meeting.

PRESENTATION OF CASE

Dr. GONZALEZ: An 11-year-old Caucasian female living in the USA was admitted to the hospital because of progressive cervical lymphadenopathy, mediastinal mass and constitutional symptoms. Eight weeks earlier, the patient had noticed several tender swellings on the left side of her neck, which enlarged over time. A month prior to admission, intermittent fevers up to 38.5° C, non-productive cough and bilateral knee pain developed. Three days prior to hospitalization, the patient developed drenching night sweats. On the day of admission, the patient was seen by her primary physician. There was no history of shortness of breath, weight loss, fatigue or difficulty in swallowing and no significant past or family history. A chest radiograph (CXR) and a blood cell count were ordered, and oral cephalixin was prescribed for presumptive lymphadenitis. The CXR revealed a mediastinal mass and the patient was admitted to hospital for additional diagnostic tests.

Physical examination revealed bilaterally enlarged lymph nodes in anterior cervical, occipital and preauricular areas, which were 1.5 - 2 cm in size, non-tender, firm and rubbery. The left supraclavicular nodes were hard and matted, forming a lobulated mass measuring about 5 cm in diameter. Physical examination was otherwise unremarkable. On the second hospital day the patient underwent computerized tomography (CT) scans of the neck, chest, abdomen and pelvis and a biopsy of the most prominent cervical node. Extensive laboratory tests revealed no abnormalities except increased WBC (17.800/mm³), ESR (79 mm/hr), and LDH (265 IU/L).

DIAGNOSIS

HISTOPATHOLOGY

Prof. MOKHTAR: Histopathological examination (Figures 1 and 2) revealed nodules of lymphocytes separated by fibrous tissue. Numerous Reed-Sternberg (RS) cells are seen in the nodules as well as a background infiltrate of inflammatory cells composed mostly of small lymphocytes and eosinophils. These findings are consistent with the nodular sclerosis type of Hodgkin lymphoma.

Dr. GONZALEZ: What problems may be encountered in making a diagnosis of Hodgkin lymphoma?

Prof. MOKHTAR: The type of specimen obtained is important. An excisional biopsy of a suspicious node is the preferred diagnostic procedure, as it permits the evaluation of the architectural as well as cellular features characteristic of the specific histological types. By contrast, a fine needle aspirate of a suspicious node is often not diagnostic because of the limited numbers of malignant cells in the affected tissue. Specimens should, ideally, be received directly from the surgeon or the oncologist in normal saline or tissue culture medium rather than formalin in order that flow cytometry and molecular studies can be performed or a piece of tissue frozen for subsequent studies. Sections of the specimen should be fixed in formalin and also in B5, if available, since the latter can be more rapidly processed. In spite of optimal processing, classic, diagnostic RS cells may be lacking, particularly in the nodular lymphocyte predominant Hodgkin lymphoma. In such cases, immunophenotyping is helpful in distinguishing Hodgkin lymphoma from Non-Hodgkin's lymphomas, in

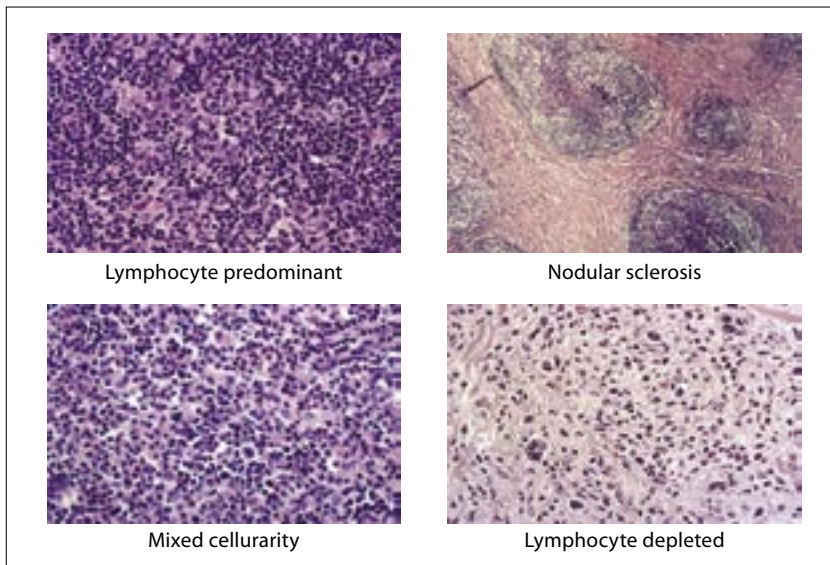


Figure 1. Appearances of the four histological types of classical Hodgkin's disease. (Hematoxylin and eosin stain) Magnification: lymphocyte predominant, mixed cellularity, and lymphocyte depleted X 20; nodular sclerosis X 40.



Figure 2. Chest X-ray showing a large mediastinal mass in a patient with Hodgkin Lymphoma.

particular diffuse large B cell lymphoma, and in separating nodular lymphocyte predominant Hodgkin's disease from classical Hodgkin lymphoma. In the former, atypical RS cells, often called "lacunae" or "popcorn" cells, express CD45+, B-cell associated antigens (CD 19, CD20,

CD22, DC79a) and epithelial membrane antigen (EMA) and are negative for CD30 and CD15. In contrast, classic Hodgkin lymphoma is defined by the presence of typical RS cells, which express CD30+, CD15+, and are negative for B or T cell markers, with architectural and cellular fea-

tures consistent with nodular sclerosis, mixed cellularity, or lymphocyte predominant Hodgkin lymphoma.

Dr. GONZALEZ: Do the different histological subtypes of Hodgkin lymphoma carry any prognostic value? *Prof. MOKHTAR:* Historically, a better prognosis was linked to a higher ratio of lymphocytes to abnormal cells, no matter which histopathology classification for Hodgkin lymphoma was used. However, since the development of highly curative treatment regimens, all histological subtypes of classical Hodgkin lymphoma are equally responsive to treatment.

IMAGING STUDIES

Dr. KHAN: The CXR, posterior-anterior and lateral views reveal a large, lobulated anterior mediastinal mass which exerts mild mass effect on the trachea, causing it to deviate to the right. The lungs are well aerated with no infiltrates, nodules, pleural effusion, or pneumothorax. The bony thorax is unremarkable. The cardiac silhouette is within normal limits. The larger tumor diameter is more than a third of the diameter of the thorax when measured at the level of the dome of the diaphragm, thus is defined as bulky disease. The CT scan of the neck and chest shows lymphadenopathy in virtually all lymph node groups in the neck, measuring, on average, about 1.5 cm. The most prominent region of lymphadenopathy is in the left supraclavicular region, which most likely represents a confluence of lymph nodes, measuring approximately 1.5 by 4.5 cm in transaxial dimensions. The CT scan of the chest shows a left upper mediastinal mass measuring approximately 3.4 by 5.1 cm, which is contiguous with the

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left supraclavicular mass. CT scans of the abdomen and pelvis show no abnormalities. Gallium scan showed intense uptake in left lower neck, left paramediastinum and right hilar and parahilar areas.

Dr. GONZALEZ: Dr. Khan, do we absolutely need CT scans for the radiographic staging of Hodgkin lymphoma?

Dr. KHAN: No, we do not need CT scans; CXR – anterior, posterior and lateral views – and ultrasound of the abdomen should be sufficient for the assessment of Hodgkin lymphoma. The neck and axillary areas can be evaluated by physical exam; any cervical or axillary node >1.5 cm in longest transverse diameter, any cluster of matted nodes, or any enlarged supraclavicular nodes should be considered Hodgkin lymphoma positive nodes, provided they are not obviously caused by infection. Gallium or FDG-PET scans can be performed when the results of other conventional diagnostic methods are not conclusive in identifying disease above the diaphragm. PET scan can be of real value when investigating abdominal involvement of Hodgkin lymphoma.

Dr. BREDEFELD: Dr. Khan, what is the value of Gallium and FDG-PET scans?

Dr. KHAN: Both FDG-PET and Gallium scans are studies that provide whole-body images and give a comprehensive assessment of disease extent. Recent reports suggest that the greatest value of FDG-PET scan lies in its positive predictive value for relapse in patients with residual masses. Positive uptake on FDG-PET scan signifies functional metabolic status, suggesting active areas of disease. Persistently positive PET scans at the end of therapy war-

rant close follow-up and additional diagnostic procedures. Conversely, a negative PET scan at the end of therapy provides very favorable prognostic information.

AUDIENCE: In my country we do not have FDG-PET scans. How useful is a gallium scan in predicting relapse in Hodgkin lymphoma?

Dr. BREDEFELD: The positive and negative predictive values of ⁶⁷Gallium scans in predicting relapse of Hodgkin lymphoma are lower than those for FDG-PET scans, which are close to 100% – at best, 80 to 85% of the predictive value of FDG-PET scans. When there is an uncertainty, on suspicious findings, histopathological verification is strongly recommended.

STAGING

Dr. GONZALEZ: Based on the history and investigations detailed by Dr. Khan and Professor Mokhtar, this patient has nodular sclerosis Hodgkin lymphoma involving more than two node regions on one side of the diaphragm, bulky mediastinal disease, and B symptoms. In addition to the investigations described, the patient underwent bilateral bone marrow biopsies that were negative for disease. Her stage, therefore, is IIB-X.

Accurate staging of Hodgkin lymphoma is of paramount importance in defining therapy. Currently, the modern treatment strategies for Hodgkin lymphoma are evolving towards a risk-adapted approach. The strategy is to give more intensive treatment to patients with more advanced disease with the goal of maintaining high overall survival rates in all stages of disease. Advanced disease would be an unfavorable prognostic factor in an unselected group of patients treated identically. The predictive value is

lost, however, when patients with advanced disease are treated with a more effective regimen, as demonstrated by recent studies in which survival curves for previously identified “risk categories” of Hodgkin lymphoma are essentially superimposable. Such risk factors include the direct measurement of tumor burden by stage, size of masses and splenic involvement, and indirect measurements such as hemoglobin, serum albumin, B symptoms and sedimentation rate. Today, most pediatric study groups divide Hodgkin lymphoma into three risk categories: early, intermediate and advanced, using these criteria.

TREATMENT

Dr. GONZALEZ: The treatment of childhood Hodgkin lymphoma consists of a combined modality approach, using chemotherapy plus or minus radiotherapy. Chemotherapy consists of a combination of several agents active against Hodgkin lymphoma which generally have a different mechanism of action. Prof. El-Gantiry will give us an overview of radiotherapy for Hodgkin lymphoma.

RADIATION THERAPY

Prof. El-GANTIRY: Radiotherapy is a very effective locoregional treatment modality in Hodgkin lymphoma and was the first therapy to produce a significant fraction of cures. The rationale rating for its use in addition to chemotherapy stems from the observation that disease progression after chemotherapy alone often occurs in sites of prior involvement. However, the long-term morbidity associated with radiation therapy has been significant – particularly with respect to

MEDICAL HISTORY with attention to presence or absence of systemic symptoms, such as unexplained recurrent fevers >38° C, unexplained weight loss >10%, and drenching night sweats.
PHYSICAL EXAM emphasizing node chains, Waldeyer's ring, and size of liver and spleen.
CHEST RADIOGRAPH with measurement of the mass-thoracic ratio.
CT-SCANS: Neck- Chest- abdomen and pelvis.
RADIOISOTOPIC EVALUATION with Gallium or FDG-PET scans, when the results of the other diagnostic procedures are not diagnostic.
BILATERAL BONE MARROW BIOPSIES of the posterior iliac crest in patients with stage IIB-IV.
EXCISIONAL BIOPSY OF A NODAL MASS.
CYTOLOGIC EXAMINATION of any effusion.
NEEDLE OR SURGICAL BIOPSY of suspicious extranodal disease.

Table 1. Recommended Staging Procedures for Hodgkin's disease. (FDG-PET: fluoro-deoxyglucose-Positron emission tomography)

second malignancies such as breast cancer, which correlate with the dose and volume of radiation. When combined modality therapy is used, radiation can be given at reduced dose to involved sites only.

The mantle field is the most complex and important treatment field used in the management of Hodgkin lymphoma. It includes the submandibular, submental, cervical, axillary, mediastinal and pulmonary hilar lymph nodes. The inverted Y field includes paraaortic, pelvic and inguinal nodes. Prophylactic pelvic irradiation is rarely used in modern treatment for supradiaphragmatic disease; subtotal nodal irradiation including mantle and paraaortic

fields is preferred. Pelvic irradiation continues to be used for patients who present with infradiaphragmatic disease with protection of the ovaries in female patients if applicable.

The usual radiotherapy dose for adults is 40-45 Gy when used alone and 30-36 Gy when used in combination with chemotherapy. For pediatric patients, the dose is 15-25 Gy in 14 fractions, confined to involved fields. Radiotherapy alone for pediatric patients is not recommended any longer because of the high incidence of associated late effects.

Dr. SHAD: I'd like to add a word about radiation therapy in children. In some developing countries, there is limited or even no access to radia-

tion, and given the high incidence of late effects, some investigators have not used radiation in children at all, while others have conducted clinical studies to examine this question. In part, the answer with respect to disease-free survival depends upon whether or not additional chemotherapy is given in place of radiation, but overall survival is similar whether or not radiation is given. Patients with bulky disease, such as those with large mediastinal masses, may benefit with respect to local disease control from radiation, but chest irradiation in young women also increases the risk for breast cancer later in life.

Dr. BREDEFELD: In recently performed trials in adults with HD, even patients with large mediastinal masses achieved high remission rates without additional radiotherapy, providing that early shrinking of the initial tumor mass after sufficient chemotherapy was observed. Careful monitoring of radiotherapy plans by an expert panel (which checked all restaging images) resulted in 50% less radiation being given compared to standard treatment.

Dr. GONZALEZ: Is there any role for radiotherapy upfront in cases of large mediastinal mass with secondary upper airway compression and respiratory distress?

Dr. EL-GANTIRY: An initial course of mediastinal irradiation in a symptomatic patient with extensive mediastinal disease often relieves respiratory distress promptly and enables the continuation of staging evaluation.

Dr. BREDEFELD: Alternatively, in this situation one can also use upfront steroids prior to definitive chemotherapy to provide a quick tumor response, with a smaller radiation field being used for consolidation.

NETWORK

THERAPY	DRUGS	LATE EFFECT	APPROACH
ALKYLATING AGENTS	Procarbazine Methchloroethamine Dacarbazine	Gonadal: males are 50% sterile after 3 cycles - Almost all after 6 cycles Secondary leukemia: up to 1% per year after MOPP + radiotherapy	ELIMINATE METHCHLORETHAMINE AND DACARBAZINE ELIMINATE PROCARBAZINE OR LIMIT TO 3 CYCLES
ANTITUMOR ANTIBIOTICS	Bleomycin Doxorubicin	Pulmonary fibrosis - Grade 3 - 10% after 6 cycles of ABVD Cardiac toxicity	LIMIT OR ELIMINATE CONSIDER USE OF DEXRAZOXANE LIMIT DOSE ($\leq 300-350$ MG/M ²) LIMIT OR ELIMINATE RADIOTHERAPY CONSIDER USE OF DEXRAZOXANE
EPIPODO-PHYLLOTOXIN	Etoposide	ANLL incidence data not yet available in children	LIMIT DOSE LIMIT DURATION
RADIOTHERAPY		Hypothyroidism, hypoplasia, valvular and atherosclerotic heart disease Secondary cancers: breast, sarcoma, melanoma, lung, thyroid, salivary gland	REDUCE DOSE AND FIELD OR ELIMINATE

Table 2. Modification of Pediatric Hodgkin Lymphoma Therapy to Decrease Late Effects.

CHEMOTHERAPY

Dr. GONZALEZ: The classic chemotherapy regimens combine usually four non-cross resistant agents (MOPP or ABVD) and are outpatient regimens with easily manageable acute toxicities but potentially significant long-term toxicities. Alternating or hybrid regimens (MOPP with ABVD or COPP with ABVD) are regimens designed to avoid reaching the cumulative doses associated with significant toxicity for any of the drugs and have been widely used in both adult and pediatric Hodgkin lymphoma trials. Other regimens that do not include alkylating agents, in order to limit long-term effects, have been studied and shown to give good results in early stage disease in children

but not for advanced stage disease. Most effective regimens for adults and children with advanced stages combine non-cross resistant agents in a dose intensive fashion, for example, in ABVE-PC, BEACOPP, or escalated BEACOPP. Instead of further dose escalation, the dose intensity approach allows doxorubicin and etoposide doses to be limited, and in the case of ABVE-PC, the elimination of procarbazine. Whether those with early response can be treated with fewer cycles is currently being investigated. In summary, the current treatment strategy for Hodgkin lymphoma, which this patient will receive, is risk- adapted, response-based, and dose/time intensive therapy. With the use of this therapeutic modality

and involved field radiation, nearly 90% of patients with Hodgkin's disease are cured with initial therapy. The challenge remains to minimize late effects of treatment. ■

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PALLIATIVE CARE CASE STUDY: PAIN IN METASTATIC BREAST CANCER

Palliative Care is a medical subspecialty that emphasizes comprehensive and holistic care (physical, emotional, spiritual) of patients with life-limiting illness. By practicing expert symptom assessment and management, palliative medicine strives to optimize quality of life for seriously ill patients across the trajectory of illness. INCTR's interdisciplinary Palliative Care Team is collaborating with Nepali physicians, nurses and others to establish palliative care programs at a number of local hospitals and cancer centers in the Kathmandu Valley area. The case study presented below illustrates the vital role of the palliative care team in the management of cancer-related pain.

SYMPTOM ASSESSMENT

Sita* is a 57-year-old Nepali woman with metastatic breast cancer to the liver and bones, referred to the palliative care team for increasing pain not responding to her current pain medication regimen. She complains of chronic, achy pain in her thoracic and lumbar spine, consistent with the location of confirmed multiple bony metastatic lesions. This pain has been present for approximately three months, but has worsened over the past few weeks and is not relieved by her prescribed doses of opioid therapy. The pain often wakes her at night, is aggravated by activity, and has prevented her from being able to participate in her day-to-day activities. She feels the pain is particularly bad upon awakening. She does not report any

signs or symptoms of spinal cord compression and denies weakness in her legs, numbness/tingling, or any urinary or bowel incontinence. She says her pain is severe, or very severe, nearly all the time. She currently rates her pain as 8/10 on a scale of 1 to 10.

MEDICATION REVIEW

Her current pain medication regimen is morphine sulfate elixir 15 mg PO (by mouth) every 4-6 hours prn (as needed). She reports moderate relief after taking the morphine, but then waits until the pain "becomes unbearable" before taking her next dose. Her typical daily usage of morphine elixir is 15 mg at 6 am, 4 pm and 11 pm. Sita says she is frightened of becoming addicted to the morphine and is reluctant to take the morphine more frequently.

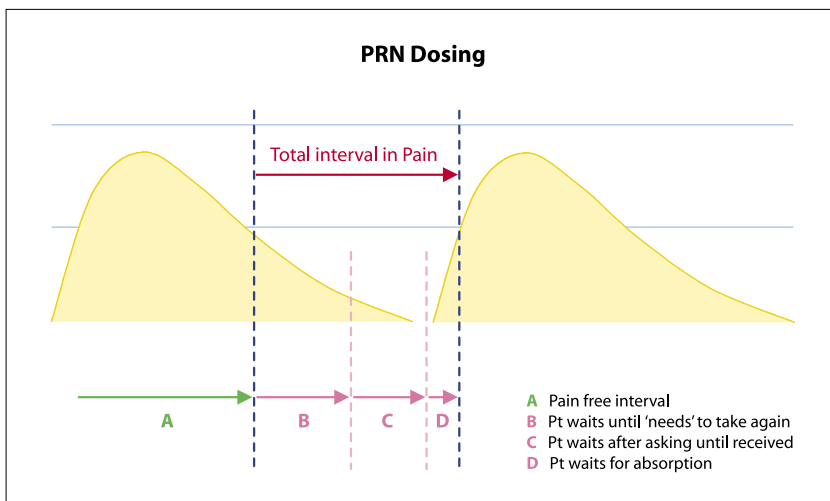
ASSESSMENT

Sita's description of pain is consistent with the deep and aching pain that characterizes bony metastatic lesions. Since the half-life of morphine is approximately 3-4 hours Sita's use of morphine on an 'as needed' basis allows for only *brief* periods of time when her pain is adequately controlled. It is not surprising that her pain is much worse in the early morning, since she has an extended period of time (from 11 pm - 6 am) when she is not taking any morphine. Also, she reports only moderate relief after taking 15 mg of morphine, suggesting that this dose is not high enough to achieve optimal analgesic effect.

PLAN

• In order to maximize a 'steady-state' level of opioid in the body, Sita is advised to take her morphine on

NETWORK



This figure illustrates that “prn” (as needed) dosing of morphine can result in intervals of significant pain. Dosing morphine sulfate around-the-clock as described in the case study above can decrease, or eliminate, these intervals of pain. Diagram provided by M. Downing, Victoria Hospice Society.

a regular, every four hour schedule *around-the-clock*.

- To avoid sleep interruption, she can try taking a **double** dose at bedtime and omit the dose in the middle of the night. This works for many people, but some individuals will have to resume *around-the-clock every four hour dosing*, **even** throughout the night to maintain good pain control.
- The dose of morphine elixir will be increased from 15 mg to 20 mg PO in order to achieve greater analgesic effect.
- To prevent opioid-induced constipation Sita is also given a prescription for a daily laxative.
- Sita’s concerns regarding morphine addiction are addressed and she is reassured that her risk for addiction is extremely low.
- She is encouraged to report any adverse side effects, such as nausea, confusion or excessive sleepiness - these are often temporary side effects experienced when starting opioids and resolve over a matter

of days and do not normally necessitate discontinuing the opioid.

- The use of other or ‘adjuvant’ medications (such as non-steroidal anti-inflammatory medications or a short course of steroids) or palliative radiation should also be considered to help with her bone pain.
- Sita should be monitored for any neurological changes, as she is at risk for spinal cord compression.
- It will be important to continue close follow-up with Sita as her opioid will likely need further titration to achieve the best pain control (eg., she may in fact require 30 mg PO every four hours). Her requirements may also increase as her illness progresses, necessitating further titration.

OUTCOME

Sita is started on her new opioid regimen, morphine 20 mg PO **every four hours** and 40 mg PO at bedtime, and reports greatly improved pain relief. She currently rates her pain as a 3/10.

This case illustrates the improved pain relief that can be achieved by optimizing our knowledge of the pharmacology of morphine. Administering the morphine on an every four hour schedule takes into account the half-life of this drug and allows for a steady state blood level to be maintained. Relieving pain can have a dramatic effect on a patient’s quality of life and allow more time to be spent with family and friends without the burden of constant pain. ■

* Sita’s case represents a compilation of palliative care patients and was developed for teaching purposes.

Presented by Virginia Le Baron with Dr. Fraser Black and Dr. Stuart Brown.

THE IMPORTANCE OF A MULTIDISCIPLINARY APPROACH TO PEDIATRIC ONCOLOGY

The prognosis for most childhood malignancies has changed dramatically over the last two decades. Childhood cancer, once seen as an invariably fatal disease, is now regarded as a life-threatening, chronic illness. Nearly all patients have long periods of remission, and for the majority, long-term survival and cure are real possibilities, although in many cases, late treatment effects occur. This achievement has resulted from improvements in the scientific understanding of childhood cancer and the incorporation of the most recent technical and medical advances into diagnosis and treatment. However, the healthcare

team must also make provision for the psychosocial needs of the patient and family, which requires excellent communication among caregivers. The patients should be seen as whole people in their own world and not as isolated individuals within the illness experience. If this is not the case, it is likely that the staff will focus exclusively on medical interventions, failing to support the patient and family emotionally. In turn, patients and families are likely to focus on the minutiae of treatment and lose perspective on the larger issues.

A life-threatening illness affects each patient and his or her family differently, while different medical situations create different challenges, both for the staff and for the patient and family. The ordeal of the moment for any individual is seen through their particular personality structure as well as their previous experiences with illness and loss. In order to deal effectively with patients or family members perceived as "difficult," the health care team must understand the roots of this perception. It is well known that children and adolescents with cancer and their families are initially in crisis. Patients and families have had little or no time to prepare for one of the most difficult, confusing and frightening experiences of their lives. They struggle to make sense of the diagnosis, the prognosis, the medical uncertainty and the potential for the patient's imminent death. They are surrounded by intimidating, unfamiliar technology and must trust a dizzying array of medical staff whose roles and the procedures they undertake are equally unfamiliar

and intimidating. The parents are often too shocked to comprehend the information reviewed with the care team. Yet it is this initial conversation on which they must rely to make the major decisions that set the course for the patient's entire medical plan. Patients and families who are emotionally numbed by the medical crisis must adjust to familial, educational, professional, social, and sometimes, cultural changes. This is the cause of many of the conflicts that can arise among patients, families and caregivers.

In general, to assess the immedi-

context. Ensuring that the many staff members work together as a multidisciplinary team is essential if the necessary information is to be collected and acted upon. Without the collaboration of non-medical professionals, the patient profile may provide only a partial or sometimes inaccurate view. In addition, through a multidisciplinary approach tailored to the collective needs of the critically ill patient and his or her family, caregivers can more effectively address the demands upon each team member, better define their roles, gain a more rounded view of



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ate medical needs of the patient, physicians use the simple concept: "start where the patient is." However, to meet the multifaceted needs of the patient, it is important to understand how the experience of having cancer affects the patient and his/her family, a process that requires learning about their way of dealing with problems which in turn, is based upon their beliefs, values, cultural references and social

potential concerns and conflicts, and form more cohesive working relationships. This results in enhanced overall communication and a more complete understanding of the patient and family, as well as providing patient, family and staff with support; in essence, an integrated approach to holistic patient care. ■

Claudia Epelman, Santa Marcelina Hospital, Sao Paulo, Brazil

NETWORK

HAND IN HAND AGAINST CANCER



The mission of ICEDOC is daunting in its simplicity: to lessen human suffering from cancer all over the world. Yet its founding president, Dr. Ahmed Elzawawy, is confident that ICEDOC can succeed because it is an organization whose currency is compassion.

The International Campaign for Establishment and Development of Oncology Centers (ICEDOC), established in September 1996, is an outreach organization that offers free consultation services and free cancer treatment to underserved populations around the globe. ICEDOC's "Experts in Cancer Without Borders" uses volunteers from the medical profession to mobilize efforts towards balanced approaches for cancer control and treatment. More than 120 colleagues now participate. ICEDOC is an associate member of INCTR.

Dr. Elzawawy – an Egyptian-born, Paris-trained oncologist affiliated with the Suez Canal University Hospital and Port Said General Hospital in Egypt – devotes considerable time and energy to what he considers a spiritual calling.

"If we think about cancer treatment merely as a profession, it's as if we are simple mechanics," Elzawawy says. "We have to remember that we're dealing with human beings, not just flesh and bone. When our fellow human beings lack funds, lack knowledge, lack capabilities, lack the ability to cure, lack the means to give palliation, that means we must put in extra effort."

Educated in a Catholic school in Alexandria, Egypt, Elzawawy grew up in a cosmopolitan family. In the late 1970s, the young Elzawawy chose to study medicine and work in France.

"I decided, in 1982, to return to my country, despite the fact that from a professional point of view my opportunities were better in Paris," he says. "I started my career at a university with no oncology or radiotherapy programs."



Dr. Elzawawy.

Professor Elzawawy became a lecturer in clinical oncology at Suez Canal University in Ismailia (one of Egypt's new universities) and launched a small unit for chemotherapy at Port Said General Hospital, a century-old facility which still functions to serve all cancer patients in Port Said free of charge. Soon he became involved in plans to build the university hospital. Today he serves as head of clinical oncology and nuclear medicine center there, while also directing the medical oncology unit at Port Said General, and the

radiation oncology center at Al Soliman Hospital, a charity center in Port Said.

Perseverance is one of Dr. Elzawawy's strongest traits. After nine years of failed attempts to fund better cancer facilities at Port Said, the hospital received a gift in 1991 from a local engineer who wanted to fund a department of radiotherapy in honor of his father. The radiotherapy department treated its first patient in July 1994, and continues to offer its services free of charge. With the advent of modern cancer diagnostic and treatment facilities, he says, fewer citizens of Port Said are avoiding delay in seeking treatment. "When patients have access to reasonable and affordable treatment facilities, we can change a lot. This is the logic behind ICEDOC - to work together to alleviate the suffering of others."

Dr. Elzawawy was among nine international consultants who prepared a global strategy for radiotherapy of cancer for the World Health Organization in 1999; WHO recognized ICEDOC as one of three primary international organizations for public education in the field in addition to its recognition in the field of professional education. A member of the advisory board of INCTR, Elzawawy travels frequently to help others establish cost-effective cancer management programs.

"When you work together hand in hand you can cause happiness while alleviating suffering of others." That's reward enough for him. ■

Marcia Landskroener for INCTR

INCTR TEAM VISITS NEPAL

A group from INCTR visited Nepal in January 8-12th this year to assess progress made with respect to the ongoing palliative care project there, to discuss dissemination of the (also) ongoing cervical cancer screening project to other regions in Nepal, to assess the status of pediatric oncology in the region, to participate in a one day workshop organized by INCTR's Branch in Nepal and to meet with the President and Board, as well as regional members of the Nepalese Cancer Relief Society regarding collaboration with INCTR.

PALLIATIVE CARE: The palliative care team, consisting of 5 persons led by Dr. Stuart Brown, gave seminars, participated in ward rounds and discussed patient care at the Scheer Memorial Hospital, Hospice Nepal, Bhaktapur Cancer Center and the Kanti Children's Hospital. Dr. Brown visited the Ministry of Health to discuss opioid availability in Nepal and how this might be improved. In addition, INCTR promised to provide \$10,000 for a vehicle to be used to develop a new home palliative care program. This promise has subsequently been met. Clinical guidelines for palliative care, written in concert with those involved in palliative care in Nepal and the INCTR palliative care team, have been completed and were made available during the visit, to the participating institutions.

CERVICAL CANCER SCREENING: A meeting was held in the Maternity Hospital of Kathmandu with the Director, Dr. Kasturi Malla, and one of the senior gynaecologists to discuss expansion of the ongoing screening programs in Nepal. Dr. Malla expressed considerable interest in INCTR's programs, and suggested that all graduates from her program should be trained

in direct visualization techniques for cervical intra-epithelial neoplasia. A first training workshop was subsequently held (see below).

WORKSHOP ON CANCER CONTROL IN NEPAL: The workshop, held on January 9th was a great success, being attended by doctors from 8 hospitals and two medical schools. ■



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REPORT FROM NNCTR/ INCTR NEPAL

WORKSHOP: A 3 day Skill Transfer Workshop on cervical cancer screening and prevention, jointly organized by INCTR's branch in Nepal and the Maternity Hospital of Kathmandu, was held on January 27-29th. Participants included 13 senior lady doctors and 10 staff nurses and matrons from the Maternity Hospital, Tribhuvan Teaching Hospital, ADRA Nepal, and other medical professionals. This was a "hands-on" workshop in the course of which 107 women were screened for cervical cancer. Plans are being made for future training activities.

DISCUSSION OF CHRONIC NON-COMMUNICABLE DISEASES IN NEPAL: A meeting was held to discuss cancer control in the context of non-communicable diseases in general. Participants from major hospitals and cancer centers in Nepal attended, as well as Dr. Surendra Shrestha from NNCTR/ INCTR Nepal, and Dr. Nirakar Man, Joint Secretary from the Ministry of

Health in charge of non-communicable diseases. Dr. Man pointed out that funding available for non-communicable diseases in Nepal is not fully utilized, and would be interested in working with the above stakeholders to developing a plan for control of chronic diseases in Nepal. ■

AGM AND GOVERNING COUNCIL MEETING

INCTR's Annual General Meeting and Governing Council Meeting took place on 5th March of this year. The previous year's budget and proposed budget for 2005 were approved, and INCTR's progress and future plans discussed. The Council approved the INCTR Charter, which is now available on INCTR's portal. ■

MEETING ON RESEARCH METHODOLOGY

A one day meeting on Research Methodology organized in collaboration with Shaukat Khanum Memorial Hospital and Research Center took place in Lahore on March 11th. ■

INVESTIGATOR MEETING FOR LEUKEMIA STUDY

A meeting of the Principal Investigators participating in the protocol entitled, "The Treatment and Characterization of Acute Lymphoblastic Leukemia in Children, Adolescents and Young Adults" was held in Chennai at the Cancer Institute (WIA) on March ... to discuss study progress since the initiation of patient accrual last August. Bhawna Sharma, who joined the INCTR India Office as data monitor in November, 2004, attended the meeting. Melissa Adde and Bhawna Sharma performed the first formal monitoring of data for protocol patients enrolled at the Cancer Institute. ■

NETWORK

SANTA MARCELINA HOSPITAL SAO PAULO, BRAZIL

HISTORICAL BACKGROUND

Brazil is a large country of 8.5 million square kilometers, 180 million inhabitants, five geographic regions and 26 states. Of its 5,561 cities, 588 have their boundary limits with Latin America countries, and 66 specifically share borders with Mercosul countries. This geographic situation has inflated the gross bulk population needing medical assistance, and strained Brazil's already limited health care resources.



Santa Marcelina Hospital.

Brazil was "discovered" by the Portuguese in the year 1500. The country gained its independence in 1822, but became a democratic republic only in 1889. Under Portugal's domination Brazil was an exploited colony, its economy built on one of the world's largest slave markets. Extensive sugar cane plantations during the 17th and 18th centuries, mining exploration (gold and precious stones) and, later, coffee plantations in the 19th century led to the Portuguese making huge sums of money — most of which, however, ended up in British coffers to pay off Portugal's debt to England.

All of these enterprises depended upon, and profited from, a mass of slave laborers (Indians and Negroes) — a population with no access to education. Even after the abolition of slavery in 1888, this population was neglected by oligarchy policies, such that they remained social outcasts. Today, the Brazilian government is confronting this cultural deficit in the hope of finding a solution to the inequities still borne by this massive population of poor people. This situation, understandably, has placed a great demand on public assistance resources.



An activities table in the pediatric oncology ward helps bring a sense of normality to sick children.

THE INSTITUTION

Hospital Santa Marcelina was founded in 1961 by the religious philanthropic organization "The Marcelinas Sisters," and operates with some financial assistance from the government of the state of São Paulo. At the time of the hospital's founding, the district it served, in the eastern part of São Paulo city, had a population of 60,000 inhabitants. Forty years later, the same region has four million inhabitants, most of them of low socio-economic status. Always struggling, because of the lack of resources, and burdened by a mushrooming population, the hospital has survived in the face of escalating public health problems. Not only has it maintained its high quality of health care, but the institution has gained another building, allowing it to expand public access. Meanwhile, both the School of Nursing and the

medical residency program (241 specialties) have also been expanded. Santa Marcelina has become recognized as one of the country's most important institutions in the education of health professionals.

Today Santa Marcelina Hospital is a referral center in Brazil for all medical specialties. The hospital has embraced the scientific approach to medicine thanks to a competent management, an expert medical faculty and state-of-the-art technology for treatment and diagnosis. Its radiotherapy program is one of the most comprehensive in the country; the hospital performs bone marrow and kidney transplants and is planning to introduce heart, liver and cornea transplants. The hospital also provides a valuable resource in the field of neurosurgery; recognized by the Brazilian Neurosurgery Society, its highly trained staff performs an

PARTNER PROFILE



Drs Sidnei and Claudia Epelman surrounded by their patients at a celebrating event at Santa Marcelina Hospital.

average of 800 operations per year.

Unfortunately, under the Brazilian national health insurance plan, which pays the hospitals a monthly fee per patient regardless of the medical care provided — the poor population cannot benefit from state-of-the-art medicine in all specialties. Poor children and adolescents with cancer, however, are able to receive state-of-the-art treatment, thanks to TUCCA (Associação para Crianças com Câncer), a not-for-profit association run by Dr. Sidnei Epelman.

TUCCA provides the necessary funds for equipment, drugs, etc. through private support. Dr. Epelman has devised one particularly successful fund-raising initiative. Invoking “Rouanet Law,” the Brazilian tax incentive designed to promote art and culture throughout the country, TUCCA organizes classical music concerts for adults and children, with the support of corporate sponsorships. Companies that contribute to premier health care resources while enjoying significant tax benefits include Fundação Elijass, Novartis, Itau BBA, Valeo, Credit Suisse/First

Boston, Multibank DTVM, Fotóptica, Bradesco, Sadia, Vivara and CBA.

Santa Marcelina Hospital has both a clinical oncology and a pediatric oncology department, both of which participate in the training of

MEDICAL RESOURCES

Total Beds	727
Beds Devoted to Cancer Care	60
Staff Physicians	433
Residents	230
Nurses	1,367
Dedicated Oncology Nurses	18
Pathologists	4
Oncologists	
- Medical oncologists	20
- Radiotherapists	3
- Pediatric oncologists	8
- Specialized surgical oncologists	8
Oncologists in Training	4
General and Specialist Surgeons	100
CT Scanners	2
MRI Scanners	1
Cobalt Radiotherapy units	no
Linear Accelerator units	2
Brachytherapy	1
Simulator	1

TOTAL PATIENTS IN 2004	930,533
In-patients	36,250
Outpatients/emergency	894,283
New pediatric cancer patients	150

residents, fellows and medical students. Its cancer registry is linked to the Cancer Registry of the state of São Paulo. An outpatient clinic for pediatric oncology is currently under construction.

As INCTR Brasil’s partner institution, Santa Marcelina Hospital participates in INCTR studies in childhood cancer. Since 2002, Dr. Epelman has played a leading role in a national media campaign to educate the public about retinoblastoma. Throughout the year, he gives radio, television and newspaper interviews to explain the importance of early diagnosis. Additionally, a 30-second film that teaches parents the easiest way to identify ocular tumors is widely shown. “Through this campaign we can save the life and also the sight of a child,” Epelman says. “In 2004, we launched the campaign internationally by offering the film to various Embassies in Brazil (it is now available in seven languages: Brazilian Portuguese, continental Portuguese, English, French, Spanish, Hindu, Chinese and Arabic)”.

CANCER IN BRAZIL

Cancer is the fourth leading cause of death in Brazil. In 2005, it is estimated that there will be 467,000 new cases.

The most common cancers in Brazil are:

- Skin cancer (non-melanomatous)
- Breast cancer
- Prostate cancer
- Uterine cervix cancer

Recent improvements in cancer outcomes are attributed to the campaigns of early detection in breast, uterine cervix cancers and retinoblastoma and to an intensive campaign against the use of tobacco. ■

*Contributed by Sidnei Epelman,
President of INCTR Brasil.*

NETWORK

PROFILES IN CANCER MEDICINE

AN ADVOCATE FOR OMANI CHILDREN

Dr. Zakia Al-Lamki, a pediatric oncologist and founding director of the hematology unit at Sultan Qaboos University Hospital in Muscat, Oman, seemed destined to enter the field of cancer medicine.

She grew up in a family of doctors, and her father encouraged her study of medicine. She was attracted early in her career to genetics because of the unique characteristics of her country's population. Oman has only 2.4 million citizens, more than 40% of whom are closely related. If marriage between distant cousins is factored in, that figure is closer to 50%. With such a high consanguinity rate, she explains, genetic disorders are very common in her country. Single-gene blood disorders such as hemophilia, sickle cell anemia and thalassemia are prevalent among Omani children.

Dr. Al-Lamki studied general medicine in Cairo, then returned to Oman.

"When I started in 1979 there was one general hospital and no teaching university," she recalls. "My mentor was a dynamic American-trained Omani physician who became an inspirational role model for me." He sent her for additional training at the Institute of Child Health in London where she obtained a diploma in child health and eventually became a Fellow of the Royal College of Physicians (UK) in her speciality of child health.

By 1989, the University Hospital (a government hospital associated with the Sultan Qaboos University) had opened in Muscat and Dr. Al-Lamki became one of the first staff members of the newly established department



Dr. Al-Lamki

of child health. A year later, she faced the greatest challenge of her medical career. Dr. Al-Lamki's third child — a two-year-old daughter — was diagnosed with osteosarcoma.

"She was the youngest patient ever recorded with that disease," Al-Lamki says. "I therefore took her to the M.D. Anderson Cancer Center in Texas for treatment. It was there that my interest in oncology was stimulated. I took up an honorary clinical attachment for six months. My daughter is now 16," she says with a broad smile.

In 1994, her career took another step.

"We had a visitor from the Baylor College of Medicine in Texas, Dr. David G. Poplack, then Head of Hematology/Oncology and now Director of the Texas Children's Cancer Center," Al-Lamki recalls. "He invited me to go to Texas for a fellowship in pediatric oncology." Today Baylor's department of pediatrics remains an important collaborative partner with doctors at SQU.

In addition to her administration of the Child Health Department and her clinical work, Dr. Al-Lamki is an acade-

mician teaching the next generation of physicians. The University graduated its first class of doctors in 1993.

Her own research focuses on "benign" hematology and leukemias, in collaboration with the Texas Children's Center. In one project funded by His Majesty's Research Trust Fund, doctors are studying the gene expression profiles in patients with acute lymphoblastic leukemia in both Oman and the USA. "We want to understand why some Omani children relapse early and to improve our ability to predict treatment outcome," says Dr. Al-Lamki.

Dr. Al-Lamki is also working with Dr. Louis Parker of the University of Newcastle in the UK to build a comprehensive children's cancer registry. Her department is participating — as the only center outside the United States — in a multi-center NIH trial in sickle cell avascular necrosis of the hip. Another collaboration with Karolinska Institute in Stockholm focuses on familial hemophagocytic lymphohistiocytosis (HLH), a very rare genetic disorder that is prevalent in Oman. Contributing new knowledge to the field, Dr. Al-Lamki and her colleagues have found two new mutations associated with the disease.

Using MRC trials to treat patients, and with access to updated protocols through Texas Children's Oncology Group, Dr. Al-Lamki has seen survival rates climb during the past 15 years from less than 10% to over 70% — outcomes comparable to Western figures. "My goal now is capacity-building," she says, "training others to carry on research and clinical activities." ■

Marcia Landskroener for INCTR