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THE PRESIDENT'S MESSAGE

PATHWAYS TO CANCER

Part 1. The Lives of People

by Ian Magrath

The nameless is the beginning of heaven and earth. The named is the mother of ten thousand things. Tao Te Ching.

One of the central dynamics of human society derives from the tension between the community and the individuals that comprise it. Social harmony, or justice, involves a balance between the contributions made and benefits received by each member of a community and results in the actions of individuals being governed by the collective good. It seems probable that such harmony existed, for the most part, in the small homogeneous bands of people that comprised human society for most of mankind's existence, pooling their collective skills and knowledge in order to survive. It was not until the development of agriculture some 8,000 years ago that centralized government emerged, leading to a dramatic change in the community dynamic. By some measures, and in spite of its inherent disparity, central government was



This horse is one of 1500 animals painted some 15,000 years ago in the Cave of Lascaux in France. Such sanctuaries may express the spiritual relationship of our ancestors with the natural world. Photograph provided by J. Grelet - Semitour Périgord.

an enormous success, permitting the rapid expansion of populations and leading eventually to undreamed of progress in science and technology. The new social order, however, carried a high and ever increasing price - measured in terms of human misery. The size and number of major conflicts escalated, reaching unprecedented levels in the 20th century,

while epidemic infections flourished in populations grown large enough to sustain them, and spread across entire continents. The industrial revolution boosted both agricultural productivity and manufacturing capacity, enriching merchants and bankers, whose wealth soon enabled them to wrest the reins of power from the ruling dynasties. But inequality

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has continued to increase, unchecked even by the recent global trend toward democracy. Industrialization led to a higher caloric intake, an increasingly sedentary lifestyle and exposure to a broad range of chemical substances. These, and most of all, the ability to manufacture billions of cigarettes, brought new health hazards and a dramatic increase in vascular diseases and cancer. Cumulative deaths from cancer now exceed those caused by the most devastating epidemics or the bloodiest wars in history, and the toll continues to rise. In 2002 there were an estimated 7 million deaths from cancer - a million more than in 2000 - but incidences are beginning to decline in the affluent countries, and future increases will occur almost exclusively in the countries struggling to expand their limited economic resources.

DREAMTIME

Peoples who have practiced their traditional ways of life within living

INCTR

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memory provide some insights into the very different mind-set of our paleolithic forebears. Small “egalitarian” bands of hunter-gatherers were the only human societies for most of the existence of modern Homo sapiens, spanning some 150 millennia. Families were of equal status, and respect was conferred upon individuals in proportion to their value to the community. Today, vanishingly few peoples retain this way of life, but in some world regions, hunter-gatherer lifestyles persisted until quite recently. Australian aboriginals, for example, were exclusively hunter-gatherers until the coming of the Europeans in 1788. They believed that the features of their land were molded by ancestral creator-beings who emerged from their slumber beneath the ground in the time of *the Dreaming*. These magical creatures, able to take the form of animals or people (e.g., Kangaroo Man and Emu Woman) and to alter their size and shape, wandered across the land, singing as they went, and molding it by their actions. The plains were places where they had rested, valleys were sculpted by a dragging tail, and precious water holes were created where they urinated. Metamorphosing into prominent features of the landscape, such as a rocky outcrop, or into the plant or animal species after which they were named, their presence was always felt by the people whose lives they sustained. For the aboriginals, their homeland comprised a sacred matrix in which the continual flow of the events of their lives took place. They were not unique. The Inuit of Northern Alaska, who call themselves Tikigagmiut, live in a place called Tikigaq, named after a prominent peninsula that projects (points) into the sea. They believe that this “fin-

ger” was originally formed by a whale - the animal on whom their lives depend - harpooned by a magical being, Raven Man.

It seems probable that our ancestors had a similar relationship to the land and to its native species. To them, the animals they hunted died, quite literally that they might live - a sacrifice for which they were eternally grateful. Then, some 8000 years ago, a few communities living in regions rich in readily domesticated plants and animals learned the arts of farming. The stories written into the land they inhabited blurred into a new set of myths more relevant to their adopted lifestyles, inscribed now in symbols on clay or papyrus. And the social structures that had served them for so long were changed forever.

EIGHT MILLENNIA OF CULTURAL EVOLUTION

While even hunter-gatherers might occasionally live in relatively permanent settlements in places where resources were sufficiently concentrated (such as in coastal fishing or whaling communities), it was not until the agricultural revolution that centrally governed communities evolved. These initially took the form of “chiefdoms,” i.e., communities governed by members of powerful families who retained their status over generations. In the fertile river valleys, where sufficient food could be produced to allow substantial division of labor, chiefdoms rapidly evolved into city-states and thence, through a process of colonization and coalescence (voluntary or not), into the larger, more inhomogeneous and more complex societies we refer to today as nation-states. The powers of chiefs, and subsequently, kings, included control over the redistribution of resources, a

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monopoly on the right to use force and the authority to arbitrate disputes. Such powers assured considerable respect and proportionate material benefits derived from tribute exacted from the farmers and tradespeople who were their subjects. This enabled rulers to acquire luxury goods, either through long-distance trading, or created by specialized craftsmen, sometimes over generations. Unique apparel, (fit for a king!), and the construction of palaces and other elaborate forms of public architecture increased the awe in which they were held and the power they were allowed to wield. Supported by specialists in religious lore and ritual (priests), they claimed to rule by divine right and built temples (cathedrals in Europe) or other religious complexes that sustained their relationship with the priests. The magic of nature became supernatural, metamorphosing into tamed gods who were increasingly confined to convenient stone edifices. Such societies flourished, in spite of their inherent inequality, because centralized control permitted the more efficient management of agriculture and better protection against the constant predation of other nation-states (e.g., through weapons production and the organization of military forces). Religious and newfound "nationalistic" beliefs made soldiers more willing to die in battles designed to further enrich their rulers. Successful military leaders were rewarded by gifts of land, creating a new and potentially competitive aristocracy.

In the East, religion eschewed a political structure and became primarily concerned with philosophical exposition and the achievement of spiritual enlightenment - through mystical experience of the ultimate

reality (although worship of multiple divinities often prevailed at the popular level). In the West, religion and politics remained more closely intertwined, often to the detriment of natural philosophy, but scientific progress was eventually seen to be indispensable to economic (and military) competition with other societies and was strongly supported by governments.

**"When man interferes
with the Tao,
the sky becomes filthy,
the earth becomes depleted,
the equilibrium crumbles,
creatures become extinct.**

Tao Te Ching

The industrial and technological revolutions, however, while accelerating socioeconomic development, exacted a significant toll on the communities in their van - a toll that is spreading to those countries that continue to lag some way behind. Slowly, but with gathering impetus in recent centuries, the natural world has receded from the daily lives of citizens. Today, almost half the world's people live in towns and cities, where they are separated from each other by the sheer mass of humanity and from the natural world by layers of concrete and packages of processed food. Modern market economies have stimulated private enterprise and encouraged ever more rapid progress in science and technology; but the priority of economic goals has led to the exploitation of natural resources and vulnerable populations, as well as to pollution and poverty. Approximately half the world's people live on less than \$2

a day, their desperate circumstances compounded by poor health and limited access to health care. Against a background of ever more frenzied activities in a world of Dickensian contrasts, seemingly light years away from the magical world inhabited by our forebears, the paradoxical words of the Taoist sage, Lao Tzu, "*by non-action, everything can be done,*" are rendered transparently clear. Action, he suggests, should not be contrary to the harmony of the natural world of which we are a part, but should move in concert with the "flow."

Non-action, or *wu-wei*, is not the path taken by those who trample roughshod over the world and its peoples in their insatiable quest for ego-expansion, deluded into seeing the world as a myriad of separate, highly desirable objects - of *ten thousand things* - rather than the single, ineffable whole, referred to by Lao Tzu as the *Tao*. But remarkably, a new science, barely a century old and requiring massive resources to verify its deepest theoretical propositions, is moving towards a vision of reality similar to that of the ancient Eastern sages, bringing East and West, in spite of their different approaches to enlightenment, into juxtaposition. Esoteric though it may seem to the uninitiated, quantum physics holds promise of lifting the enveloping veils of illusion (*maya*) and reconnecting, in the process, mankind to its moorings while simultaneously, in Blake's prescient words, *putting infinity into the palms of his hands*.

FROM PARADOX TO PARADIGM

In 1935, Albert Einstein, Boris Podolsky and Nathan Rosen published a paper of pivotal importance in the evolution of quantum mechanics, one of the two major 20th century revolutions in

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physics. They drew attention to an apparent paradox of quantum theory (subsequently known as the EPR paradox) which predicts that two once-linked sub-atomic particles, no matter how far apart they travel, will remain forever *entangled* such that measuring a particular characteristic (e.g., the direction of spin, or polarization) of one of the particles will instantaneously result in the other “acquiring” a complementary characteristic. Despite Einstein's profound discomfort with the notion of “action at a distance,” leading him to suggest that quantum theory must be incomplete, experiments performed decades later have confirmed the theoretical prediction, and excluded the presence of local “hidden variables” that could account for the phenomenon. The particles behave as a unit. Entanglement has practical implications for the development of new technologies, such as quantum teleportation, quantum cryptography and quantum computing, but it has even greater implications for the reality behind the constructs of our senses. For whereas the macroscopic world we perceive appears to be comprised of individual elements (the *ten thousand things*) which are subject to the influence of local factors - a perspective that even Einstein was reluctant to discard - the reality is that all events are probabilistic - that is, they arise in the context of a vast interconnected and self-consistent web, fitting into place according to their probability of occurrence. Particles thus exist as “probability waves” with a certain amplitude (encompassing the range of possible locations) and become “real” only when a measurement is made - implying that the observer, and, therefore, consciousness, is an integral part of

the system. These concepts - both the wave-particle duality and the influence of the observer - are difficult to grasp after centuries of Cartesian dualism (separation of mind and body), and Newtonian mechanics (whereby the cosmos is perceived as a giant deterministic machine - a clockwork universe put into motion by a god who is somehow separate from it), but have profound implications for the nature of the world in which we live.

Measures known to decrease smoking, such as a high tobacco tax and smoke-free workplaces, would be more easily introduced before the smoking epidemic reaches its height in poor countries which still have relatively low smoking rates.

The proposition that all particles are entangled is inherent in the *big bang* theory, according to which the Universe evolved from an infinitely small, infinitely curved and infinitely dense point, a *singularity*, which, some 15 billion years ago, released its contained energy in a tremendous explosion. From the resultant, rapidly expanding four dimensional web of electromagnetic vibrations particles emerged, eventually aggregating, in areas of sufficient density, into stars, which continue to recede rapidly from each other in the present-day Universe. This well substantiated theory, incidentally, relegates *absolute rest* and *nothing* to the status of purely relative concepts. Science has moved distinctly away from Aristotle's elaborate theory of causality and

now sounds remarkably similar to the philosophical concepts of the great Eastern religions. Hindus and Buddhists, particularly in Tantric philosophy, described the embryonic Universe as a *bindu* (a point), which contained the totality of the energy and form of being (the goddess Shakti), intertwined with pure consciousness (her consort, Shiva, also both creator and destroyer). From this arose the primordial vibration, *om* (equivalent to Brahman or the Tao), that gave rise to the world we perceive.

Impossible though it may be to comprehend the nameless underlying *oneness* - whether from a scientific or religious perspective - and to escape from the illusory world (*maya*) to which our senses confine us, mystics can experience the unity of being through meditation, whilst scientists can create maps (largely in the form of mathematical equations) that provide guides to the pathways of being and non-being. One such mathematical map, S-matrix theory (which concerns hadrons, such as protons and neutrons), states that interactions between particles follow certain rules that determine the energy levels at which the probability of one or several particles emerging, disappearing, or transforming into other particles, dramatically increases. Such enhanced probabilities have been termed “resonances” in analogy with the optimal frequencies at which sound waves are transmitted in bounded spaces. Resonances, or energy channels (familiar to Eastern philosophers), must surely influence the macroscopic world that we perceive. Cancer, for example, occurs when and where the set of factors that govern its emergence achieve maximal complementary. And although seemingly unrelated to the esoterica of particle

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physics, cancer is the end result of a series of genetic changes brought about by the interactions of molecules and their constituent atoms, the pathways of which are ultimately defined by the mathematics of quantum mechanics.

PROBABILITY PATHWAYS IN CARCINOGENESIS

We often speak of the genetic and environmental determinants of cancer, but this language is misleading, for such factors do not act independently, but are part of the *interpenetrating* web referred to by both Eastern philosophers and quantum physicists. The environment, through a process of Darwinian evolution, molds the genome of living creatures, and is, in turn, affected by their actions (particularly those of humans). Carcinogens do not cause cancer, but rather interact with a myriad of other factors to create "resonant" frequencies in time and place, i.e., they significantly increase the probability that cancer will occur. Carcinogens in tobacco smoke, for example, are capable of greatly influencing the probability of cancer, but whether a particular smoker develops a particular cancer depends upon the age at which smoking began, the duration and intensity of smoking, exposure to other environmental pollutants, and in some cases dietary and/or hormonal factors. It also depends upon the particular set of relevant genetic alleles (i.e., very slightly different versions of the same gene) inherited by the smoker. Such alleles include genes relevant to behavior and physical dependence on nicotine, the absorption and processing of the carcinogens in tobacco smoke, the ability of cells to prevent or repair the damage caused, and the inherent

likelihood of mistakes arising or persisting in the course of gene replication (during cell division), which may, in some cases, be a major contributor to the cancer "probability wave." Which alleles are inherited will depend upon the genetic constitution of the smoker's ancestors, itself molded by the selective effect of the environment(s) in which they lived. We cannot possibly know all of these variables for all cancers, but we can recognize particularly potent predisposing factors for some cancers, and develop strategies to modify their influence (Figure 1).

The probability of cancer developing in an individual (except in the

valuable statistic - the average (or subpopulation-specific) annual incidence rate. Incidence rates can be compared to the rate of radioactive decay of a radionuclide - whereas the intervals between disintegrations of an individual atom are unpredictable and not related to local conditions, the decay rate of a large population of atoms can be predicted with extraordinary precision since it is the sum of the probabilities of radioactive decay of each atom. This, again, points towards the generally unrecognized relationship between familiar events in the macroscopic world and the seemingly strange events in the world of quantum physics.

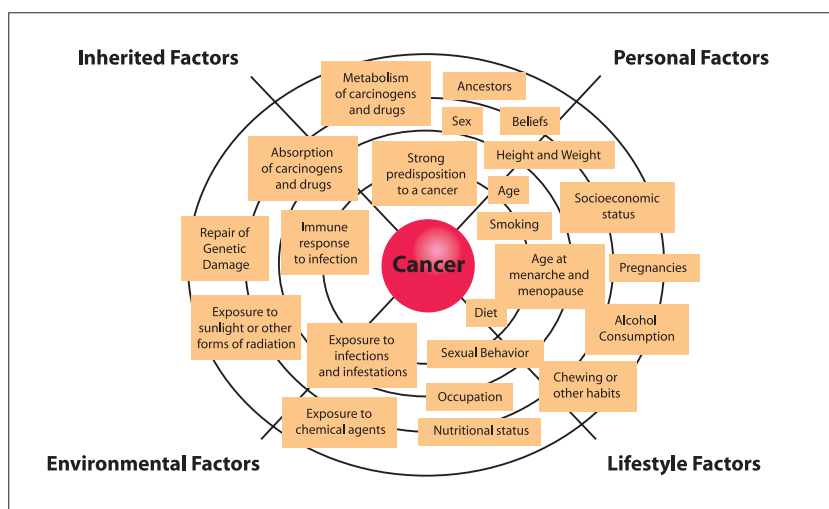


Figure 1. A simplified version of the web of cancer probability. Each factor (which may be composite) as well as many factors not shown and others yet to be identified contributes to the overall probability of cancer. The relative weight of each factor varies from one individual to another and from one cancer to another.

case of familial cancer) is difficult to determine accurately, and is of limited value to the development of public health policies relating to the control of cancer. In sufficiently large populations or subpopulations living in a relatively homogeneous environment, however, probability translates into a rather accurate and

CHANGING CANCER RESONANCES

It is, of course, impossible to have any clear idea of the incidence of cancer in paleolithic populations although both the incidence and spectrum of cancers must have differed greatly from the patterns observed today - even in modern aboriginal peoples.

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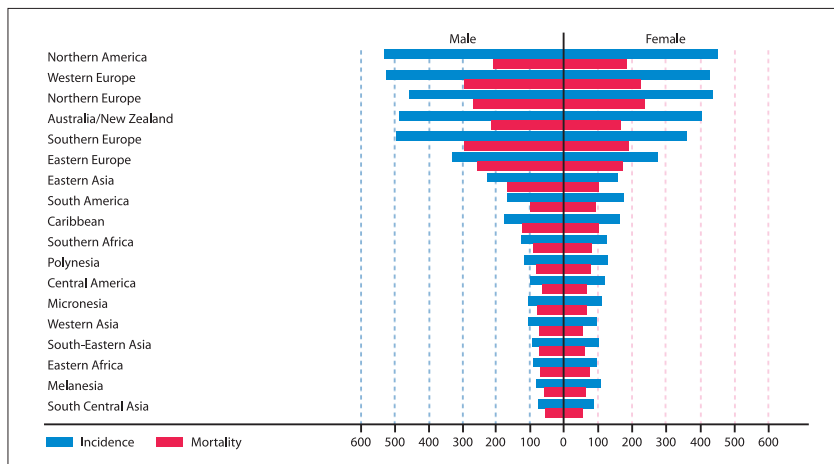


Figure 2. Crude (actual) annual incidence and mortality rates per 100,000 of cancer in WHO world regions. Data from Globocan 2002.

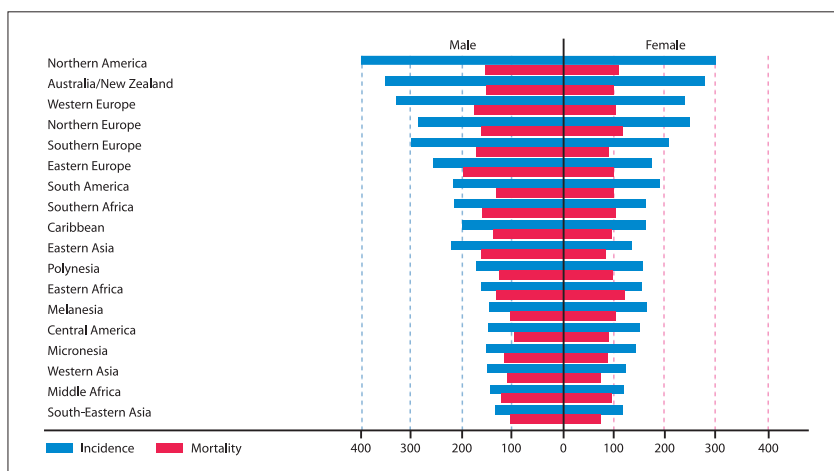


Figure 3. Age-standardized (to a world population structure) annual incidence and mortality rates of cancer per 100,000 in WHO world regions. Data from Globocan 2002. Age standardized rates are used for comparative purposes, but show (compare with figure 1) how overall rates increase when populations age. Age intensifies many factors, e.g., environmental exposures, but sometimes, e.g., in pediatric cancers, its effect derives from age-related physiological differences.

Once exposed to technically advanced societies, however, aboriginals usually give up their traditional lifestyles and tend to succumb to unhealthy behaviors such as smoking and heavy alcohol consumption, contributing to their high premature mortality rates. In the Pima "Indians" of Arizona, genetic selection over many centuries of those best able to survive the

adverse circumstances of their traditional lifestyle has led to a strong susceptibility to obesity and its consequences, including type II diabetes (present in 50% of the tribe between the ages of 30 and 64 years), hypertension, gall stones, and gall bladder and bile duct cancers. This example vividly demonstrates how genetic and environmental factors interact,

and how beneficial genetic traits in one set of circumstances may be deleterious in another. Other diseases may be transmitted by direct contacts with new populations. In Quechua Indians, descendants of the Incas, the commonest cancer is cervical cancer, but a study of Human Papilloma Virus (HPV) subtypes known to be strongly associated with this disease has shown the majority to be of European origin.

Unlike their modern relatives, ancient hunter-gatherer populations probably had an extremely low incidence of cancer. Peto and Doll have proposed that approximately one third of cancer risk in affluent societies is related to tobacco, a third to diet, and perhaps a sixth to chronic infectious diseases. The remainder stems from a miscellany of factors, including prolonged exposure to physical or chemical agents - all subject to the inherited ability to maintain the integrity of the genome. Apart from sunlight and infectious diseases, most environmental factors relevant to cancer today did not apply to hunter-gatherer peoples in their natural state. Pre-industrial farming communities were at risk for additional infectious diseases, in part because of increased population density, but also because of their close proximity to animal and human waste - excrement was used as fertilizer, building material and fuel. It is highly probable that the majority of their cancer risk was attributable to infections, although factors such as indoor pollution (e.g., from open fires) and dietary habits doubtless played some role. A number of chronic diseases caused by bacteria, viruses and parasitic flatworms (flukes) are known to be important risk factors in the development of certain human cancers, including

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stomach (*Helicobacter pylori*) liver (hepatitis B and C, and *Clonorchis sinensis*), bladder (*Schistosoma hematobium*) and intestinal cancer (*Schistosoma mansoni*). The need to locate agricultural communities close to water, and the use of irrigation canals to extend arable land increased the risk of infestation by flukes, whose transmission requires water snails and sometimes fish as intermediate hosts. The frequency of sexually transmitted diseases probably also differed markedly across the span of history, and the prevalence of HPV doubtless increased as societies became larger and more inhomogeneous, thereby lessening the influence of culturally-determined restrictions on sexual relations - a process hastened, no doubt, by coordinated military expeditions associated with routine violation or enslavement of female populations.

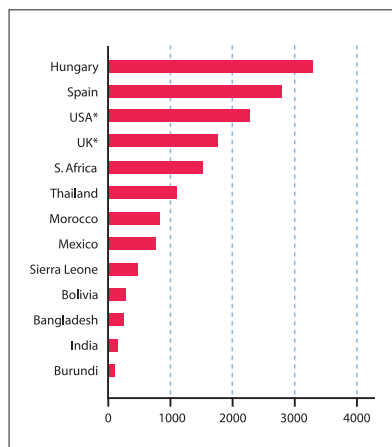


Figure 4. Cigarette consumption in selected countries. *Indicates countries in which consumption is declining. Data from *The Tobacco Atlas*, WHO, 2004 (available on-line).

HIV/AIDS is an example of a recently emerged sexually transmitted infection associated with an increased risk of cancer. Interestingly, fertility rates

may also influence cancer risk. The incidence of breast cancer, a hormone-dependent disease, for example, has increased in parallel to the decreased size of families and much more limited breast feeding in the affluent populations that emerged after the technological revolution.

Cancer then, like major warfare, global epidemics, poverty and environmental damage, can largely be considered an unwanted, potentially avoidable effect of socioeconomic development. Not surprisingly marked regional variations in the global cancer pattern exist, reflecting differences in socioeconomic development, lifestyles and the pattern of relevant infections - influenced to a greater or lesser degree by the intrusion of the unhealthy attributes of industrialization, particularly smoking. Unfortunately, more limited industrialization is often associated with more limited protection against exposure to industrial and agricultural chemicals, so that associated health hazards can be more, not less. Cancer, however, has a relatively low incidence in many developing countries (Figures 2 and 3), particularly those in which the smoking epidemic is still in its early phases (Figure 4) and caloric intake is low. Thus, in many of the poorer countries, there is an opportunity to pre-empt some part of the expected rise in cancer, i.e., to introduce prevention policies *before* anticipated increases in risk factors, such as smoking, amplified by aging of the population, dominate the cancer pattern.

It is one of the tragedies of socioeconomic development that even when the factors that increase the incidence of specific diseases, such as cancer, are recognized, economic considerations (that may benefit only a small sector of society) lead to

attempts to inhibit appropriate countermeasures, or even to promote unhealthy behaviors. Such actions are clearly antisocial, but are difficult to oppose without strong support from international governmental and non-governmental organizations. In an era also faced by the twin dangers of nuclear proliferation and major environmental degradation it is difficult to discount, lightly, the possibility of an approaching Armageddon.

WU-WEI (NON-ACTION) AND CANCER CONTROL

**Avoid smoking;
avoid excessive alcohol
consumption;
avoid high fat diets;
avoid excessive exposure
to potentially harmful
environmental agents.**

Yet the Nobel prize in physics this year was awarded for the discovery of asymptotic freedom, whereby the strong nuclear force that binds the quarks within atomic nuclei increases as they move further apart - explaining why quarks have more freedom when close together, and why they cannot exist as individual particles. This step towards the physicists' dream of a unified theory of space-time, energy and matter could also be a description of an ideal human society and its relationship to the interconnected cosmic web. Perhaps quantum physics will finally help us to understand what it is that the Tikigamiut feel when they look in the direction of the pointing finger that is Tikigaq. ■

Part 2 - The Lives of Cells - will follow in the next newsletter.

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CANCER CONTROL IN AN ECONOMICALLY DISADVANTAGED SETTING: NIGERIA

INTRODUCTION

The World Health Organization (WHO) has identified aging, infections, cancer and mental health as the four major health problems confronting mankind this century. The improvement in child health care and general health in the last quarter of the last century, especially in affluent societies, has resulted in a significantly increased proportion of older individuals in populations across the world. Care of the aged has therefore become a major health challenge in the world. The incidence of infectious diseases is also on the increase in all nations and HIV/AIDS and pulmonary tuberculosis have reached epidemic proportions in sub-Saharan African countries. Growing unemployment, poverty and stress have jointly contributed to an increase in mental health problems in the world, and cancer, which is the focus of this article, is a major health challenge in all populations, albeit underplayed in the past in developing countries. Neoplastic diseases are now known to also be a major cause of morbidity and mortality in these countries; more patients die from cancer than from HIV/AIDS, tuberculosis and malaria combined.

The WHO Technical Report No. 804 of 1990 reported that over 50% of cancer victims live in the poorer nations, which have less than 10% of the resources for cancer care and control. The dilemma of cancer patients in third world countries was further brought into focus with the realisation that they consume only 5% of cytotoxic drugs, the remainder being

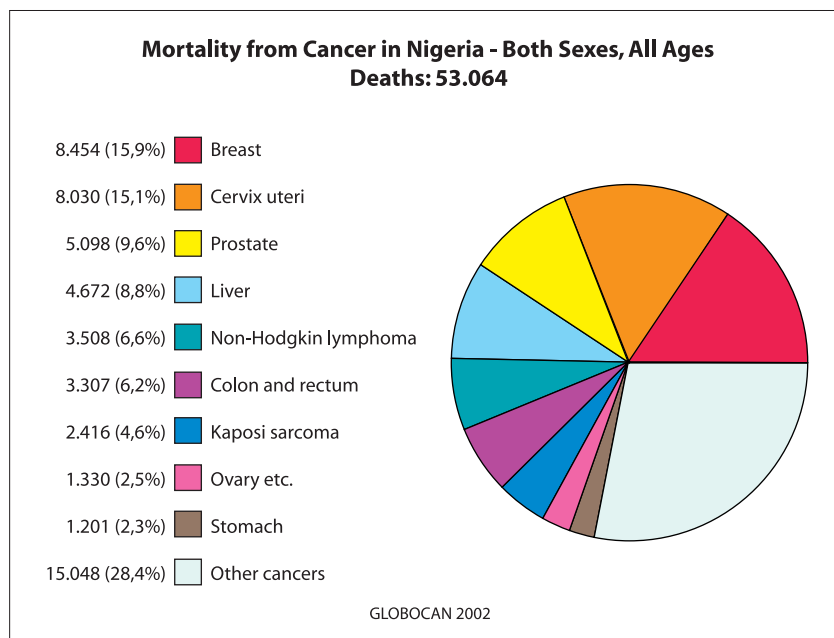
sold in the richer nations which account for only 39% of cancer cases.

In Nigeria, with a population of 120 million people in 2002, there are fewer than 100 practicing oncologists and no center exclusively focused on cancer research. There are only four active radiotherapy centers giving a ratio of one machine to about 30 million people, as against the recommended one per quarter million. The available spectrum of anti-cancer drugs is very limited and such drugs are not readily available. Imaging facilities for staging patients with cancer, such as computerized tomography (CT) and magnetic resonance imaging (MRI), are difficult to come by, and when available the cost of such studies puts them out of reach of the average citizen. The inability to properly classify the various types of hematological cancers owing to lack of Immunophenotypic, immunocytochemical and cytogenetic diagnostic facilities is of great concern to hemato-oncologists practicing in this part of the world.

This article will discuss the efforts made so far to control cancer in Nigeria and the factors militating against effective cancer care. Possible solutions to the problems identified will be highlighted.

THE DEVELOPMENT OF CANCER REGISTRATION IN NIGERIA

Cancer is a major health problem in Nigeria, as it is in other African countries. Unfortunately, the importance of cancer as a health problem has been underplayed or totally neglected by all agencies that have been advising on and/or financing health projects in Africa over the years. These agencies, including the World Bank, USAID, the European Union's Directorate of Development, and many others, give priority to infant and maternal health, family planning and sexuality, malaria, control of HIV/AIDS and some other infectious diseases. The apparent neglect of cancer by these agencies, and the consequent lack of emphasis on this problem on the part of



successive Nigerian governments, have resulted in a lack of development of cancer treatment facilities and cancer therapists. The result is the current situation in which cancer is, for the most part, an incurable disease in Nigeria, but less because of the nature of cancer, and more because of the limited resources and lack of education of the population. Unfortunately, prospects for improvement in the short term are bleak.

In Nigeria, neoplastic diseases were well known to traditional medical practitioners long before the advent of modern medicine. Cancer was then, and is still believed to be incurable. It is described by the Yoruba speaking people of South-west Nigeria as "Jejejeje ara" i.e, a disease that eats the body.

Early efforts at cancer control in Nigeria started with the establishment of the first cancer registry in the Department of Pathology, UCH Ibadan, in 1960 by Prof GM Edington. The main objective of the registry was to record cancer incidence for use by health planners and research workers. In October 12, 1968, also at UCH Ibadan, the Nigerian Cancer Society (NCS) was founded. Its aims were, **(1)** assisting in the development of facilities for diagnosis and treatment of cancer, **(2)** educating the public on the problems of cancer and **(3)** conducting research in all aspects of cancer. The society has grown beyond Ibadan. Branches have spread to other parts of the country, although their impact is felt more in the urban centers than in the larger rural populations of the country. The first major success of the NCS was the publication in 1982 of the book *Cancer in Nigeria-the proceedings of the NCS conference held in December 1979*. The society remains in the forefront

of cancer control in Nigeria, through its educational activities, publication of cancer education modules and cancer newsletters.

The Ibadan cancer registry is a population-based registry, serving a population of 1.22 million (1991 census) within its defined area of 70 square km in Ibadan, in the Oyo state of South West Nigeria. Data are collected from permanent residents suffering from cancer (i.e, persons who have been living in the area continuously for at least 12 months). Registry staff collect data on cancer by visiting all hospitals and health facilities (public, mission and private) in all the local government areas in the registry area at regular intervals. The chief sources of data are the histologically and/or cytologically confirmed cases of cancers from the pathology and hematology departments of the hospitals. Data are also abstracted from autopsy reports, hospital wards and clinics. Data are normally manually treated at all phases; the registry acquired its first CANREG computer program for data recording and management in 1997.

The success of the Ibadan cancer registry soon led to the establishment of other centers in university teaching hospitals across the country, including Zaria, Jos and Ilorin in northern Nigeria and Calabar and Enugu in South East Nigeria. The new centers in South West Nigeria are located in Ile-Ife, Eruwa and Lagos. Eruwa is the only registry established in a general hospital. With the exception of Ibadan cancer registry, all the other registries are hospital-based. In recognition of the role of cancer registries in cancer control in Nigeria, the Federal Ministry of Health established the "National Headquarters for Cancer Registries in Nigeria (NHCRN)"

at UCH Ibadan in 1990, with the main objectives of coordinating the establishment and development of cancer registries in the country and organizing training programs in cancer registration.

Nigerian cancer registries contribute data to important publications such as *Cancer Incidence in Five Continents in 1970 and 1976* (Ibadan Cancer Registry), the 1986 IARC Scientific Publication No. 75 on *Cancer Occurrence in Developing Countries* (Zaria cancer registry 1976-1978) and the 1988 IARC Scientific Publication No. 87 on International Incidence of Childhood Cancer (Ibadan Cancer Registry 1960-1984). The latest IARC Scientific Publication No. 153 of 2003 included a large quantity of data from six cancer registries in Nigeria (Ibadan, Zaria, Eruwa, Ile-Ife, Calabar and Enugu).

The estimated number of cases per year in Nigeria is predicted to be 100,000 at the present time, and by 2010, it is estimated that about 500,000 new cases will be diagnosed annually. A critical review of published data from Nigerian cancer registries (IARC publication 153 of 2003; 8797) and several other publications have confirmed some changing trends in the relative incidence of major cancers in both adults and children (Tables 1-3). In males, colorectal and non-melanoma skin cancers have displaced stomach and Hodgkin's lymphomas in the 1981-95 report (Table 1). In females, cancer of the breast has outstripped cancer of the cervix, with liver and colorectal cancers displacing choriocarcinoma and connective tissue cancers (Table 2). Burkitt's lymphoma remains the commonest cancer in Nigerian children, although the incidence is falling, most probably as a result of the better

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diet in children. Urbanization and increased awareness, diet, changing lifestyles, and many as yet unknown factors contribute to the increasing incidence of cancers of the breast, prostate, colon and rectum in Nigerians.

There is no doubt that cancer is a serious public health problem in Nigeria, but regrettably, its management has not been satisfactory due largely to the adverse effects of unfavourable economic factors. This experience is similar to that in other African countries which have similar economic problems.

CANCER MANAGEMENT

The main objectives of cancer management are to enhance the quality of life of the sufferers, cure the disease with available resources and minimize the side effects of cancer therapy. Pre-therapy counseling of patients/relations is always emphasized with the aim of allaying their fear and providing emotional stability, even when the prognosis seems bleak; in particular, following repeated tumor recurrences and the development of refractoriness to cytotoxic drugs. The major limiting factors to successful treatment of cancer in Nigeria are the high cost of hospital care and the inability of a majority of the patients to obtain chemotherapy, poor supportive facilities and a high default rate.

The unhealthy state of cancer therapy in this country is best illustrated with reference to our experience with the management of 213 patients with Burkitt's lymphoma over a period of 13 years. Over 75% of patients presented in advanced stages C or D; 132 (62%) of the patients received less than the recommended number of cycles of chemotherapy before voluntary

Site	Frequency (%)	Site	Frequency (%)
1960-80		1981-95	
NHL (including Burkitt's)	14.9	NHL (including Burkitt's)	19.9
Liver	10.4	Liver	11.2
Prostate	6.3	Prostate	10.8
Connective tissue	5.4	Colorectal	4.9
Stomach	5.2	Connective tissue	3.7
HL	4.5	Skin (non melanoma)	3.6

Table 1. Relative frequency of the six commonest tumors in Nigerian males between 1960-1980 and 1981-1995. (Source: JO Thomas. Archives of Ibadan Med 2000, 1:5)

* NHL = Non-Hodgkin's lymphoma. HL = Hodgkin's lymphoma.

Site	Frequency (%)	Site	Frequency (%)
1960-80		1981-95	
Cervix	19.9	Breast	25.7
Breast	11.2	Cervix	22.6
Choriocarcinoma	8.5	NHL (including Burkitt's)	4.4
NHL (including Burkitt's)	7.4	Ovary	4.0
Ovary	6.1	Liver	3.4
Connective tissue	3.7	Colorectal	2.8

Table 2. Relative frequency of the six commonest tumors in Nigerian females between 1960-1980 and 1981-1995. (Source: JO Thomas. Archives of Ibadan Med 2000, 1:5)

* NHL = Non-Hodgkin's lymphoma.

discharge from the hospital and, 41 (31%) of these did not complete a single chemotherapy cycle. The default rate was unacceptably high, with 166 patients (77.9%) failing to return for outpatient visits after a median follow-up period of 2.3 months (range = 0,67 months). A 5-year survival rate of only 1.9% was obtained, compared to almost 50% reported in E. Africa, using a similar combination therapy - cyclophosphamide, oncovin and methotrexate (COM). Our experience

with Burkitt's lymphoma is similar to that of most other cancers, in that a large majority of patients present very late and are unable to purchase anti-cancer drugs.

Lack of human and material resources account, in large part, for the dismal results of cancer therapy in Nigeria, but poor planning and lack of positive political will are also major factors militating against effective cancer care in Nigeria. Here, and in many other sub-Saharan African countries, these difficulties

have been compounded in the last 1 to 2 decades by the introduction of the disabling IMF/World Bank structural adjustment program (SAP) and by the emerging HIV/AIDS pandemic, which is now incapacitating millions of the economically productive members of society.

CANCER PREVENTION

The ever-dwindling government funding of health care is inconsistent with the increasing needs brought about by the increasing incidence of cancer in Nigeria. What then can we do in the face of this dilemma? Bearing in mind the WHO statement of 3rd of July 2002, that "of the 10 million cancer cases occurring annually, 1/3 can be prevented, another 1/3 can be effectively treated with early diagnosis, and palliative care can improve the quality of life of the last third", it is reasonable to conclude that effective and sustainable cancer control measures are feasible, but will require a concerted effort on the part of all stake-holders in the country. In particular, it will be important to adopt preventive measures for many cancers, including education against behavior associated with an increased, risk and immunization and screening where feasible and cost-effective. For example, cancer of the liver can be effectively prevented through immunization against hepatitis B virus (HBV), as well as through compulsory screening of blood and blood products for HVB and HCV markers and by using disposable needles and syringes. Cervical cancer can be controlled through early detection by a "Pap smear" or by the more sensitive 'visual inspection technique' with acetic acid or Lugol's iodine. Vaccines against human

Site	1960-1984 Frequency		1985-1992 Frequency	
	No	%	No	%
Leukaemia	86	9.0	46	12.0
ALL	33	3.4	15	3.9
Lymphoma	539	56.3	152	39.7
Burkitt's	446	46.6	102	26.6
Hodgkin's	35	3.7	18	4.7
Brain & spinal tumours	47	4.9	61	15.9
Neuroblastoma	41	4.3	1	0.3
Retinoblastoma	67	7.0	37	9.7
Wilms tumour	67	7.0	24	6.3
Bone tumours	7	0.7	11	2.9
Soft tissue sarcomas	46	4.9	29	7.6
Kaposi sarcoma	1	0.1	0	0.0
Others	57	6.0	22	5.7
Total	957	100.0	383	100.0

Table 3. Patterns of childhood cancers in Nigeria: 1960-1992. (Adapted from Parkin et al. Cancer in Africa IARC Pub No 153, 2003, 96)

papilloma virus (HPV) have already been shown to be effective, and could eventually effectively prevent cervical cancer. Regular self-examination of the breast during monthly periods and regular mammography examination of the breast will facilitate early detection of breast cancer, although mammography is unlikely to be cost-effective as a screening procedure in resource-poor countries such as Nigeria. Prevention could have a major impact on tobacco-related cancers as well as other tobacco related diseases. Lung cancer, a difficult disease to treat, is easily (in theory!) prevented by not smoking, but it is disappointing to note that, following recent aggressive campaigns against the tobacco industry in most western populations, tobacco companies have now shifted their advertisement to poorer parts of the world. Tobacco abuse has reached epidemic proportions in many such countries,

including Nigeria, and we can anticipate a major increase in tobacco-related diseases in the coming years.

Lastly, cancer control would greatly benefit if the government were to establish a National Cancer Institute, with the objectives of providing clinical and investigative facilities for cancer care and research, the provision of postgraduate training in cancer, the coordination of cancer control activities in Nigeria and the encouragement of collaboration with cancer centers in other parts of the world. In order to identify areas deserving of major efforts, and to monitor the outcome of interventions, a Nigerian Cancer Institute should also monitor cancer trends in the country. ■

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NETWORK

TWO CASES OF ACUTE MYELOID LEUKEMIA ASSOCIATED WITH ORBITAL GRANULOCYTIC SARCOMA (CHLOROMA)

In acute myeloid leukemia (AML), extramedullary disease often occurs as a mass or tissue infiltration. Generally referred to as granulocytic sarcomas (GS), but also known as myelosarcoma, myeloblastoma or chloroma (because of the greenish hue of the cut surface) these tumors may occur at various sites of the body, including the skin, bones, orbits, soft tissue, gingiva and central nervous system. In Western countries, GS occurs in less than 10% of patients with AML⁽¹⁾ and is more common in childhood, but GS as the primary manifestation of AML in childhood is rare - Reinhardt et al., reported that 2.8% of their children with AML had an isolated GS prior to bone marrow involvement⁽²⁾. The association of acute myeloid leukemia (AML) with GS, especially when the latter is in an orbital localization, has rarely been reported in the industrialized world, when compared to less developed countries but orbito-ocular granulocytic sarcoma (OOGS) represents a unique and relatively frequent subgroup of AML in Turkish children⁽³⁾.

Isolated GS can precede bone marrow involvement by just a few weeks or by as much as 1 to 2 years. They can also appear after or concomitantly with hematological evidence of leukemia⁽⁴⁾. We report here 2 consecutively diagnosed AML patients, who presented with OOGS and were seen at the Department of Pediatrics, Division of Pediatric Oncology, Ankara University School of Medicine. Permission was granted by the families to publish all clinical photographs.

CASE REPORTS

Case 1: A 12-year-old girl presented in November 2003 with a 3 month history of a progressively protruding right eye and an uneventful past medical history. Her family was of low socioeconomic status. Physical examination was unremarkable except for a right orbital mass 5x5 cm in size.



Figure 1. Case 1, showing initial presentation with proptosis and chemosis.



Figure 2. Appearance of the child shown in Figure 1 after treatment.

Hemoglobin level was 12.8g/dl, total white blood cell count, 6,900/ μ l, and platelet count 367,000/ μ l. Bone marrow aspiration revealed 20% blast cells with Auer rod positivity characteristic of AML. Her cytogenetic analysis did not show any chromosomal abnormality. MRI of the cranium and orbits revealed a right orbital mass of 5.5 x 5 x 3 cm causing destruction of the right frontal bone and protruding into the cranium. She was diagnosed as OOGS preceding definitive acute myeloid leukemia (which requires a bone marrow blast count of 25%) and treated with a protocol designed by the US Children's Cancer Study Group, CCG-2961. Her orbital mass resolved following induction

with the IDA DCTER/DCTER regimen. After the re-induction with the same regimen, she developed pulmonary aspergillosis, documented by computerized tomography-guided transcutaneous biopsy. She required intensive supportive care and full dose combination therapy with antifungal drugs as well as blood and blood components. After her pulmonary lesions resolved she received orbital irradiation to provide local control of the disease and modified chemotherapy. She completed chemotherapy successfully and has now been "off-therapy" for 2 months.

Case 2: An 18-month-old girl who presented in June 2003 had a 3 weeks history of protrusion of both eyes, the right being worse than the left. Her past medical history was uneventful. She was the fourth child of a family of very low socioeconomic status. Physical examination revealed bilateral orbital masses, more apparent on the right side, and hepatosplenomegaly. Hemoglobin level was 8.1g/dl, white blood cell count 5700/ μ l, and platelet count 395.000/ μ l. Bone marrow aspirate revealed 60% blasts with morphology, immunocytochemistry and flow cytometry all consistent with a diagnosis of AML of FAB M4 type. Cytogenetic analysis did not reveal any chromosomal abnormality. Magnetic resonance imaging of the cranium and orbits showed the bilateral orbital masses. She was also treated according to protocol CCG-2961 and tolerated the chemotherapy reasonably well, although she required intensive supportive measures. Her orbital lesions regressed after the completion of induction therapy but within 6 months of the completion of the protocol, she relapsed with isolated central nervous system leukemia without any recurrence in the primary orbital sites. Though

CASE REPORT



Figure 3. Case 2, showing initial presentation with bilateral orbital masses.



Figure 4. Case 2 showing disappearance of orbital masses after treatment.

she had received high dose cytosine arabinoside ($12\text{g}/\text{m}^2$) during her consolidation therapy, this had not prevented the development of meningeal leukemia, and craniospinal irradiation was added to the relapse regimen. This has recently been completed.

DISCUSSION

Although the prognostic impact is still controversial, the clinical outcome of children with AML associated with OOGS is generally poor. There are only a few reports that describe the biological and clinical features of these children.

In 1989 Cavdar et al reported (2) a retrospective analysis of clinical, hematological, ultrastructural and therapeutic results in 33 Turkish children presenting with OOGS and acute myelomonocytic leukemia (AMML) between the years 1963-1983. OOGS, characterized by exophthalmos, chemosis and orbital masses, was observed in 33 (27.2%) of 121 patients with AMML. Light and electron microscopy of the eye tumors demonstrated primitive

myeloid and monocytic cells similar to those seen in the bone marrow. The patients with OOGS were compared with 41 children with AMML without ophthalmic tumors seen during the same period. Hematological results in the two groups were not significantly different. Identical chemotherapy regimens were administered to all patients, and although this was not a randomized trial, the mean survival time of 8.7 months in the OOGS group was significantly shorter than that of patients without OOGS (28.6 months) ($p < 0.01$) (Figure 5) (3,8), consistent with other reports of a poor prognosis (2).

In this series the OOGS patients had low socioeconomic status. They also had diminished delayed hypersensitivity reaction, and low T-cell counts prior to the commencement of chemotherapy protocol (5), although whether this is relevant to the presence of GS is not known. Indeed, the etiology of OOGS remains an enigma. Characteristically, OOGS occurs in patients with FAB M4 (myelomonocytic) or M5 (monocytic) subtypes, both of which include monoblasts and monocytes in the leukemic infiltrate. Thus, local transformation of monocytes or histiocytes to malignant blasts (6) or the "homing" of such cells to the tumor sites (7) have been considered as possible mechanisms of OOGS development. However, GS has been described in other FAB types, and associated with a number of the chromosomal translocations that occur in AML, including t8;21, t15;17, inv16, trisomies 9 and 16 and translocations involving 11q23.

Our recent studies have been focused on detecting the expression of tissue adhesion molecules (CD44 and CD56) on the blast cells of the patients with OOGS, which could account for homing to certain tissue sites. We have also studied the expres-

sion of the P-glycoprotein, associated with pleiotropic multidrug resistance (9), which could account for the worse prognosis of these patients. The strikingly high rate of relapses in GS, however, might also result from initial misdiagnosis, or to less intensive or delayed therapy. Regardless of the reason for a poor prognosis, Cavdar et al. have suggested that patients with OOGS should be classified as a 'high risk' subgroup of childhood AML, and that such children should receive more intensive chemotherapy with hematopoietic stem cell rescue and local irradiation to the orbits in an attempt to improve the overall survival.

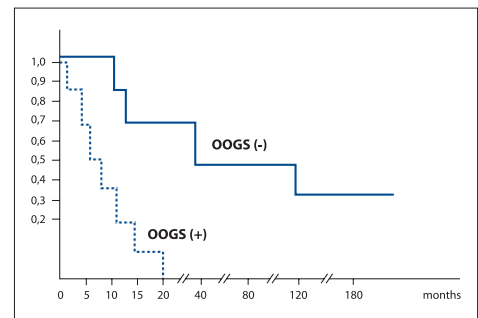


Figure 5. Comparison of survival curves of OOGS (+) and negative AML patients (8).

In conclusion, we believe that patients presenting with OOGS and AML comprise a distinct subgroup arising in several AML subtypes. Turkish children, who have a high incidence of OOGS associated with AML, appear to have a poorer prognosis compared to patients without OOGS. Further studies are necessary to identify the reasons for tissue involvement, and to improve the clinical outcome of these patients in our setting. ■

G. Yavuz, E. Unal, N. Tacyildiz, H. Ugur, A. Ikinogullari, S. Gozdasoglu, E. Babacan, A. O. Cavdar, Ankara University School of Medicine, Ankara, TURKEY
References available on INCTR's Website.

NETWORK

UNDERSTANDING PROBLEMS FACED BY PARENTS OF CHILDREN WITH RETINOBLASTOMA PRIOR TO TREATMENT

In early 2001, the Retinoblastoma Strategy Group, comprised of investigators from several developing countries, designed a survey of parents of children with retinoblastoma in an attempt to identify problems faced by parents prior to their child's diagnosis and to identify other factors that may have contributed to delays in diagnosis and treatment. The objectives of this on-going study are to determine whether there is an association between stage at presentation to the treatment center and the interval between the date that the first sign of disease was noticed and the date of diagnosis or treatment; to identify factors influencing these time intervals; and to determine whether such factors arise from parents' education, demographics or primary specialists health care. The survey is designed to obtain information through an interview with parents and to retrieve clinical data relating to the presentation of the child's illness.

After undergoing ethical approval both by the INCTR Ethical Review Committee and the local ethical committees at the participating institutions, the study was initiated. Nine institutions representing 6 countries (Brazil, Mexico, Turkey, India, Pakistan and Zimbabwe) have conducted interviews and collected clinical data for the study. A preliminary analysis of the 289 surveys has been performed. The majority of participants in the interview were fathers (50%). Fathers tended to be older than the mothers of these children. There were more male than

female children with retinoblastoma (57% versus 43%), although Indian institutions had significantly more male patients when compared to other participating institutions. The median age of the children at the time the interview was conducted was 29 months (range 3 months to 15 years). Mothers were generally the first to notice that the child had a problem (59%), followed by other relatives (19%), then fathers (15%). After the first sign was noticed, most parents sought advice or help, the majority from ophthalmologists (70%), although in Mexico, parents tended to seek advice from family doctors or pediatricians. Approximately a third of parents sought a second opinion after receiving the initial advice. At the time of diagnosis, 39% of children had bilateral disease. Children with higher stages of disease (St Jude Stages II, III and IV) tended to be older than children with less advanced disease. Longer intervals between the time when the first sign was noticed to the date of diagnosis were also associated with higher stages of disease. Both findings suggest that the vast majority of tumors arise early in life and grow progressively in the first few years. The father's education level was positively associated with the duration of symptomatic disease - the duration was longer in fathers who were either illiterate or who only had primary school education. Fathers with lower education levels also had children with higher stages of disease. These preliminary findings suggest that public awareness campaigns must also target fathers, who have the primary decision-making role in families in developing countries.

The questionnaire component of the study was recently revised. It will continue in the countries in which it is presently ongoing, but will be expand-

ed to institutions in other countries including Nigeria (Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife) and Tanzania (Ocean Road Cancer Institute, Dar Es Salaam, Tanzania). ■

Melissa Adde on behalf of the Participating Investigators and Institutions: Dr. Sidnei Epelman, Santa Marcelina Hospital, Sao Paulo, Brazil; Dr. Carlos Leal, Instituto Nacional de Pediatria, Mexico City, Mexico; Dr. Emel Unal, Ankara University, Ankara, Turkey; Dr. Kamer Uysal, Dokuz Eylul University, Izmir, Turkey; Dr. LS Arya, All India Institute of Medical Sciences, Delhi, India; Dr. Anita Chandra, Cancer Institute (WIA), Chennai, India; Dr. Shripad Banavali, Tata Memorial Hospital, Mumbai, India; Dr. Alia Zaidi, Shaukat Khanum Memorial Hospital and Research Center, Lahore, Pakistan; Dr. Inam Chitsike, University of Zimbabwe, Harare, Zimbabwe.

CERVICAL CANCER STRATEGY GROUP MEETING REPORT

A meeting of the Cervical Cancer Strategy Group took place on August 6 and 7th. The meeting was attended by investigators representing institutions in 6 countries - Peru, Mexico, Tanzania, Pakistan, India and Nepal. Dr. Sankaranarayanan of the International Agency for Research on Cancer (IARC) also took part in the discussions. The objective of the meeting was to identify specific activities or studies related to screening and treatment that could be undertaken by the group.

CERVICAL CANCER SCREENING

It was agreed that an important goal for the Strategy Group is to expand population coverage using well-established approaches to the detection and treatment of CIN. Initially, these programs will be established in small

selected populations as “demonstration programs.” If successful, it may be possible to catalyze wider programs in different low resource settings through the national/regional health services.

The following activities will be part of the group's strategy to expand coverage:

- 1.** Dissemination of information to geographically proximate institutions about how to establish cervical cancer prevention programs, including the recruitment of women for screening, and to couple this, whenever possible, with hands-on training.
- 2.** Use of established cervical cancer detection programs as regional training centers.
- 3.** Use of existing health care infrastructure, such as smaller health centers or their equivalents, family practitioners and general hospitals, as cervical cancer screening points in a centrally coordinated program (by regional training centers).
- 4.** Development of specific “measures of success” for screening programs such as the number of care providers trained, the number of women screened (expressed also as a fraction of women at risk within the region), CIN/cancer detection rates, and treatment rates.
- 5.** Development of approaches to professional education about cancer prevention for medical students, nurses and health assistants, as well as gynecologists and family practitioners; meetings, training courses, educational modules within student syllabuses, and visits to screening centers will be some of the approaches taken.
- 6.** Development of approaches to widen community involvement, including the enlistment of local and regional governmental support as well as public education and awareness campaigns.

TREATMENT STUDIES

The group expressed an interest in the development of two treatment protocols - one for early stage disease

and one for locally advanced cervical cancer. Investigators from India (Drs. Dinshaw and Shanta) agreed to develop an outline of a treatment schema for patients with locally advanced cancer and investigators from Mexico and Peru (Drs. Duenas and Santos) will propose a treatment protocol for early stage cervical cancer. Other relevant details of both studies will be decided upon in a future meeting that will take place in early 2005. ■

AN EDUCATIONAL WORKSHOP: THE VALUE AND CONDUCT OF CANCER CLINICAL TRIALS IN LATIN AMERICA

An educational workshop entitled, “The Value and Conduct of Cancer Clinical Trials in Latin America” was held September 1 - 3, 2004 in São Paulo, Brazil. Hosted by INCTR Brasil, it was designed in collaboration with several INCTR branches as well as the Brazilian Society of Pediatric Oncology (SOBOP), the Brazilian Society of Clinical Oncology (BSCO) and the Brazilian Cooperative Oncology Group (GBOC). Generous support was provided by Eli Lilly (which has partnered INCTR in this endeavor), Novartis,

Shering AG and Baxter Oncology.

The workshop focused on the science, ethics, and regulation of clinical cancer research as well as the training of data managers and research nurses. The philosophy and processes of good clinical practice and the importance of quality assurance were emphasized. It was hoped that the workshop would stimulate interest in specific areas of clinical oncology research in Latin America. The following topics were covered: **1.** The pattern of cancer in Brazil and other Latin American countries. **2.** Clinical trial design in cancer research. **3.** Ethical and regulatory issues. **4.** Implementation and management of clinical trials. **5.** Development of a strategy to promote clinical trials in Latin America. **6.** Training of data managers and research nurses.

Ten Latin American countries/regions were represented among the 120 delegates, including Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico, Peru, Uruguay, Venezuela and Central America. Participants included adult and pediatric oncologists, nurses, biologists, medical residents, fellows in training and senior representatives of pharmaceutical companies. The faculty was from Brazil, Belgium, the UK and the USA. ■



Drs. Epelman (left) and Schlüsselberg take front row seats at the workshop.

NETWORK

NEPAL CANCER RELIEF SOCIETY



Diwakar Rajkarnikar, a Nepali restaurateur, doesn't have any hobbies, unless one considers social work, fundraising, health advocacy and medical team building hobbies. For the past 14 years, Rajkarnikar has been a key player in the success of the Nepal Cancer Relief Society, which, with 36 branches established throughout Nepal and 7,000 cancer volunteers, has made significant inroads in cancer management.



NCRS members at a local event.

Rajkarnikar has been secretary general, Vice President, and now President of the Nepal Cancer Relief Society, which was established in 1982 by the late Princess Jayanti Shah. He is also chairman of the Bhaktapur Cancer Hospital inaugurated in 1998 by His late Majesty the King Birendra Bir Bikram Shahdev, and run by Nepal Cancer Relief Society and the Charter President of the Rotary Club of Bagmati. Through partnerships with 32 other Rotary Clubs in Kathmandu, and 33 more throughout the country, the Nepal Cancer Relief Society has enlisted the aid of the country's more affluent citizens who are working to spread the word about cancer prevention programs, the importance of early detection, and the dangers of smoking. Their success in raising money for cancer treatment, cervical and breast cancer screening programs and anti-smoking campaigns is impressive.

"Every walk of life is represented in Rotary, an organization committed to social work," he says. "We asked all the presidents and district officers to present a program on cancer, so we could provide them with information. We did one educational program in Kathmandu Valley, and now they all understand the importance of advocacy and are stepping forward to join hands with Nepal Cancer Relief Society to fight against cancer. Our annual Walkathon is just one example. We had 6,000 participants and raised 2.6 million rupees (about \$35,000 USD) in cooperation with Rotary for the free treatment of destitute cancer patients in Bhaktapur Cancer Hospital.

Rajkarnikar takes his message to anyone who will listen: such as school children, women's organizations, nursing students, journalists, college students, volunteers of political parties, film artists, sports organizations and religious groups, both Buddhists and Hindus. "We've talked to church groups of 800 to 1,000 people, with the message that cancer is preventable, and that those with cancer can be cured if treated early. Nepalese women get married at a very young age and generally have six or seven children. We are advocating that young girls wait to get married. We encourage married women to be screened for cervical cancer, and we encourage everyone to refrain from using tobacco. That is especially difficult. It is a tradition in Nepalese homes to offer their guests tobacco and in some rural districts. 72% of the population smokes."

His efforts are working. More than 6,000 women have been screened for cervical cancer through clinics held in Bhatkapur Cancer Hospital and at Scheer Hospital, and operated with the support of INCTR and IARC. Posters, pamphlets, even popular music geared to young

people are giving the message. And, for the past 18 months, a corporate partnership with Kodak Film has generated 100,000 rupees a month for cancer prevention and treatment in Bhaktapur.

"Many successful businessmen in Nepal are men of faith who have a sense of social responsibility," says Rjkarnikar. "Because I know the chairman of Kodak, I encouraged him to give something to cancer. He immediately agreed and proposed to donate two rupees for every roll of film sold in Nepal. After one year, sales of Kodak film have increased tremendously. It's a win-win situation. The company is profiting and Nepal Cancer Relief Society is benefiting."

Rajkarnikar has persuaded Castroll executives to donate 2% of sales to the Nepal Cancer Relief Society, and he is approaching Noodles manufacturing companies with similar proposals. Even the government is pitching in. At the suggestion of the Nepal Cancer Relief Society, the Minister of Health agreed to levy a tax on cigarettes in order to generate money for a Health Tax Fund, which is used for the prevention and treatment of tobacco-related disease such as cancer and heart disease. The Bhaktapur Cancer Hospital has been receiving 2% of that fund, with the remainder going to government hospitals. About \$3.5 million USD is deposited in that fund each year.

But Rajkarnikar has struck another deal. For the next five years, the Nepal Cancer Relief Society will receive 15% of the Health Tax Fund in start-up money, needed to purchase hospital equipment and for infrastructural development.

"At the end of five years, we'll be self-sufficient," Rajkarnikar says. "The government has said that this is the best example of collaborative work in the whole of Nepal." ■

Marcia Landskroener for INCTR

PROTOCOL IMPLEMENTATION MEETINGS

LEUKEMIA PROTOCOL

On July 14th, a meeting of the investigators and data managers involved in the protocol entitled, "The Treatment and Characterization of Acute Lymphoblastic Leukemia in Children, Adolescents and Young Adults" was held by video-conference. INCTR personnel joined the conference via the National Cancer Institute's Liaison Office in Brussels which was linked to both the Sir Ganga Ram Hospital in Delhi and the Tata Memorial Hospital in Mumbai, where our Indian colleagues gathered. Four institutions in India will participate in this study. These institutions are the All India Institute of Medical Sciences, Delhi, Cancer Institute (WIA), Chennai, the Jaslok Hospital, Mumbai and the Tata Memorial Hospital, Mumbai. The objectives of this meeting were to review the protocol and procedures for data management and data quality assurance prior to the initiation of the study. During the meeting, it was agreed to begin patient accrual on August 1st. It was also decided that a training workshop for the data managers and data manager would be held in November, 2004 in order to discuss issues pertaining to basic data management and to study specific data management procedures. This training will be interactive and will include "hands on" experience in the use of the remote data entry system, developed for the study by Capitol Technology Information Services, Inc in collaboration with INCTR Clinical Trials Office staff.

AFRICAN BURKITT'S LYMPHOMA PROTOCOL

An implementation meeting for the

investigators and data managers participating in the protocol, "The Treatment and Characterization of Burkitt's Lymphoma in Africa" was held on August 12th and 13th. The meeting was hosted by Twalib Ngoma, one of the participating investigators, and his staff at the Ocean Road Cancer Institute in Dar-es-Salaam, Tanzania. INCTR staff were joined by other investigators and their respective staffs representing University of Ibadan, Ibadan, Nigeria, the Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria, the University of Nairobi's Kenyatta National Hospital, Nairobi, Kenya and Mbarara University of Science and Technology, Mbarara, Uganda. During the course of the meeting, the protocol document was reviewed in-depth, with particular attention being paid to patient eligibility, pre-treatment evaluation, and the treatment itself. In addition to the protocol, the case report forms (i.e., data collection forms) were reviewed in detail and instructions for completing the forms were provided. A demonstration of the data entry system was given and the procedures for data submissions discussed. The role of the study committee, comprised of the principal investigators, was agreed upon. Their responsibilities will include monitoring protocol progress and identifying the need for protocol amendments. In addition to the study committee, INCTR will also monitor the quality of data and organize central pathology review. It was agreed that patient accrual would begin on August 16th. ■

SECOND MEETING OF GRUPO MEXICANO DE RETINOBLASTOMA (GMR)

The GMR held its second meeting, again sponsored by INCTR, in Hidalgo, Mexico, on 26th and 27th August. Delegates, mostly pediatric oncologists and ophthalmologists, from 19 centers throughout Mexico attended.



Second Grupo Mexicano de Retinoblastoma meeting at Hidalgo.

The group decided to unify Mexican protocols for retinoblastoma, and to treat, if possible, all patients with bilateral disease at a single center. ■

SEMINAR ON THE NEED FOR A MULTIDISCIPLINARY APPROACH IN PEDIATRIC ONCOLOGY

A multidisciplinary educational seminar was held simultaneously with the Workshop on Clinical Trials in Sao Paulo in early September. Organized by INCTR Brasil and the Sociedade Brasileira de Oncologia Pediátrica, the goal was to emphasize the importance of interdisciplinary team work from diagnosis to cure, or terminal care, in the support of cancer patients and their families. The highly successful meeting was attended by psychologists, social assistants, nurses, occupational therapists, physiotherapists, audiologists, teachers and other health professionals, and was the first INCTR meeting of its kind. ■

NETWORK

ALLAMA IQBAL MEDICAL COLLEGE, JINNAH HOSPITAL, LAHORE

Pakistan is a developing country with a limited budget for health care - only 0.7 of the gross national product is allocated to health. The major focus of the government is on maternal and child health and infectious diseases. Health care is provided by



The Allama Iqbal Medical College.

the public (government-sponsored) hospitals to the poor and low middle class - approximately 30-40% of the population live below the poverty level - and private sector hospitals, which are expensive, cater to patients from the upper socioeconomic strata.

Allama Iqbal Medical College/Jinnah Hospital is a medical college for undergraduate and post-graduate students. It was created in 1975 in response to the rapidly expanding population in and around Lahore and a corresponding growing need for hospitals beyond the city centre. The clinical facilities of this large hospital (1,100 beds) include five surgical units, five medical units, two gynecology units, pediatrics and a range of other speciality units, including ophthalmology, ear, nose and throat, orthopedics, neurosurgery, urology, dermatology, plastic surgery and cardiology.

The Department of Medical Oncology was established in 1993 as a two-bedded day care unit on one of the hospital verandas. Twelve years later it has grown to a 40-bedded unit with 100% occupancy rate and is recognized as a major tertiary care referral center for oncology patients. Approximately 3,000 new cancer cases are seen each year, 80% from the province of Punjab and the remainder from all parts of Pakistan. Approximately 90% of the patient population of the Oncology Department live below the poverty level, but essentially all patients are provided with free medicine through zakat (a wealth tax paid by affluent Muslims). In addition, breakfast and lunch are provided free of charge and, through an outreach initiative, 100 of the children of our cancer patients are being educated, using funds provided by our donors. In lieu of a population-based registry in the region, which we are in the process of developing, we maintain our own institutional tumor registry.

As in other developing countries, most cancers in Pakistan are preventable, and are related to smoking, diet and infections. The most common cancer in women is breast cancer. The most common cancers in men are lymphomas, leukemias, lung and hepatocellular cancers.

GOALS OF THE DEPARTMENT

The primary goals of the department are:

- To constantly improve patient care
- To teach medical students and residents, who rotate through the department
- To provide post-graduate teaching in medical oncology (resulting in a degree awarded by the College of Physicians & Surgeons)
- To conduct research, both at national and international levels

- To undertake public and professional education directed toward early diagnosis (75% of patients currently present with advanced disease and are incurable).



Our collaboration with INCTR has been a rewarding and enlightening experience. Through this, we have developed research collaboration with other developing countries. New projects have started and others are taking shape. Professor Ama Rohatiner, who heads the INCTR's Education Program, spent a week with us earlier this year, during which time she was actively involved in patient management as well as teaching of undergraduate and post-graduate students. Students are now going to her hospital, St. Bartholomew's Hospital in London, to receive additional training. Most importantly, we are developing new lifelong friendships and benefiting from learning experiences which would not otherwise have been possible.

PARTNER PROFILE

BREAST CANCER

Breast cancer is a particular interest of the department, in part because it is numerically of great importance, and in part because there are potential approaches to both its early detection and treatment. Unfortunately, approximately 75% of all of our patients, as with all our cancer patients, present with advanced disease, where cure is not possible. The medical center is therefore conducting an intensive campaign aimed at early diagnosis.

Factors predisposing to the development of breast cancer in the USA and Europe include pregnancies later in life, not breastfeeding, and having few children. However, these parameters are not particularly relevant in Pakistan, where 70% of patients have no identifiable risk factors. There is a need to collect better information pertaining to the epidemiology of breast cancer in Pakistan, since we believe the incidence of this disease is rising. Given recent advances in understanding the genetics of the disease, we have investigated the prevalence of mutations in the genes BRCA1 & BRCA2, which are known to predispose to breast cancer. We have also studied the frequency of breast cancer in women born of consanguineous marriages.

Recently, we examined the outcome of treatment in 286 women with breast cancer according to their socio-economic status. Data was collected on the size of the tumor, the time of diagnosis, the type of treatment given and survival rates. Early stage breast cancer was seen in nearly three-quarters of the women with high socio-economic status and 89% received adequate treatment. In contrast, nearly half the women from poorer, less educated backgrounds,

did not seek medical help until the cancer had reached an advanced stage, and only 44% received adequate treatment. This resulted in an overall survival rate at 10 years of 73% of women in the high socio-economic status, 49%, in the middle tier and less than one quarter, 22%, in the lower group.

Clearly, poorer people do not seek help soon enough, and in any event have poor access to appropriate medical care. A significant component of the problem is that in their sector of society, breast cancer carries a stigma that greatly lowers self-esteem. Both sexes view women with breast cancer (or who have had a mastectomy because of breast cancer) as sexually unattractive. Thus women are afraid to bring attention to a lump because



Dr. Zeba Aziz, Professor of Oncology at AIMC, is Pakistan's first trained medical oncologist to practice in her native country. She has been instrumental in raising breast cancer awareness and conducting breast cancer research.

of fear of mastectomy and the resultant stigma. Emotional and physical abandonment is a common end result, and many women do not even complete their treatment. Gross ignorance also leads to breast cancer being considered contagious. We have seen women isolated to the point of not being allowed to touch their children or to use household utensils.

Educating people, including health professionals (many surgeons, for example, still perform mastectomy, even in circumstances where it may be avoided), is a vital tool in the fight against this cancer. In our public education programs we urge women to put the stigma aside and seek medical advice early in order to avoid surgery to remove their breast. It is important also for women to participate in clinical trials, for only then will we be able to determine the best approaches to therapy in our own situation, and to move towards a reduction in the fraction of women who require mastectomy. ■

Zeba Aziz, Allama Iqbal Medical College, Jinnah Hospital, Lahore, Pakistan

RESOURCES AT AIMC

Total Beds	1,100
Beds Devoted to Cancer patients	40
Staff Physicians	85
Nurses (approximately)	200
Dedicated Oncology Nurses	8
Pathologists	6
Oncologists	2

Equipment:

CT Scanners	1
Ultrasound Machines	4
MRI Scanners *	0
Cobalt Radiotherapy Units	1
Linear Accelerator Units	1
Brachytherapy Units	1

Pathology Department - Routine Services:

Histopathology
Microbiology
Haematology
Biochemistry

PATIENTS IN 2003

Total visits, entire hospital	347,547
Total patients admitted	40,697
New adult cancer patients	10,500
Adult cancer patients admitted	2,670
New pediatric cancer patients	115
Total number of new cancer patients	3,120

** To be installed in the near future*

NETWORK

PROFILES IN CANCER MEDICINE

DR. YAO-PING WANG: SAVING CHINA'S CHILDREN

Dr. Yao-ping Wang, Professor in the Department of Pediatric Hematology/Oncology at Shanghai Children's Medical Center, has devoted much of his career to the treatment of childhood acute lymphoblastic leukemia in China, where remarkable progress is being made in improving survival rates. Now, the nationally recognized pediatric oncologist is expanding his leadership role in pediatric medicine to encompass all of Asia. Serving as president of the Chinese Pediatric Oncology Society since 2001, Dr. Wang was recently elected as the president of the International Society of Pediatric Oncology-Asia (SIOP-Asia). "I am trying my best to serve the entire Asian children's population," he says, "in countries where the main problem is not the cancer protocols, but the economics."

Dr. Wang graduated from Shanghai Second Medical University in 1961, and then joined the Department of Pediatrics in the University's Xin-Hua Hospital as a resident, then attending physician and Vice Chief. He moved into pediatric hematology/oncology in 1979 as an Associate Professor, and in 1994 was promoted to Chief Clinician and Professor in the Department of Pediatric Hematology/Oncology. With the support of the Hope Foundation, the Shanghai Children's Medical Center opened in June 1999 with a dual mission: to serve as a national training center for healthcare professionals and to provide state-of-the-art clinical care for the children of China. It was the first such hospital in China and set the standards for others to follow. Members of the medical staff also hold positions in the University's Xin-Hua Hospital.

In the early 1980s, Dr. Wang received training in pediatric hematology/oncology at the Hospital for Sick Children in Toronto, and at the Mayo



Dr. Yao-ping Wang

Clinic in Rochester, Minnesota. It was then that he became familiar with bone marrow transplantation, and today he is taking advantage of advanced Western protocols, including stem cell transplantation, in his patients' treatment. He also spent some time in 1994 conducting research at St. Jude's Children's Research Hospital in Memphis, Tennessee. That year, he attended the SIOP meeting in San Francisco, California, where he first met Ian Magrath. Dr. Wang has been involved with INCTR since its inception.

Presently, Dr. Wang and his colleagues - most of whom have been trained in the United States, Canada, Germany or France - are conducting cutting-edge research in the treatment of leukemia and advanced malignant solid tumors. Of 27 children participating in a recent clinical trial of autologous stem cell transplantation, 22 are now disease-free, he says. Four died of relapse five months after transplantation, and a fifth patient with non-Hodgkin's lymphoma is alive, although with disease, 17 months after the procedure. These results were published in the November 16, 2003, edition of the journal *Blood*.

But despite these sophisticated treatment approaches, Dr. Wang is well aware

of the basic problems pertaining to the care of children with cancer in China.

"No matter how good the protocol," he says, "it won't work if the patients don't have access. We have to solve the problem of economic support."

Dr. Wang, in his role as a national leader, is attempting to solve this problem by lobbying drug companies to donate drugs for use in young cancer patients and by encouraging China's Minister of Health to recognize the value of pediatric oncology in a country where the average monthly income is \$100 USD, and where each family is permitted to have only one child.

"If a child under five has cancer, the family will sometimes give up, because they can have another child," Wang says. "If the child is older, the relationship between parents and child is much stronger, and the parents will do everything they can to save their child."

Wang's message to his government, and to other Asian nations, is that childhood cancer is highly curable. "With acute lymphoblastic leukemia there's a 70-80% cure rate achieved with chemotherapy that is not very expensive" he says. "We use less intense treatment dosage in Shanghai and can still get good results. Our task as researchers is to develop simple but effective treatment protocols for the lowest and intermediate risk groups, which account for the majority of cancers, are the most curable, and cost less to treat."

Today Dr. Wang is completing the circle his parents - both physicians - started when they encouraged him to enter the field of pediatrics. "My job now is to help young doctors in the diagnosis and treatment of cancer. In my 40 years I've treated lots of patients. In my home I have two volumes of photographs of children whose lives have been saved. That is a wonderful gift." ■

Marcia Landskroener for INCTR