N E T W O R K

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THE PRESIDENT'S MESSAGE

REACHING TOWARD THE OUTER CIRCLE

by Ian Magrath

"Through me you pass into the city of woe, through me you pass into eternal pain."

When, in his *Inferno*, Dante, guided by the poet Virgil, arrives at the gates of Hell, it is with a mounting sense of dread that he reads the malediction inscribed on the arch above. Beginning with the lines quoted in the epigraph to this message, and ending with the words, *"All hope abandon, ye who enter here,"* the inscription surely captures the emotions of many patients when they first learn that they have cancer. Yet Dante's self-stated purpose in writing his poem was to "remove those living in this life from their state of misery, and lead them to the state of felicity." And indeed, the *Inferno* is only the first canticle of a three-part poem, *The Divine Comedy,* which describes a journey, first into the depths of despair, then up the mountain of purgatory (*Purgatorio*) and beyond, into the joys of paradise (*Paradiso*).

This literary voyage is comparable, perhaps, to the emotional journey of those who overcome the hardships and challenges of cancer treatment,

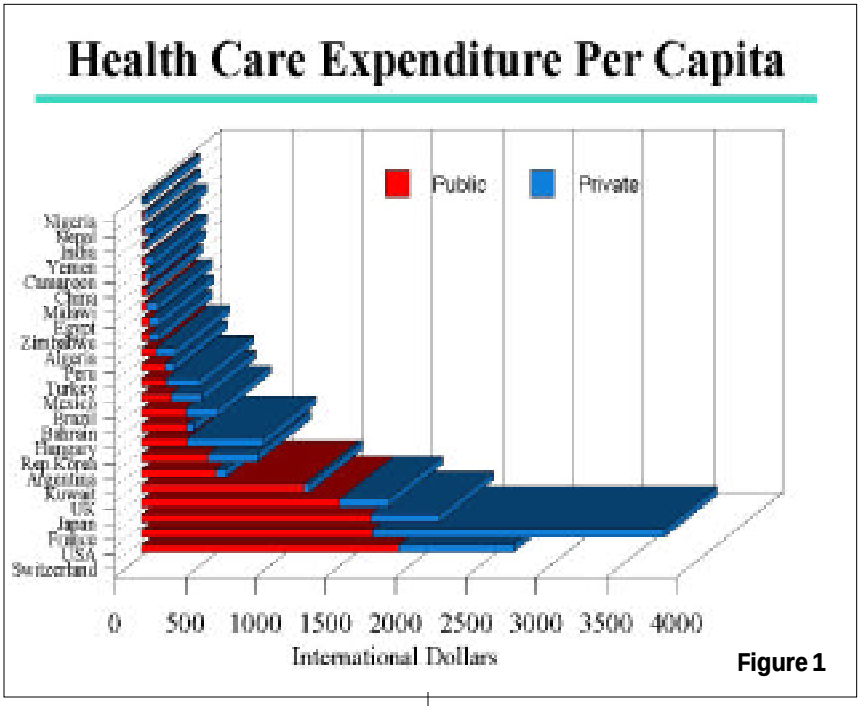


Figure 1

Data from World Health Report, 2000.

and quite frequently find that they have learned to appreciate the life they might easily have lost more than ever before—each new day is a gift to be savored. Dante's poem contains several other parallels. According to the World Bank, 1.2 billion people in the world live on less than a dollar a day (2.8 billion on less than $2 a day), in circumstances that, in comparison to the economically uppermost billion, resemble those experienced by some of the inhabitants of Dante's *Inferno*. Scarcely able to provide food for their families, the added burden of a potentially fatal illness would surely bring, had they ever heard of Dante, the words of his famous inscription to mind. Dealing with cancer is difficult enough for educated and wealthy families, but the experience for poor and illiterate patients is doubly frightening. Denial, common enough in upper economic echelons, takes on a different hue in the poor, for whom the loss of a

breadwinner or parent has a devastating impact. With extremely limited supports, patients from the lowest socioeconomic strata, particularly women, are tempted to ignore early symptoms of serious illness in the vain hope that they will go away. If aid is sought, it is often from a local "healer" with the hope that this latest physical and (potentially) financial burden can be spirited away as if by magic. In India, for example, nearly half of those with a health problem (from all social strata) seek help from "alternative" systems of medicine. While these systems may be beneficial in certain circumstances, their value in cancer has not been demonstrated, and as such, they may do harm by causing inordinate delay in the patient reaching a practitioner capable of treating cancer. Even medical practitioners may not consider an ailment to be cancer, particularly in its early stages. If cancer is detected, it may be assumed to be incurable, an assumption that becomes self-fulfilling as the weeks and months, even years, go by. Delaying treatment reduces the chances of cure and permits its purchase only at the cost of much more complex and expensive treatment than would have been needed if the cancer were detected earlier (see case report on page 7). Even when the diagnosis is made, the fear of treatment, particularly mutilating surgery, may prohibit patients from going to see specialists able to provide specific therapy.

There is another relevant point that is made forcefully in the early part of Dante's allegorical journey. Overcoming his fear and passing through the gates, he encounters the souls of those who had passed their time on earth in a state of apathy and indifference. Concerned only with themselves, they were doomed to continue their mean existence in a state of hopelessness, relieved neither by suffering nor death. This is a sobering message indeed, and one that, in our context, is directed particularly at those in a position to positively influence the lives of the world's poor. The World Bank, in its latest *World Development Report*, states that poverty is an "outcome of interacting economic, social and political forces, and in particular, an outcome of the accountability and responsiveness of state institutions." Clearly, the elimination of poverty will require political will, but in the case of the poorer countries, a favorable international socioeconomic climate helps. South Korea has demonstrated what can be achieved when both are present. We may safely presume that until the elimination of poverty becomes a high priority of the world's governments, it is unlikely to go away. In the meantime, what can we, in the field of cancer, do to assist the most deprived of the world's populations, which have minimal health resources ? (see figure 1)

The task of reaching out to communities with limited access to the usual forms of communication is daunting, and any approach needs to be multifaceted, possibly combined with other health and education programs and developed over many years. Educational efforts must be directed not only toward the poor (pamphlets and written advertisements, for example, are of no value in illiterate populations), but also toward the persons whose help they are most likely to seek. Unfortunately, many physicians, particularly those operating on a fee-for-service basis, pay less attention to their poorest patients. While subsidized care does exist, most patients in developing countries (more than 70% of the population in India, for example) receive health care from private practitioners and must pay for treatment they receive. Health care costs, particularly for cancer, can

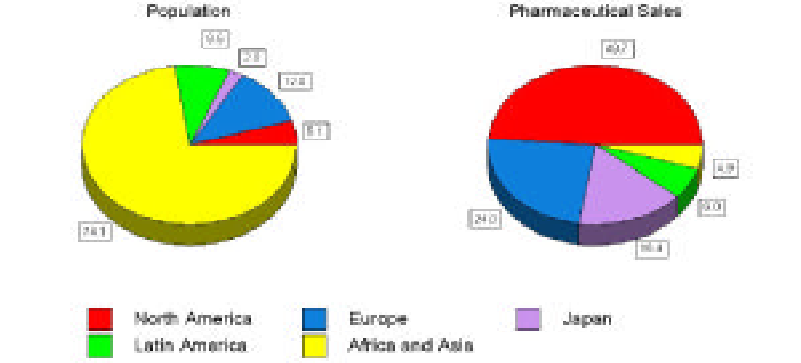


Figure 2

Population data from Globocan, IARC; Drug sales data from IMI Health.

be prohibitively expensive, often considerably more than 100% of the family's income. Moreover, physicians in private practice generally function outside the governmental and academic systems in which consultation, continuing education, and other means of ensuring high standards of medicine exist. Health insurance programs, although strongly advocated by the World Health Organization and the World Bank, are not easy to establish among poor populations. Such programs should be pursued, however, and local authorities might best supervise them. Indeed, informal associations and reciprocal gift giving often exist in the poorest communities as a means of mitigating risk. These groups might form the basis for expanded, more formal health insurance programs. Coupling these with screening and educational programs would help to ensure that benefits accrue at a population level and that premium payments are considered not merely provision for possible future misfortune, but also for health services provided.

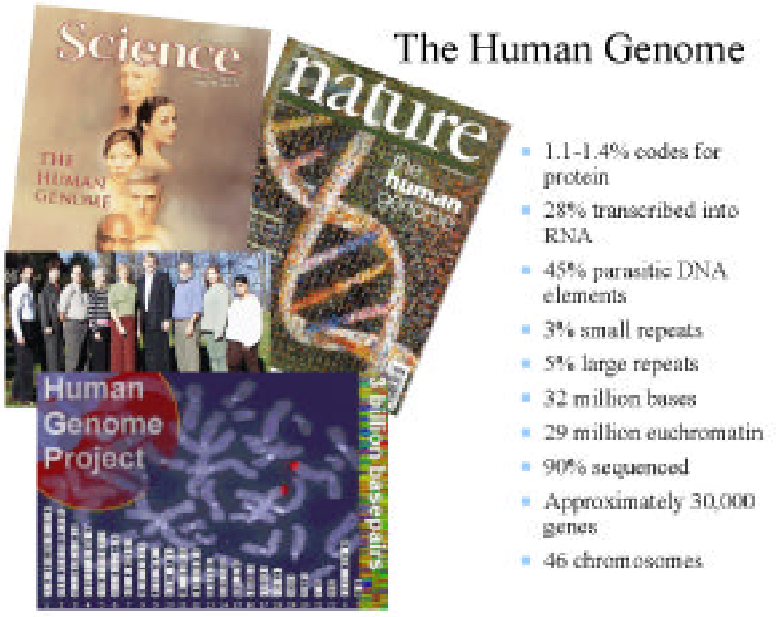
If the outer circles of populations are to be reached, and sustained improvements in cancer care made in these populations, the approaches must come largely through existing infrastructure, although external help in building capacity can make a critical difference. There are many excellent hospitals and cancer centers in developing countries, although not nearly enough to serve their populations adequately. In general, major cancer treatment facilities are found near the centers of population — essential in countries whose transportation systems may leave much to be desired, but creating added access problems for the rural poor. Because these centers are few, relative to the population size, they tend to be overwhelmed with patients. And because of the delays in diagnosis or in accessing skilled medical care, they are confronted with patients with much more advanced disease than would be encountered in an affluent country. Finally, because of the lack of health insurance programs, difficult policy decisions must be made regarding how best to use available funds. These decisions are made more difficult by the problem of treatment costs, particularly of imported drugs and drugs still under patent—which may remain beyond the reach of most patients in developing countries regardless of insurance schemes. This issue is put into some perspective by the dramatic differences in drug sales compared to population size in various world regions (see figure 2).

Just as aircraft passengers are instructed to put on their own oxygen masks before assisting others, it is important that the centers of excellence first strive for the highest standards and efficiency of services. When their resources are sufficient, they will be in a position to form local networks with smaller institutions in the region and to work with other organizations, including state and local authorities, to develop a portfolio of programs for dealing with the problems at their source. Like Dante, we cannot expect the journey to "Paradise" to be short or easy, nor will we always have a Virgil to guide us. But at least we can avoid being numbered among those who fail, not because of what they did, but because of what they did not do. ■

CARTOGRAPHY IN THE NEW MILLENNIUM— THE MAPPING OF THE HUMAN GENOME

In February of this year, initial maps (there are two) of the human genome were simultaneously published in the journals *Science* and *Nature*. This technological feat, which comes within 50 years of Watson and Crick's description of the structure of DNA, is a milestone in human achievement, and will have a profound effect on our understanding and treatment of a variety of diseases, including cancer. Some surprising statistics emerge from the extraordinary amount of information now available, even though the project remains incomplete—only about 25% of the genome is in "finished" form, i.e. there are no gaps in the sequence. Very little of the genome, which is estimated at 3.2 million base pairs, actually codes for protein (less than 2%), while present estimates of the number of genes suggest that there are only approximately 30,000 (32,000 and 39,000 from the two versions of the genome)—far fewer than previously thought. Since this is barely twice the number in the nematode worm, *Caenorhabditis elegans* (19,099), and only three times that of the fruit fly, *Drosophila melanogaster* (13,601), it would seem that species diversity is accomplished more by the way in which genes work together in molecular pathways within cells, and by relatively small differences in the specific sequences of genes, than by the acquisition of new genes. In this respect, perhaps we ought to be thinking in terms of the functional properties of protein *domains* rather than in terms of whole genes, for it is ulti-

mately the pattern of functional interactions of gene products, i.e., proteins, that creates different cell types, different arrangements of cells, and different organisms. This is also relevant to cancer, since the joining of one gene with another through the mediation of a chromosomal translocation frequently produces a fusion protein comprised of parts of two different proteins, while the inappropriate expression (or lack of it) of relatively small subsets of proteins, due to a variety of changes that lead to altered expression of genes, can clearly wreak havoc with the functional properties of cells. In both of these respects, it would seem that genetic processes that lead to cancer are closely related to those involved in the evolution of species.



Another remarkable finding is that approximately 45% of the human genome arises from parasitic DNA elements of one type or another, mostly inserted via RNA reverse transcription—indicating that our concepts of vertical evolution have to be rather drastically modified to take into consideration lateral contributions from other organisms. Transgenic organisms clearly occur naturally, and are not the invention of molecular biologists. This phenomenon, which enriches the vertical process of genetic variation within a species, is paralleled at the psychosocial level by the essential role of other living organisms in the development of the human ethos, and by cross-cultural fertilization in the evolution of peoples, religions, and languages.

What will be the influence of this giant step forward on human health? There can be no doubt that it will be extraordinary, although at this point in history, we should not expect sudden dramatic changes. Already approximately 1,000 genes associated with human diseases have been identified, and doubtless, all genetic associations will be ultimately described. In the case of cancer, we can now perceive that the identification of *all* potentially neoplastic changes in the genome is simply a matter of time. Similarly, understanding the functional differences induced by these changes, or indeed, those created by single nucleotide polymorphisms (*snps*) that can induce, for example, individual variation in the metabolism of carcinogens or of drugs, is all eminently within our grasp. Indeed, given that the bulk of the sequencing of the human genome was completed in just 15 months, we can safely predict that technology will improve sufficiently rapidly that it will not be long before the genomes of individual persons, or multiple cells from a specific cancer, will be able to be mapped in a matter of hours. Massive computing power and statistical methods, also yet to be developed, will doubtless lead to ultra-rapid methods of manipulating these huge quantities of information and extracting for the patient and /or physician information relevant to the prevention or (probably an increasingly minor role for the health care service provider of the future) the treatment of disease. Prediction of disease (and cancer) risk will be honed to a high degree of accuracy, although potentially marked variations created by the less readily measured interactions with the environment will still need to be taken into consideration. Treatment, which, in the future, will be precisely targeted to the genetic abnormalities, or, more likely, their consequences at the protein level, will also be adjustable to take into consideration individual handling of drugs, and cancer will be curable by therapy no more toxic than is present treatment of dis-

ease caused by micro-organisms (the advent of small molecular weight drugs, such as the BCR-ABL tyrosine kinase inhibitor, STI571 is evidence enough for this). It is to be expected that drug combinations will prove necessary to avoid resistance to specific agents through mutation or the use of alternative pathways. The precise cocktail of drugs required, however, will be individualized on the basis of the particular mix of genetic abnormalities in each tumor—this will be much more important than the type of tumor, although it is probable that particular sets of molecular abnormalities, or their manifestations as gene expression patterns (signatures), will lead to considerably more precise classifications of cancer.

There is much that must be learned before these capabilities become commonplace, such as understanding how minor differences in sequence (e.g.,snps) translate into significant functional differences, how protein structure is consequent upon amino acid sequence and how protein structure is modulated by interactions with other proteins. We shall also need to be able to reduce the vast physico-chemical intracellular milieu, comprised of multiple, simultaneously functioning and interdigitating biochemical pathways, to patterns comprehensible to the human mind. Much of this milieu, or *proteome,* as the pattern of expressed proteins has been called, will be related to the basic processes necessary to the survival (and death) of the cell, whilst others confer upon the cell its particular characteristics, thereby permitting it to play its preordained role in the organism as a whole. And just as a map of the world provides only the crudest of foundations on which to build a true understanding of the geophysical features of our planet, and in turn, of the myriad of interdependent life forms that it supports, so the map of the human genome provides just a beginning to what really matters —the understanding of all aspects of protein structure, function and interactions in cells (a discipline that has been referred to as *proteomics*)—for this is the means by which the information encoded in the genome becomes manifested as a living organism. A greater challenge, perhaps, than mapping the human genome, but one which, we can now surmise, is not beyond the power of human ingenuity to meet. There will surely be additional surprises along the way, and hosts of bioethical questions raised as we learn to manipulate the genomes (or proteomes) of not only other creatures, but of ourselves —for good or ill. All human knowledge can be used wisely i.e., to the long-term benefit of all, or unwisely, i.e, to the short-term benefit of a few. We can only hope that the powers of Darwinian "natural" selection, subject, henceforth, to increasing adaptation via Lamarckian acquisition of inheritable characteristics, will have been enough to ensure that the wisdom of human beings will eventually be the equal of their technical prowess, for otherwise, nature's introspective gaze will have probed unprotected into the Medusa's[1] eyes, and we shall, eventually, have contributed to nothing more than the fossil record! – *IM*

[1]Medusa: a creature of Greek mythology, with snakes for hair, which had the power to turn anyone who looked directly at it to stone. Use of a mirror, to view it indirectly, provided sufficient protection against its petrifying powers.

RETINOBLASTOMA

Retinoblastoma is a malignant tumor of childhood that arises in the retina of the eye. The majority of cases are diagnosed before the age of five years. The incidence of retinoblastoma is higher in developing countries than in Europe and the United States, where the age standardized annual incidence rate is about 4 cases per million. In some developing countries, the incidence rates per million may be two to six times higher (Figure 1) or even more, since very little information is available from rural areas, where retinoblastoma appears to be particularly common. About 20 to 30% of patients have bilateral disease. The disease may occur sporadically or it may be inherited. It is characterized by a rapid growth rate. When the disease is detected at early stages and confined to the eye, children have a good prognosis and the anticipated five-year disease-free survival rate (DFS) is 90% or greater. However, in children with disease that extends beyond the eye, particularly to distant parts of the body, the five-year DFS is poor, less than 10%. The percentage of children with extraocular disease (outside the eye) at diagnosis is much higher in developing countries (approximately 35 to 50%).

The two most common early symptoms observed in children are leucocoria (cat's eye reflex) (Figure 2) and strabismus (squint). Other signs of the disease include redness of the eye, fixed pupil, or other more subtle changes. When the disease is more advanced, patients may experience swelling of the tissues around the eye, proptosis (protruding eye), or sunken eye. Change in or loss of vision may

also occur, but this is difficult to assess in very young children. In addition to a detailed ophthalmologic (eye) examination performed while the patient is under anesthesia, special x-rays and ultrasound evaluations are used to establish the diagnosis.

Ophthalmologists, pediatric oncologists, and radiation oncologists are all essential members of the multidisciplinary team needed to effectively treat patients with retinoblastoma. The goal of treatment is cure and preservation of sight. The therapeutic approach is dependent upon factors such as whether disease is unilateral or bilateral, the potential for vision, the size, location and number of lesions, and whether the disease has spread beyond the eye. Availability of treatment modalities as well as the expertise of a particular center in the management of patients with retinoblastoma are also important considerations. For small tumors within the eye, treatment consists of external beam radiation, photocoagulation (laser), or cryotherapy (precise freezing). When tumors are large or if there is little expectation that vision can be preserved, the eye is removed. The use of systemic chemotherapy to reduce tumor volume prior to a physical treatment modality to permit preservation of vision is currently under investigation in Europe, the USA, and many developing countries. The most common chemotherapy drugs used for chemoreduction are carboplatin, vincristine, and etoposide. In patients with extraocular disease, particularly those with spread to the central nervous system or bone marrow, chemotherapy is the primary component of treatment. ■ - *Melissa Adde*

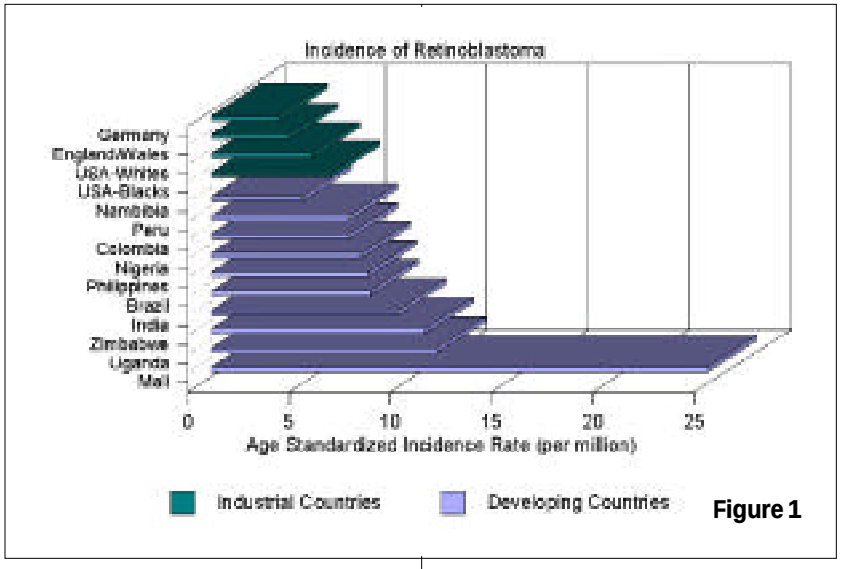


Figure 1

Data from IARC.

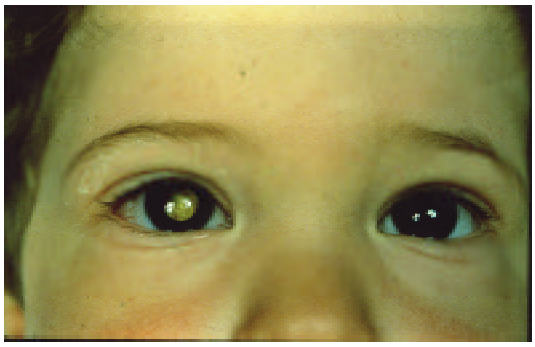


Figure 2

The child at left has leucocoria, also known as "cat's eye" or "white eye." The whitish appearance of the pupil is caused by the tumor in the eye, and is, with strabismus (squint), the most common early sign of the tumor. If not dealt with at this stage, when it is eminently curable, the tumor continues to grow and may become sufficiently advanced to make cure highly unlikely with presently available therapy—as illustrated by the case history presented on page 7.

A CASE REPORT OF RETINOBLASTOMA

By Sidnei Epelman
Albert Einstein Hospital, Sao Paulo, and INCTR Retinoblastoma Strategy Group

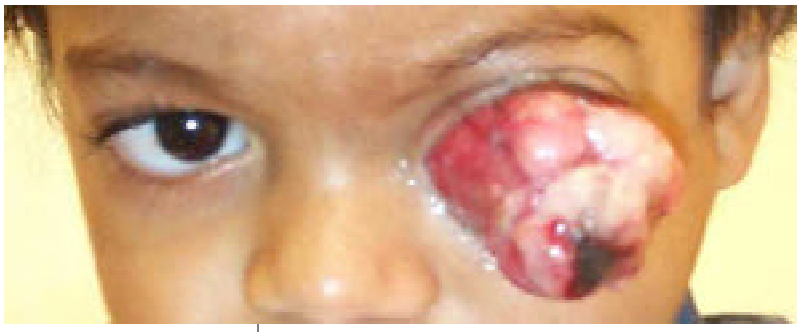
The following case history of a four-year-old child from a slum area in the capital city of a state in north western Brazil, is not unusual in countries with limited resources, and illustrates the extent of the problem of late diagnosis/presentation of retinoblastoma in such countries.

The patient was noted by the parents (who are illiterate) to have strabismus (squint) of the left eye at the age of six months. They were told not to worry about this, and nothing was done. Approximately six months later, they noticed redness of the eye and what appeared to be bleeding within the eye. The parents took the child to a local clinic and eyedrops were prescribed, which he continued to take for approximately two years. By this time, the eye had begun to protrude, and eventually, after further medical

consultations, enucleation (removal of the eye) was performed at a local hospital in January 2001. Approximately eight days later, it was noted that tumor was growing in the orbit (eye socket) and after two months of additional delay, the patient was sent to Sao Paulo where he was seen by Dr Clelia Erwenne, an ophthalmologist at the Albert Einstein Hospital in Sao Paulo (see figure at right). Repeat biopsy showed retinoblastoma, and investigations revealed that the tumor had spread to the brain. Malignant cells were found in the spinal fluid.

The delay in diagnosis for this child was in excess of three years. Had the diagnosis of retinoblastoma been entertained at the time when the only evidence of abnormality was squint, or even when the redness and bleeding in the eye were first noted, it is highly probable that the child would have been cured, and, depending upon the extent of tumor at that time, it may even have been possible to preserve the eye with simple chemotherapy and local treatment. With the extent of disease currently present (stage IV, with nervous system involvement), there is very little hope of survival, even with very intensive chemotherapy.

Because many children's lives, and probably many eyes, could be saved by earlier diagnosis and treatment, the INCTR retinoblastoma strategy group is planning to launch a program to identify more precisely the reasons for late presentation of retinoblastoma to centers able to manage this disease. Educational programs designed to lead to earlier diagnosis and therapy will then be instituted, their primary target audiences (the public, primary care physicians or other health advisors, pediatricians, or ophthalmologists) and content being determined by the findings of the initial survey. ■



The child above has advanced retinoblastoma. The tumor is protruding from the left orbit, after removal of the eye approximately two months earlier.

RETINOBLASTOMA STRATEGY GROUP MEETS

The Retinoblastoma Strategy Group convened in January to develop a multi-national program for retinoblastoma. Investigators from institutions in Brazil, Bolivia, Mexico, Turkey, Saudi Arabia, India, and the Philippines met in Brussels to set a course of action that promises to improve early detection and to provide a common treatment protocol for retinoblastoma in developing countries.

Each investigator presented information about the incidence of retinoblastoma and the problem of late presentation within their own country. All of them observed that the majority of patients present to their centers with advanced stages of the disease. Factors contributing to late presentation include:

- inability of primary health care providers to recognize the significance of patient symptoms;
- inability of ophthalmologists to make the diagnosis, often due to failure to perform the required eye examination (fundoscopic examination under anesthesia);
- lack of patient referral systems and lack of experts to treat children with this disease;
- lack of public awareness;
- lack of family financial resources; and
- fears of the treatment itself, particularly removal of the eye.

Public and professional awareness programs could have a huge impact in alleviating the problem of late presentation. If more patients are seen in earlier stages of the disease, more eyes could be saved, at less cost and with a decrease in mortality.

The group decided to collect more information about the problem of late presentation. A questionnaire will be administered to parents of children who are about to start treatment at participating centers.

The group also agreed that edu-

cational materials need to be developed for three audiences—the public, primary health care workers, and ophthalmologists. Posters intended for the public could be displayed in areas where people are most likely to see these materials (i.e., well-baby clinics, schools, bus stops, shops) while posters and brochures for health care professionals could be displayed at professional society meetings.

The strategy group also agreed to develop a common protocol for the treatment of patients with advanced retinoblastoma. A sub-committee is designing a proposed treatment schema. This will be circulated this spring and after objectives, patient eligibility criteria, treatment, and evaluation parameters are agreed upon, the group will draft a formal protocol document by October 2001. ■

Members of INCTR's Retinoblastoma Strategy Group are working to improve early detection of retinoblastoma in developing countries. Pictured at top are: Clelia Erwenne (Brazil), Sidnei Epelman (Brazil), Anslim Narinesingh (INCTR), Shripad Banavali (India), Carlos Leal (Mexico), Ian Magrath (INCTR), Yolanda Ernst (Bolivia), and Laxman Arya (India). At bottom: Melissa Adde (INCTR), Amani Al-Kofide (Saudi Arabia), Kamer Uysal (Turkey), Nurdan Tacyildiz (Turkey), and Emel Cabi Unal (Turkey).

INCTR IN NEPAL

INCTR staff visited Nepal in January to discuss with oncologists in Kathmandu and the mayor of Banepa the possibility of working with the Cancer Relief Society of Nepal (CRSN) to improve cancer control. The CRSN has volunteers working in 25 districts.

The IARC estimates that in this country of 23.9 million people, there are at least 17,000 new cases of cancer per year, a high fraction of which are either cancers of the uterine, cervix, or breast. The next most frequently observed neoplasms, oral cancers and other neoplasms of the upper aero-digestive tract, are more frequently seen than lung cancer, although the incidence of the latter is rising. Oral cancers are associated with chewing habits. Indoor pollution from use of open fires remains a problem. Cancer services in Nepal are limited, with only two cancer centers and three radiotherapy units (all cobalt-60 machines), one of which is in need of a new cobalt source and renovation. Although a few physicians and surgeons have specialized knowledge of cancer treatment, the vast majority practice general medicine or surgery, and cancer patients are largely treated in general wards.

Banepa is developing rapidly, and according to its mayor, Dr Shrestha, the city is destined to become the gateway to Kathmandu. Within five kilometers of Banepa are two well-established hospitals, a traditional medicine health center (Ayurvedic) and a new university (Kathmandu University), which will soon open a medical school and an information technology center. The new medical school— the seventh in Nepal—will contribute to the graduation of some 700 doctors per year in Nepal. This compares to just 30 per year only a few years ago. One of the hospitals in Banepa, Scheer Hospital, is supported by the Seventh Day Adventists, and has considerable undeveloped space. A major new road is to be built between Banepa and the eastern part of Nepal, so that this region could become a major element in the socio-economic development of Nepal. In this respect, Banepa would seem an ideal site for an INCTR Collaborating Unit to work closely with the CRSN and local physicians to improve cancer registration, early detection (particularly for cervical cancer and oral cancer), and cancer treatment in Nepal.

Nepal is a relatively small country with a total expenditure on health of some 41 international dollars per capita, only 11 dollars of which are provided by the government. Hospi-

tals are overcrowded in Kathmandu, and many populations are underserved with respect to family health care. Clearly, early detection of cancer could do much to ease the present burden on medical services, and because of the importance of women's cancers, programs of this kind could be integrated with other aspects of health care. Although it will take a number of years to extend services to the outlying communities, screening camps and educational programs are high on the list of potential collaborative activities between the INCTR and the devoted members of the CRSN, working in close conjunction with Nepalese health care professionals and regional and governmental health authorities. ■

INCTR REACHES OUT TO PAKISTAN

INCTR is exploring ways to focus on the priority areas of cancer treatment in Pakistan. In February, Dr Ian Magrath and Dr Anslim Narinesing visited cancer facilities in Lahore and attended the 5th Symposium of the Shauhat Khanum Memorial Cancer Hospital & Research Center.

Facilities there are comparable to well-run hospitals in developed countries. Patients referred there from throughout the country have access to clinical services in medicine, surgery, medical oncology, pediatric oncology, radiation oncology, nuclear medicine, radiology, and pathology. Dr Narinesingh also visited other state-run hospitals in Lahore, including the Jinnah Hospital and the Mayo Hospital.

Among the important cancers affecting the population in Pakistan are female breast, leukaemias, lymphomas, and lung cancer (primarily in men). As in most developing countries, the majority of cases present at a late stage, leaving limited scope for effective treatment. Both the public at large and the primary health care workers would benefit from community programs encouraging early detection. ■

INDIAN ONCOLOGISTS CREATE COOPERATIVE GROUP TO STUDY LEUKEMIA

During a recent visit to Hyderabad, India, to discuss progress in protocols MCP 841 and MCP943 for the treatment of acute lymphoblastic leukemia (ALL), leading Indian oncologists decided to form a cooperative group for the study of leukemia. Protocol MCP 841 has been used for many years in India with good results. Within a few years of its introduction, and with collaboration between present staff members of the INCTR then working at the National Cancer Institute in the USA and Indian cancer centers, survival rates in ALL patients treated with this protocol had more than doubled.

The success of the protocol led to its use in many smaller Indian centers. To assist these less experienced centers to use the protocol effectively, the major centers, including the Cancer Institute, Chennai (Madras), Tata Memorial Hospital and the All India Institute of Medical Sciences, decided to form a cooperative group to include smaller institutions, some of which are now staffed by oncologists trained at the premier cancer centers. This group will greatly assist in the dissemination of information regarding the use of reasonably intensive, standardized chemotherapy regimens and supportive care in Indian medical colleges and larger hospitals. This should result in better care of patients, even those unable to reach the larger cancer centers or to undergo the necessary two-year period of treatment far from home. In addition, it is hoped that more data will be collected regarding the clinical patterns, prognostic patterns and biology of ALL in India so that treatment can be better tailored to risk groups identified in Indian populations. Eventually, studies will be expanded to other types of leukemia as well as leukemia in older adults.

At the Hyderabad meeting it was agreed to undertake an analysis of approximately 1,000 patients treated with protocol MCP 841 in India between 1990 and 1997. The results will be used to develop risk-based stratification of ALL patients in Indian centers using this or successor protocols. A meeting of the INCTR's leukemia strategy group, which will initially be formed around institutions with experience in the use of protocol MCP 841, will take place in Brussels after the INCTR's Annual Meeting. Results of a successor protocol to MCP 841, MCP 943, which has been piloted in several Indian cancer centers, will also be discussed, along with future plans for ALL studies in India. At the same meeting, a proposal developed by INCTR collaborators from the King Fahd Children's Medical Center in Riyadh, Saudi Arabia, for the molecular characterization of ALL in South Asian and Middle Eastern countries will also be presented. ■

Editor's Note: In each edition of Network, *a brief article about one of the institutions with which the INCTR collaborates will appear. These articles are solicited by the editorial staff.*

Pediatric Hematology Oncology at the National Institute of Pediatrics in Mexico City

by Dr Roberto Rivera-Luna
Head, Division of Hematology/Oncology

The National Institute of Pediatrics in Mexico City is struggling to reverse escalating cancer mortality among children aged 4 to 15. Cancer is the second leading cause of death among this age group.

INTRODUCTION

The Instituto Nacional de Pediatria (INP), or National Institute of Pediatrics, exists within the framework of the National Institutes of Health in Mexico City. It is a tertiary care, university-affiliated (Universidad Nacional Autónoma de México) referral institution dedicated exclusively to pediatric care. Founded in 1970 by presidential decree as a not-for-profit organization supported by the federal government, its sole purpose is the care of sick children.

The physical structure consists of four separate buildings. A four-story hospital includes outpatient clinics, a 260-bed in-patient section in which all pediatric specialties are represented, general and specialty laboratories, an imaging section with CAT scan, X-rays and nuclear medicine, and a radiotherapy (cobalt 60) unit. A second, 10-story building is dedicated exclusively to basic research and includes an animal facility housing 16 animal species. A third building comprises the Residency, with accommodation and a cafeteria sufficient for 214 full-time house staff. The fourth building is an administrative unit. The INP is one of the three tertiary pediatric care hospitals in the Republic of Mexico, and the Pediatric Oncology Division is considered by the Mexican Federal Health Authority to be a national referral center for acute leukemias, brain tumors, retinoblastoma, and bone marrow transplantation. The tertiary care hospitals are dedicated to academic pursuits, research, and patient care, in that order.

Mexico is a developing nation with a population of 98 million inhabitants, of whom 60% are under 18 years old. Until three years ago, cancer was the fifth leading cause of death in children aged from 4 to 15 years. However, federal health officials have reported that since 1998 cancer is second only to accidents as a cause of death in this age group. Currently there are 86 Mexican Board Certified pediatric oncologists all over the nation, 21 of whom are practicing in Mexico City. Among the 31 states of the republic, 12 do not have qualified pediatric oncologists and here, children with cancer are generally diagnosed and treated by adult hematologists or oncologists.

CLINICAL SERVICE

The Division of Hem/Oncology at the INP is made up of the Departments of Hematology, Oncology and Radiotherapy as well as a Bone Marrow Transplantation Unit. Twelve full- time board-certified physicians work in the three departments. In addition, a full-time psychologist is dedicated exclusively to oncology patients and three social workers. There are 46 beds assigned to the division. Each department has a full-time pediatric head nurse and several nurses per shift. An average of 700 new patients per year are registered in the three departments and 4,800 follow-up patients are seen per year, giving a total of 5,500 patients seen per year. Unfortunately, 25-30% of these patients fail to complete their treatment or are lost to follow-up, mostly due to the fact that 60% of the patients come from

rural and semi-rural areas 1,000 kilometers or more away from the INP.

The departments of hematology and oncology have their own laboratories, which include automatic instruments for routine hematology and chemistry. There is also a cryopreservation unit and tissue typing laboratory for bone marrow transplantation.

RESIDENCY PROGRAM

In its 30 years of existence the INP has trained 38 pediatric oncology fellows, of whom six have been from other Latin American countries. In 1979, a clinical residency program was established. The requirements for enrollment in this program include having a Mexican medical license, approval for the National Residency Board Examination, completion of a three-year university pediatric residency program, and having Mexican Pediatric Board-Eligibility or Certification. Foreigners must have their pediatric certificate validated by the National University of Mexico and must pass the National Residency Board Exam. The residency program in pediatric oncology at our institution, and nationwide, is a two-year program. It includes being on-call every four days. The hospital provides accommodation and meals for all residents. Currently there are three junior and three senior fellows. The first academic year has clinical rotations through the outpatient department, bone marrow transplant unit, in-patient department, ambulatory care, radiotherapy (visiting fellow) and the oncology laboratory. The senior fellows, besides supervising the junior house staff, make daily rounds with the pediatric residents rotating through the Oncology Division, and in addition, are required to undertake clinical and/or basic research. They also participate in all consultations with senior staff members, direct the weekly seminars, journal club and the weekly Joint Tumor Board Conference, have active participation in the development of leukemia, lymphoma and solid tumors protocols, and are required to produce at least one scientific medical paper. They may choose to spend six weeks in any pediatric oncology department/institution in the USA as a visiting fellow.

The Pediatric Hematology Residency Program has similar requirements for national and foreign fellows who undertake the two-year residency. Residents are trained in the care of all benign hematological conditions of childhood as well as the treatment of leukemia. A Visiting Professor Program, established 20 years ago, brings an expert pediatric hematologist or oncologist from an American institution to visit the department of oncology. For three days each year, visiting professors participate actively in ward rounds, see patients in the out-patient department with the fellows, participate in the weekly Tumor Conference, and give a presentation at the Tuesday Formal Hospital Conference. Visiting professors may also discuss in-house treatment protocols and suggest modifications. Occasionally a pediatric hematology/oncology fellow from USA has elected to spend several weeks at the INP.

RESEARCH ACTIVITIES

Research is being conducted in both clinical and basic areas and inter-departmental collaborations include ongoing studies with the departments of genetics, molecular biology, endocrinology, pharmacology, microbiology, infectious diseases, epidemiology, pediatric surgical oncology, pathology, psychology, ophthalmology, and with the oncology research laboratory. Inter-institutional research is conducted with various institutions in Mexico City, but mainly with the National University of Mexico. Currently, 21 research protocols and two international protocols are in progress.

OVERALL GOALS

Due to the limited financial resources that our developing nation can muster, it is necessary to optimize all the active programs and protocols within the division. This will entail obtaining local/national/international funding for protocols (including cost of drugs), laboratory equipment, participation of staff in international meetings, subscriptions to appropriate medical journals, and Internet access.

We plan to continue to enhance our pediatric oncology residency program in order to maintain a high level of excellence, and further, to encourage our residents to participate not only in patient care, but also in teaching and research after finishing their training. We shall continue to encourage graduates to practice in those geographical areas in Mexico where they are most needed. We hope, also, to develop more professional links with the international community, including active participation in INCTR activities. Through such collaboration, we hope to further develop our clinical and basic research programs in order to improve our understanding and treatment of pediatric cancers. ■

INCTR ESTABLISHES ETHICAL REVIEW COMMITTEE

The INCTR established an Ethical Review Committee (ERC) in January. The ERC includes scientists, medical experts, ethicists, patient representatives and laypersons, all of whom volunteer their services to the INCTR. At least two members of the committee will have first-hand experience in clinical practice or conducting research in developing countries.

The ERC functions similarly to an institutional review board (IRB) in the USA or a French "Comité consultatif pour la protection des personnes dans la recherche biomédicale" (CCPPRB). The specific tasks of the committee are:

- to provide guidance, advice and decision (in the form of approval/disapproval) of research protocols sponsored by or otherwise significantly engaged in by the INCTR;
- to provide ethical guidance and advice on specific ethical issues presented to it by the INCTR staff; and
- to develop and/or review, as requested, ethical guidelines for the INCTR.

The ERC is guided by principles expressed in the *Declaration of Helsinki* and also refers to the *International Ethical Guidelines for Biomedical Research involving Human Subjects* (CIOMS), the *Belmont Report* and the *European Convention on Human Rights and Biomedicine*. Its standard operating procedures are based on the *Operational Guidelines for Ethics Committees That Review Biomedical Research of the World Health Organization* (WHO) and *Guidelines for Good Clinical Practice* (WHO and International Conference on Harmonization).

All protocols that the ERC approves will also need to be approved by national and/or local ethics committees prior to implementation in participating centers in developing countries.

The INCTR is fortunate to have, as committee chairman, Dr Francis P Crawley, Chair of the Ethics Working Party of the European Forum for Good Clinical Practice. The ERC recently met to decide upon its procedures for decision-making and to review the INCTR-Osteosarcoma Strategy Group protocol for the treatment of patients with newly diagnosed metastatic osteosarcoma. ■

US BRANCH ADDRESSES CERVICAL CANCER

The US Branch is initiating a new program for cancer of the cervix in Latin America. While of diminished importance in much of the Western world, this tumor is endemic in many developing countries, especially Central and South America, Africa, and South Asia.

Screening is well established as a means of detecting the early stages of epithelial transformation, thus providing an opportunity to interdict the process. Studies of etiology have implicated a role for the Human Papilloma Virus (HPV), and several new vaccines against this virus are under development. Lastly, recent data from controlled trials have demonstrated that improved survival for patients with locally advanced tumors can be achieved with combined modality treatment. Therefore, this is an appropriate time to attempt to exploit the recent advances in the understanding and management of this important cancer in countries where it is a major source of morbidity and mortality.

The US Branch held a planning meeting in Miami, Florida, in late March. Investigators working in the fields of public health, prevention, detection, and treatment from Latin America and the United States met to exchange information and concepts of management. The group intends to focus on issues of technology transfer and the formation of new collaborations that can introduce new strategies in countries or regions where they are underrepresented. It is hoped that any initiative for cervical cancer piloted in Latin America will be extended to many other regions of the world. ■

LET US HEAR FROM YOU

We welcome letters and case reports from our readers on topics related to cancer in countries with limited resources. Please send your submissions to:

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