N E T W O R K

THE NEWSLETTER OF THE INTERNATIONAL NETWORK FOR CANCER TREATMENT AND RESEARCH

INCTR

Volume 2, Number 2, Autumn 2001 — **Inside**: News Briefs - **5** INCTR's Model Spokesperson - **7** Profile in Cancer Medicine - **8** Special Report on Liver Cancer - **9** Case History -**12** Philippine Children's Medical Center - **13**

THE PRESIDENT'S MESSAGE

ENCOURAGING HEALTH RESEARCH IN DEVELOPING COUNTRIES

by Ian Magrath

A "NEW" APPROACH: EVIDENCE-BASED MEDICINE

Having spent the best part of my career in medical research, I was puzzled some years ago by a new term—*evidence-based medicine*—that was suddenly on everyone's lips. I had always assumed that the use of evidence to guide clinical interventions is a fundamental principle of medical practice. The term seems to have "gone public" in November 1992, when the *Journal of the American Medical Association* (JAMA) published an article titled *"Evidence-based Medicine: A New Approach to Teaching the Practice of Medicine."* In the nine years that have since passed, PubMed lists over 7,400 publications in which the term is used. Somehow, the sudden preoccupation with evidence just a few years before the close of a century in which so many scientifically and technologically-based advances in health care had occurred suggested a rather belated recognition of a paradigm shift in the practice of medicine—probably by those more concerned with education and service delivery than by medical scientists. The latter, after all, had been responsible for the unprecedented progress made, and presumably had long been convinced of the value of evidence, as well as its variability in quality. Still, I remain surprised that this debate took so long to emerge.

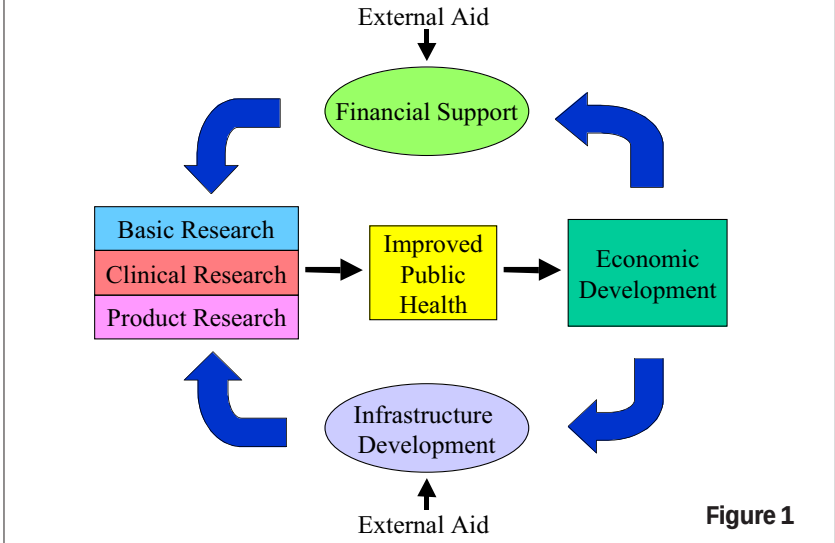

Figure 1

The benign cycle of research-induced socioeconomic benefits—health research improves health, which accelerates economic development, which permits better financing and infrastructural support, thus having an ever-increasing effect. Input to start the cycle is required in the form of external aid. This need should decrease over time.

A CENTURY OF PROGRESS

An idea of just how far medicine has come in the last 100 years may be gained by perusing Osler's famous textbook of Medicine, written at the turn of the 20th century. Despite the myriad of salves, potions, tonics and herbal remedies which had abounded since the days of the ancient civilizations of Egypt, China, India, and later, Greece, little beyond palliatives and placebos was available for most medical conditions. As

pointed out by Osler himself, essentially the entire pharmaceutical armamentarium could be carried in the physician's bag. Pharmacy had progressed little since the days of the great Arab physicians, pharmacists and alchemists of the Córdoban caliphate, which finally yielded to the Spaniards in 1492—the same year that Columbus discovered America. In Osler's day, there were no antibiotics, no effective anti-cancer agents, and surgery—still remarkably primitive by today's standards—was the only available therapy for cancer. Although Roentgen had discovered X rays in 1895, and only two years were to pass before their astounding effect on cancer was to be observed, it took many years for radiotherapy to become a standard component of the therapeutic repertoire. Still, a dramatic acceleration of the march of progress was about to begin, based on a painfully accumulated foundation of knowledge that extended back to the mists of prehistory. Whether ancient peoples realized it nor not, much that they did, whether relating to agriculture, navigation, the development of tools or the practice of medicine was based on scientific observation, frequently blended inextricably with magical and religious practices, and clouded by a liberal helping of misconceptions. Evidence-based medicine then is in fact nothing new, for the evidence referred to is empirical—i.e. the clinical test of the likelihood of a history or physical sign being something indicative of a specific diagnosis, or whether an intervention works or not, regardless of whether the mechanism is understood. The Egyptian medical papyri, for example, are clearly based, at least in part, on empirical observation. Unfortunately, an evidential basis for clinical practices, however ancient the concept, is often difficult to discern, and even now, individual physicians have considerable license in recommending treatment. The monitoring of clinical practices and outcomes remains limited (except in the context of clinical research), even if the concept of evidence-based medicine has led to the creation of more practice guidelines and more reference to the results of clinical trials.

> *Teach thy tongue to say I know not and thou wilt progress.*
>
> *—Moses Maimonides*

SURGICAL STRATEGEMS

Surgery for example, is a discipline which has evolved dramatically in the course of the last 100 years (thanks to the use of anesthetics, aseptic techniques, blood transfusions and antibiotics), but more, perhaps, through the efforts of surgical virtuosos than through team efforts and carefully conducted clinical trials. Originally limited to the lancing of abscesses and the management of wounds, with amputation being among the more ambitious of procedures, it moved rapidly in the early years of the last century to the introduction of routine abdominal and thoracic surgery, through the conduct of ever more extensive resections, particularly for cancer and, finally, to its present phase in which restoration and replacement procedures (whether by transplantation or prosthesis) represent the pinnacle of the surgeon's achievements. In part because of the awe inspired by technical feats of this kind, coupled to the powerful influence of tradition, we are still only just moving beyond the grossly mutilating procedures (ranging up to hemicorpectomy—removal of the lower half of the body) that were used to control local spread of cancer. Like radiotherapy, they were all that could be offered to the cancer patient, and it has taken decades to recognize that many have been rather over-enthusiastically applied, or remained standard practice long after evidence of less mutilating but just as efficient alternatives had been obtained. Halstead, for example, described radical mastectomy (en bloc resection of the breast, pectoral muscles and axillary nodes) in 1894, and this remained unchallenged as the surgical approach to breast cancer for 70 years. Eventually, after a phase of even more extensive surgery (extended radical mastectomy) but also, many randomized trials conducted in the 1970s and 80s, the operation was replaced by total mastectomy and axillary dissection. It was not until 1990 that the National Cancer Institute was able to develop a consensus view in which it was accepted that breast-conserving surgery and radiotherapy is as effective, in stage I and II patients, as removal of the breast and axillary lymph nodes. Such patients would, in an earlier era, have been subjected to radical mastectomy.

Old habits clearly die hard, and innovators often receive short shrift (Semmelweise, for example, was driven out of Vienna in 1850 for his novel views on hand washing be-

tween performing autopsies and examining patients!). Perhaps we should not be surprised, then, that in the presence of a conservative profession, benefits to the patient and public and new educational approaches may lag far behind the march of science.

A PARALLEL DEBATE

Delayed though the debate on the basis for medical decision-making may seem to have been in a century in which medical science made such huge strides, a similar and equally surprising debate on the role of research in improving health in developing countries was simultaneously taking place. In 1999, Dr Gro Harlem Bruntland, Director-General of the World Health Organization (WHO), pointed out in a keynote address to the Global Health Forum that it was only in 1990 that the World Health Assembly had "*emphasized the need to develop health research and the necessary knowledge on which national health policies should be based*." One might have expected, as in the case of evidence-based medicine, that such a conclusion would have been made sooner, being a natural corollary of the paradigm shift that had occurred in medicine decades before. In that same year, in her words, "*the concept of Essential National Health Research took root ...and on that basis, the Council on Health Research for Development (COHRED) has developed collaboration with developing countries and gathered useful experience*." Reviewing the remarkably brief history of the concept among policy makers that research is an essential element to improving health, and that the health of a population has a significant impact on its economic development, Dr Bruntland mentioned that in the World Bank's *World Development Report* of 1993, which was focused on health, the central importance of research was underscored. In 1996, she continued, the WHO Ad Hoc Committee on Health Research Priorities published a report on the need and criteria for investing in health research and development, while in the same year, the Global Forum for Health Research was established. In 1999 the WHO Report "*demonstrated that a large proportion of the health achievements of the 20th century can be attributed to advances in scientific knowledge as they were translated into more effective technologies and health-promoting behaviours.*" Such a conclusion would surely seem to be self-evident to medical researchers.

> *Health research is the ultimate international public good.*
>
> *—Gro Harlem Bruntland*

Nonetheless, given the new cloak of respectability for research, in January 2000 the World Health Organization announced the creation of a Commission on Macroeconomics and Health to clarify the link between health and poverty reduction and to study how concrete health interventions, based on scientific research, can lead to economic growth and reduce poverty in developing countries.

It is remarkable that only in the report of this commission, dated December 2001, was it recognized that not only does poverty cause ill health, but that ill-health contributes to poverty. The Commission drew attention to the huge global inequities that exist and provided specific recommendations for "Investing in Health for Economic Development." A key recommendation was improvement of access of the world's poor to essential health services through partnership with high-income countries (see figure 1). This is, in the context of cancer, a major objective of the INCTR.

HEALTH RESEARCH FOR ECONOMIC GROWTH

All countries, no matter how rich, will suffer at an economic level when a fraction of the population not only consumes resources during periods of ill-health, but fails, while ill, to contribute to the economy. In the case of sickness in mothers, negative family consequences often result, whilst a child's education may suffer greatly as a consequence of repeated illness or chronic ill health. Yet in an era in which research into agriculture, manufacturing, transportation, energy and defense have been considered of vital importance to economic progress, national health research has, in comparison, been neglected. Governments of industrial countries as well as developing countries have assumed that adequate health of the population can be assured on the basis of existing knowledge (or has a minor economic impact), and, ergo, the conduct of country-specific health research is a luxury. Much of the focus of the last several decades has, therefore, been on the administration of health systems. Governments, particularly of affluent nations, have made major contributions to the expansion of medical knowledge, albeit with the emphasis on basic research. Such emphasis is not neces-

sarily inappropriate since, for example, an understanding of the cellular and molecular changes associated with cancer will eventually lead to more rational treatment, and also make it possible to prevent disease through non-behavioral interventions. However, the relative paucity of clinical research, and the tendency to consider empirical observations as "not real science" has had a deleterious effect, particularly when one recognizes that the bulk of the advances in interventions in cancer have been based on empirical observations (chemical compounds, for example, have been screened for anti-cancer activity, and only now are we entering an era in which drug design is possible).

The lag phase between knowledge acquisition and translation into benefits for people may have contributed to the uncomfortably high proportion of the educated public throughout the world that looks upon biomedical research as serving only to enhance the careers of biomedical scientists through publication of their results in scientific journals. Politicians have often regarded research as a drain on scarce resources that could be used directly for health interventions rather than a means of ensuring the most efficient use of existing resources, and as such, an essential tool in the evolution of a rational and effective national health policy. Even the scientifically trained have often espoused the same opinion, at least in the context of health research in developing countries. Thus, the recognition that health research is likely to enhance macroeconomic development, even in the poorest countries, is a welcome development, since instead of being considered an unaffordable luxury, developing countries will hopefully recognize that they cannot afford *not* to conduct research relevant to their own national health problems. In policy parlance, health research has finally been recognized as being of "strategic importance."

OPPORTUNITIES MISSED

While recent emphasis has been on essential *national* health research, it is worth pointing out that science knows no boundaries, and that knowledge, wherever created, will likely be of broad benefit. Indeed, one might hope that the term "strategic" will eventually take on a global connotation, rather than implying narrow national interests. Meanwhile, according to the Global Forum for Health Research, 90% of health research is directed toward 10% of the global disease burden. Clearly, the world is missing a huge opportunity to increase the sum total of biomedical knowledge and to use this information to more effectively solve health problems. To rectify this, major investment in the capacity of developing countries to conduct research must be made. They represent the bulk of the planet's human resources, and provide unique opportunities to conduct epidemiological, genetic and therapeutic research in a wide range of health problems, including cancer. They also provide numerous opportunities to examine new approaches to the financing and delivery of health care, and health-related behavioral modification. For these reasons, the twin benefits of health research—improving the lot of individual patients while speeding up the process of socioeconomic development—surely constitute a universal good. It will be for each government to decide the degree to which it will support the creation of basic knowledge, which may have no immediate relationship to a clinical problem even though it should eventually translate into human benefits, and how much will be spent on acquiring more empirical information in the form of clinical studies— i.e. expanding the foundation of evidence on which clinical decisions are made. Both are important, but the poorer countries may be less able to invest in basic research as opposed to extending their foundation of evidence on which to base health policy and specific interventions. Government spending, of course, will be supplemented by the efforts of private organizations, which may significantly alter the overall pattern of ongoing research. Nonetheless, the recognition that solutions cannot simply be "taken off the shelf" but must be tailor-made for the problems of particular developing countries represents a critical step forward.

RESEARCH - THE WAY FORWARD

The recognition of the role of research in improving health care in developing countries and the clear commitment of the WHO to research are important steps forward which should help to ensure that available resources—present and future—are put to the most efficient use. There is much to be done, but the ambience has been created at the beginning of the new century that should make it easier to accelerate the rate of progress in improving health and combating poverty through the conduct of relevant health research followed by application of the lessons learned. As progress is made, and epidemiological transitions continue, cancer will have an ever increasing importance as a cause of premature mortality. There will be much for the INCTR to do. ■

AWARD LECTURES SLATED FOR ANNUAL MEETING

Two distinguished cancer professionals have been selected to present Award Lectures on the opening day of the INCTR annual meeting on cancer control in developing countries. The award lectures were established to honor people who have made outstanding contributions to treating cancer in developing countries.

Dr V Shanta, Chairman, Cancer Institute (W.I.A.), Chennai, India, will give an address titled "My Encounter with Cancer." Dr Shanta, whose medical career spans five decades, helped to build one of the largest, most comprehensive cancer centers in India.

Dr John L. Ziegler, from University of California at San Franciso Cancer Center, USA, will discuss "Clinical Research in Uganda: Partnerships in Progress." Ziegler spent five years in Africa, working on Burkitt's lymphoma.

The thematic focus of this year's annual meeting includes the epidemiology of cancers of particular importance in specific geographic regions, the supportive and palliative care of cancer, and breast cancer, the most common cancer in women in the world.

The meeting is set for May 29 – June 1 at the Hilton Hotel in Brussels.

On the day preceding the conference, INCTR strategy group and committee meetings will be held, during which new and ongoing programs and projects will be discussed. New strategy groups, that will meet for the first time, will be formed to develop programs in breast cancer, cervical cancer and lymphoma. The latter will be initially focused on Burkitt's lymphoma in equatorial Africa, and will include representatives from other organizations that are interested in participating.

Those who wish to attend the annual meeting, but who have not yet registered, are urged to do so by March 1. A registration form is available on the web site at www.inctr.org. ■

NEW BRANCHES AND OFFICES

At the end of 2001, INCTR established a new branch in Paris: "Alliance Mondiale Contre le Cancer." Dr de Thé, one of INCTR's Vice-Presidents, is President of AMCC, the work of which is expected to dovetail with another of Dr de Thé's interests–women's and children's health. The branch will have a particular focus on working with sub-Saharan Africa.

Additionally, branches are being established in Cairo, Egypt (President, Dr Sherrif Omar, General-Secretary, Dr Hussein Khaled), and Saõ Paulo, Brazil (President Dr Sidnei Epelman), and an office in New Delhi, India (Director, Dr Manorama Bhargava). The Indian Office will be located in the Sir Gangaram Hospital, where Dr Bhargava is a staff member. The branches and offices will coordinate INCTR programs and projects in each of these countries and where possible, nearby countries, as well as assist in developing new associate member institutions and corporations from these regions, and working with national organizations with overlapping goals. ■

PRESIDENT'S TRAVEL

This autumn, Dr Magrath visited China, Kuwait, the Philippines, Vietnam and Brazil. Each visit granted him opportunities to provide information about the INCTR's work, to discuss INCTR programs and projects with staff of associate member institutions, and to set the stage for closer or new collaborative activities.

In China, Dr Magrath attended a meeting of the International Society of Pediatrics in Beijing. He also met in Shanghai with Drs Wang and Tang, who are participating in the INCTR oseosarcoma study.

In the Philippines, in addition to taking part in the Asian Pacific Cancer Congress and visiting the Philippines Children's Medical Center, highlighted in this issue of NETWORK'S "Partner Profile," Dr Magrath was honored to be invited to the inauguration of the new Philippines Society of Pediatric Oncology.

In Brazil, Dr Magrath attended a meeting of the Brazilian Society of Pediatric Oncology. INCTR hopes to work closely with both pediatric oncology organizations in the future through Dr Julius Lecciones (Philippines) and Dr Sidnei Epelman (Brazil).

Vietnam is a country with which the INCTR previously has not had contact. Dr Magrath visited the Ho Chi Minh City Cancer Center, where he had valuable discussions with Dr Hung, the Director, presented the INCTR's work to oncologists from all over the country, and toured the center as well as area hospitals . His Vietnamese hosts expressed considerable enthusiasm for participating in INCTR projects, and we hope that both Dr Hung and Dr Khuong, the pediatric oncologist from the center, will take an active role in INCTR strategy groups as a means of establishing strong ties with centers in Vietnam.

continued on page 12

NETWORK

INCTR MEETINGS

GLOBAL ALLIANCE FOR THE CURE OF CHILDREN WITH CANCER

The Steering Committee of the Global Alliance for the Cure of Children with Cancer (GACCC) met in December. Participants gathered to discuss the goals and objectives of the alliance and to plan activities that could be undertaken in developing countries. Two activities will be initiated within the next year. Because Burkitt's lymphoma (BL) accounts for half of all childhood cancer in equatorial Africa, and is curable with rather simple therapy, the committee agreed to develop a project in BL. The project will include education and training elements, review of diagnosis, improved treatment, patient follow-up and data management. A second activity will be to develop a compendium of activities relevant to pediatric cancer being undertaken in developing countries as well as information about resources available within developing countries for the care of children with cancer. ■

EDUCATION STEERING COMMITTEE

The Steering Committee of the Education Committee met in October. Participants discussed their role in the development of INCTR educational programs and tools. Subcommittees of members will develop specific projects, programs, and educational tools within their area of expertise. Sub-committees to be formed include Medical Oncology, Pediatric Oncology, Radiotherapy, Surgical Oncology, Oncology Nursing, Data Management, Pathology, Imaging, Laboratory Based Oncology Research and Education. Each Steering Committee member agreed to identify priority activities for their respective sub-committee and to devise a plan for initiating these activities. Members agreed to assist the INCTR in its goal of creating a library of various educational tools that can be made available to developing countries. ■

CORPORATE LIAISON COMMITTEE

Dr Nassir Habboubi chaired a meeting of the Corporate Liaison Committee in December. Participants discussed how to encourage more corporations to become associate members and how to solicit sponsors for INCTR meetings and activities, particularly the Annual Meeting. In the afternoon, visiting representatives from Belgian corporations and the Belgian Association of Pharmaceutical Manufacterers were provided with information about INCTR. Several expressed an interest in working in some way with the INCTR. In future, a core committee, consisting of Dr Habboubi and Dr Frans Dhaenens, is to meet with INCTR staff monthly. In addition to discussing progress with sponsorship development, INCTR will host visitors from the corporate world in order to provide them with information about INCTR activities. In this way, INCTR should be able to establish more linkages and partnerships with the corporate world. ■

ONCOLOGISTS TO MEET IN NEW DELHI

The second SIOP-Asia conference, a significant milestone for pediatric oncology in the developing world, will held in New Delhi, India, November 22-24, 2002.

The conference will bring together pediatric oncologists, hematologists, pediatricians, surgical oncologists and radiotherapists practicing in the developing world, with leading pediatric oncologists and health care professionals from around the world.

With the central theme being "childhood cancer is curable," the conference is committed to forging better links between parents and healthcare professionals.

The conference is under the auspices of the International Society of Pediatric Oncology, the Pediatric Hematology Oncology Chapter of the Indian Academy of Pediatrics, the International Confederation of Childhood Cancer Parent Organizations, the Indian Society of Medical and Pediatric Oncology, the All India Institute of Medical Sciences, New Delhi, and INCTR

For further information please contact: Prof. L.S. Arya, Department of Pediatrics, Division of Pediatric Oncology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India. Tel: 91-11-6523147, 6594610; FAX: 91-11-6862663; e-mail: lsarya@aiims.ac.in, lsarya@rediffmail.com. Web site: www.aiims.ac.in. ■

MODEL COMPASSION

Her face has graced the covers of countless fashion magazines. Considered one of the world's most beautiful women, Amber Valletta has modeled for such international fashion houses as Versace, Armani and Donna Karan. She puts on the flawless face of Elizabeth Arden. She has the perfect female form for high fashion.

Yet Amber Valleta's beauty is much more than skin-deep, and her interests go well beyond Prada pumps. Her compassion for others, particularly those with cancer, has distinguished her from all the other pretty faces. A member of the professional advisory board of St. Jude Children's Research Hospital, Valletta recently joined INCTR as an associate member. She intends to assist with fundraising activities and to serve as an INCTR spokesperson.

"Cancer has affected my family greatly," Valletta says. "My mother and both grandmothers had breast cancer. And I learned a lot about cancers from my work with St. Jude's. Michael Saba [INCTR's development officer] brought INCTR to my attention, and it intrigued me because of the importance of treating people with cancer in third world countries. I like to have a bigger view of the world, and there is such a great need. Whatever we do in the U.S. can help the rest of the world. I know that we have the resources to do a lot to fight cancer, and it's really important for us to do our part to aid those who don't have the same resources."

Valletta is planning to participate in a fundraiser for INCTR in Los Angeles, California, to be held later this year. Details are not firm yet, but other fundraisers she has been involved in have taken the form of charity fashion shows and auctions. Her favorite charities include Dishes, Covenant House, World Wildlife Federation, Habitat for Humanity, Special Olympics, The Village for Tibetan Children and the Nelson Mandela's Children's Fund. Because of her interest in breast cancer, she also donates time and money to The Nina Hyde Foundation.

Amber Valletta is helping to raise funds for the INCTR, while elevating its visibility among the general public.

It will be a busy year ahead for Valletta, who is juggling her charitable work with modeling, motherhood (she has a 14-month-old son) and a burgeoning film and television career. Her recent film credits include *Drop Back Ten*, *What Lies Beneath* and *Family Man*. She is presently considering offers for the small screen.

"I'm really excited to be on board with INCTR," she says. "Especially since 9/11, we tend to define ourselves by our borders. We are all one people, trying to communicate through our different cultures. America is very affluent and we can help." ■

--Marcia C. Landskroener

If you or your organization would like to contribute financially to the mission of the INCTR, please contact:

Michael Saba
INCTR, USA
sabamps@aol.com
phone: 901-759-7001
fax: 901-759-2407

PROFILES IN CANCER MEDICINE

DEVELOPING PEDIATRIC ONCOLOGY IN MEXICO

When Dr. Roberto Rivera-Luna first started practicing pediatric oncology, he was one of only two such specialists in his country. Twenty-eight years ago, he used to see as many as 80 patients a day. Thanks to his efforts to establish formal training at the National University of Mexico and elsewhere, today there are 72 pediatric oncologists working throughout Mexico. During the course of his career, Rivera-Luna helped to train 51 of them at his own institution, the National Institute of Pediatrics. Four hospitals—all in Mexico City—are now training physicians in this specialty.

Still, it's not enough.

"My institution is unique among those in under-developed countries because our standards of care and therapeutic results are comparable to those anywhere in the world," says Rivera-Luna. "The problem is that this is one of a few institutions in Mexico that take care of children with cancer. I wish there could be many more. There is a need to really admit a country such as ours has a problem with childhood cancer. Among children ages 4 to 15, it is the second-highest cause of mortality."

Not only is the incidence of childhood cancer in Mexico on the rise, as it is in many developed nations, more children are dying because of lack of care. Thirty-eight percent of children who die of cancer are never diagnosed. Those doctors trained in pediatric oncology are concentrated in urban areas, Rivera-Luna says, making it difficult for families to seek treatment. Even more heartbreaking is the prevailing attitude of many general practitioners and even some adult oncologists who refuse to treat children with cancer.

Roberto Rivera-Luna is director of hematology-oncology at the National Institute of Pediatrics in Mexico City.

Rivera-Luna is leading a national effort to institute outreach programs in the 12 states without any pediatric oncologists. The intent is to encourage adult oncologists and hematologists to diagnose young patients with cancer and refer them for treatment.

"We hope to sensitize physicians to accept their responsibility as physicians, as specialists, and as Mexicans, so they accept pediatric patients and become part of multidisciplinary approach to children," Rivera-Luna says.

Another initiative involves developing regional institutions that can make treatment more accessible. "Some families now come from as far away as 1,000 miles," he says. "There is no need for someone to come from a Tijuana-border town to Mexico City. There is a big pediatric hospital that has an excellent pediatric oncology department in Sonora-150 miles from Tijuana."

As a way to produce more doctors, Rivera-Luna would like to see university hospitals in large cities around the country develop pediatric oncology departments and, eventually, pediatric oncology training programs. When Rivera-Luna was a young physician he worked for a year as a family doctor with Dr. Herbert Nassour at a private hospital in Austin, Texas. With time this man became his mentor.

Dr. Nassour, a Texan of Lebanese extraction, guided Rivera-Luna to return to Mexico and work in rural areas. He did so for a year before going back to the USA to pursue formal training, first as a resident in pediatrics at Baylor College of Medicine and then as a fellow in pediatric hematolgy/oncology, both in Houston, Texas. Once again, as a friend, Dr. Nassour insisted Rivera-Luna go back to Mexico and work for children with cancer from low socioeconomic backgrounds.

"He made a big impression on my professional life," Rivera-Luna recalls. "I remember very vividly, at night after six surgeries, Dr. Nassour would invite me to his home to discuss the philosophy of patient care and the need to develop different approaches to medicine in underdeveloped countries." ■

--Marcia C. Landskroener

HEPATOCELLULAR CARCINOMA

Alternative Names: hepatoma; cancer of the liver; liver cancer; primary liver cell carcinoma; tumor –liver

Hepatocellular carcinoma (HCC) is the most common malignant liver cancer. It has considerable variability in incidence worldwide. Eighty-five per cent of HCCs arise on the background of cirrhosis. The risk of developing HCC seems to be related to the degree of activity of cirrhosis. It is high in macronodular cirrhosis secondary to hemochromatosis (genetic predisposition of excessive iron deposition of iron within the liver) and lower in alcoholic micronodular cirrhosis. There is a strong link with chronic hepatitis B (HBV) & C (HBC) infections. In Korea and Taiwan 80% of patients with HCC have chronic HBV infection. Surgery offers the best chance of survival but the percentage of patients who are candidates for surgical treatment ranges from 3% to 30% depending upon the series. In the author's experience 3% is probably the most accurate figure. Non-surgical treatments are available and the results are encouraging.

CAUSES, INCIDENCE AND RISK FACTORS

In Japan, HCC is the third most common cancer in men. In the United States approximately 9,000 cases occur each year, an incidence similar to Hodgkin's lymphoma. It is one of the most common visceral tumors especially in the high-risk populations of South Eastern Asia, sub-Saharan Africa, Japan, Greece and Italy. The incidence of HCC is rising worldwide. HCC is more common in men than women, with a sex ratio ranging from 3:1 to 6:1. In low incidence areas such as the United States and parts of Europe, the average age at diagnosis is between 60-80 years but in areas of high incidence the patient presents earlier between 30-50 years. A low-grade carcinoma is seen in younger patients, 20-40 years of age, in the absence of underlying cirrhosis.

The risk factors for HCC include chronic liver disease, viral hepatitis, hemochromatosis, known liver carcinogens, and aflatoxin B1 found in foods in parts of Africa and Asia. A fungus growing on peanut (groundnut) meal that has been stored in hot and humid conditions produces aflatoxin. Mutations/deletions of tumor suppressor gene, p53, have been linked to the development of HCC. Epidemiologic studies have linked aflatoxin B1 exposure and p53 mutations. Such mutations are common in HCC in patients from mainland China, Africa, and Mexico where aflatoxin B1 contamination of food is high, and rare in Hong Kong, Singapore, Japan, Europe and in Caucasian patients in the United States where food contains little or no aflatoxin B1. HCC may occur in children and has two age peaks: < 4 years and between 12-15 years. Childhood HCC is associated with essentially all types of cirrhosis due to malnutrition, and certain metabolic or structural congenital abnormalities of the liver. Hepatitis B surface antigen (HBsAg) acquired through maternal transmission may result in the development of a HCC by 10 years of age.

DIAGNOSIS

Patients usually present with abdominal pain or tenderness particularly in the right upper abdomen, swelling of the abdomen due to the liver mass or ascites, easy bruising or bleeding and jaundice. We are detecting increasing numbers of HCCs in patients who are being examined for gallstones by sonography. HCC should be suspected in a person with known chronic liver disease who presents with any of the signs or symptoms listed above. The liver function tests

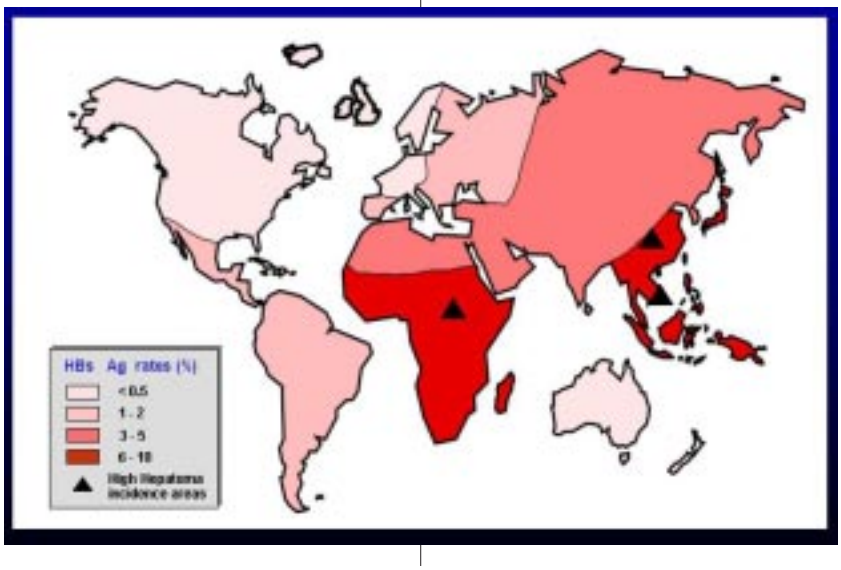

Figure 1: Map of the world showing the incidence of hepatitis B surface antigen and HCC hotspots.

Figure 2: A post-mortem specimen of the liver (bisected) showing a large HCC occupying the upper half of the right lobe (pale colored tumor) invading the portal pedicle (the blood supply to the liver). Note a satellite tumor within the cut left lobe. HCCs are often multiple, which makes surgical treatment difficult. The underlying liver appears very nodular, suggestive of cirrhosis.

Photo courtesy of Dr David Butterworth, Consultant Histopathologist, North Manchester General Hospital

are usually abnormal and a specific protein produced by the liver tumor –alpha-fetoprotein–is raised in approximately three-quarter of patients. Before treatment is considered the tumor needs to be imaged with ultrasound, computed tomography (CAT scan), magnetic resonance imaging (MRI), angiography and image guided biopsy. Not all these scans may be required. The purpose of the scans is to detect cancer, assess operability and detect complications.

Since most patients with HCC have underlying cirrhosis, it is important to use clinical criteria to classify the severity of cirrhosis, which has a considerable bearing on therapeutic decisions. The Child-Pugh classification is usually used to stage cirrhosis into Child-Pugh A, B or C, with Child-Pugh A carrying the best prognosis and Child-Pugh C the worst. The parameters measured to stage liver cirrhosis by the Child-Pugh classification include blood biochemical and clinical criteria. Alternatively, hepatic insufficiency can be staged using a Paul Brousse classification and HCC staged by Okuda staging. Diagnostic imaging not only depicts the primary hepatic disease but also shows the presence of complications and the extent of disease.

NATURAL HISTORY

The natural history of HCC in Asia is said to be different from that in Europe and America. Although the etiology is multifactorial, there is a stronger association with hepatitis B and C viruses in Asia and Africa (see Figure 1). Prognosis in HCC without treatment is poor. Okuda et al have reported an overall median survival of only 1.6 months. In the West, a similar study on unselected patients showed a median survival of 14 weeks, with only 13% surviving more than a year. Surgery offers the best chance of cure but resectability is low. HCC is multifocal in 76% patients with underlying cirrhosis in the majority of patients (81% to 87%) [see Figure 2]. The percentage of patients who are candidates for surgical treatment ranges from 3% to 30% depending upon the series. Our own experience suggests 3% is a more accurate figure. Small tumors less than 3 cm have the best outcome; the three-year survival rate without recurrence is 83% when hepatic transplantation is performed. The results of hepatic resection are poor.

TREATMENT OPTIONS

Numerous treatment options are available for patients with HCC. Surgery offers the best chance of survival with HCC in non-cirrhotic liver or Child-Pugh A patients with stable cirrhosis. Vascular invasion is the most important predictor of survival following resection. The prognosis for patients with unresectable HCC is extremely poor. Chemotherapy is ineffective. Even in the case of small nodular lesions detected by ultrasound screening, patients receiving no treatment had a mean survival rate at three years of 12%. Six minimally invasive techniques are available for treatment of HCC, which include chemoembolization (TACE), ethanol ablation (PEI), radio-frequency ablation (RF), microwave ablation, laser ablation and cryoablation. TACE has been used the longest (since the mid-seventies) whilst the other therapies have been comparatively recently introduced. Among non-surgical options, Percutaneous Ethanol Injection (PEI) can be considered the treatment of choice for patients with small tumors (3 cm or less in diameter). Studies in Japan and in Italy have demonstrated that patients treated with PEI showed high long-term survival rates, comparable to those of patients submitted to surgical resection. The greatest drawback of PEI is the difficulty of treating tumors larger than 3 cm. In such cases alcohol diffusion into the tumor is incomplete. As a result, residual viable tumor tissue can be found after treatment, particularly along the periphery of the nodule.

In the early 1980s it was discovered that when iodised poppy seed oil is injected into the blood supply of an HCC, it is retained selectively within the tumor. Here then, is a vehicle for delivering anti-cancer agents to tumor sites within the liver. This is the basis of TACE. The blood supply of the liver is approached via the groin by a catheter (a tiny tube) under local anaesthetic. A mixture of poppy seed oil and an anti-cancer drug is delivered into the blood supply of the tumor. Anti-cancer drugs delivered this way are retained within the tumor for several weeks and have no systemic side affects (see figure 3). Radio frequency (RF) ablation is suitable for patients with four or fewer 5cm or smaller HCCs. The tumors should be completely surrounded by normal liver tissue and at least 1cm deep to the liver capsule and at least 2cm or more away from major liver vessels. Patients with sepsis, severe debility and blood coagulation disorders cannot usually be treated with RF. Not all patients can be treated with RF but the results are promising.

PREVENTION

Control of known hepatic carcinogens may have a preventive effect. Prevention and treatment of viral hepatitis may be beneficial in reducing risk. In Taiwan, the nationwide vaccination against HBV, administered to all newborns since July 1984, showed effective results, and has been found a successful method to the control of HBV infection in an endemic area. The overall prevalence rate of serum HBsAg decreased significantly, from 9.8 % in 1984 to 1.3 % in 1994. Evidence that HBV vaccination reduced the average annual incidence of HCC in children was also obtained. The incidence in children 6 to 14 years of age declined from 0.70 per 100,000 between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994. The corresponding rates of mortality from HCC also decreased. The mortality rates of HCC in children 6 to 9 years of age declined from 0.52 for those born between 1974 and 1984 to 0.13 for those born between 1984 and 1986 - after universal vaccination was initiated in Taiwan. A vaccine for HCV has not yet been developed. However some evidence has emerged that antiviral therapy may be affective in some patients with HCV. In children, tackling malnutrition may reduce the risk of HCC from malnutrition associated cirrhosis. A future development may be gene therapy against inherited metabolic liver disorders. Long-term abstinence from alcohol is the single major factor that may modify the course of liver disease in the alcoholic and thus prevent the development of HCC. ■

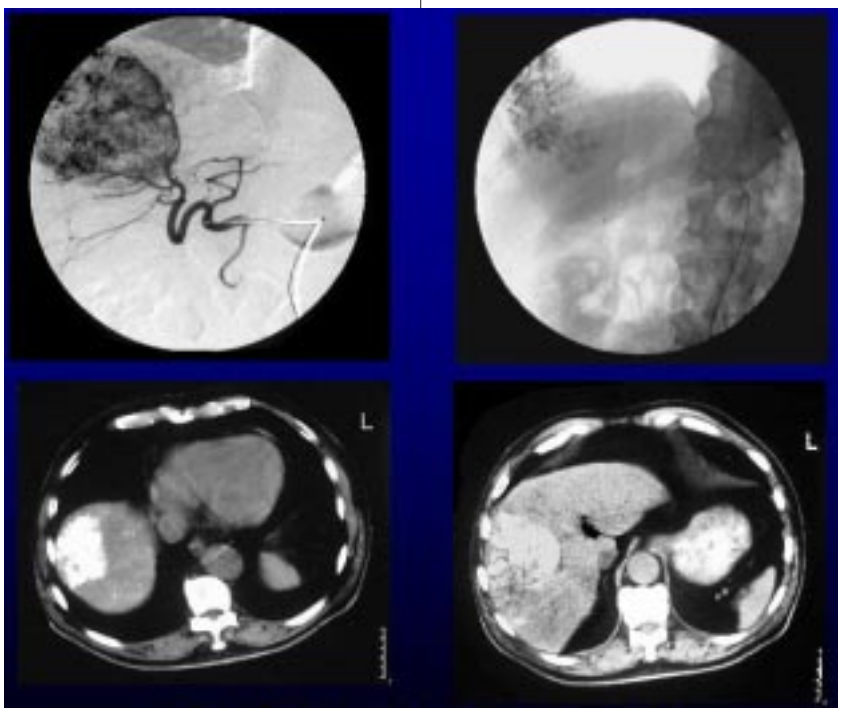

Figure 3: The procedure of TACE. The top left picture shows a catheter within a blood vessel, demonstrating an angry-looking blood supply to the tumor (top left corner). The top right picture, taken following TACE, shows concentration of the poppy seed oil (along with an anti-cancer drug) within the tumor (the black grainy appearance in the top left corner). The bottom two pictures are CAT scans taken ten days following TACE, showing intense concentration of the poppy seed oil (along with the anti-cancer drug), which appears white within the HCC.

--Ali N Khan FRCP, FRCR
Consultant Radiologist, North Manchester General Hospital, U.K.

A list of references to this article is available on request to the INCTR.

A TALE OF TWO CHILDREN WITH LIVER TUMORS (…IN THE SAME CITY!)

A three-year-old boy was admitted to a major hospital in a large city in Saudi Arabia with upper abdominal swelling. Imaging revealed a mass in the liver and a blood test showed thrombocytosis and an extremely high serum level of alphafetoprotein (α–FP). There were no lung metastases. A needle biopsy of the mass confirmed the clinical diagnosis of "hepatoblastoma". After the biopsy, the child deteriorated with increasing abdominal girth, pleural effusions and hypoalbuminaemia and was transferred to the Intensive Care Unit (ICU) where he continued to deteriorate, despite supportive care including fresh frozen plasma, diuretics and parenteral nutrition. He was judged to be "too ill for chemotherapy," despite advice to the contrary from a paediatric oncologist. He died six weeks after admission, having had no cancer treatment whatsoever.

A 10-month-old girl was admitted at around the same time to a different hospital in the same city also with a large upper abdominal mass and a very high serum α–FP level. Biopsy confirmed hepatoblastoma and a CT scan of the lungs showed no metastases. Within a few days she was treated with cisplatin and doxorubin ("PLADO") chemotherapy at doses and on a schedule similar to that of the International Society of Pediatric Oncology's first collaborative liver tumor study (SIOPEL-1). The patient's condition stabilized and then steadily improved, with reduction of abdominal girth and a steep fall in serum α–FP levels. After four courses of PLADO given at 3-4 weekly intervals and with only one complication—an episode of febrile neutropenia, which rapidly resolved after broad-spectrum intravenous antibiotic treatment—she was referred to a tertiary pediatric surgical center for removal of the primary tumor. Near-complete excision was successfully achieved though a small amount of tumor, immediately adjacent to the hepatic artery and vein, was so closely adherent to these vessels that the risk of removal was deemed unacceptable. Histopathology examination confirmed that there was major tumor necrosis due to the chemotherapy with only around 10% residual viable tumor in the resected mass, most of which comprised scar tissue. After 48 hours in the ICU the baby—now 13 months old—returned to the children's ward. She left hospital on the fifth post operative day and completed her treatment with two more courses of PLADO, via a Portacath which had been placed during her stay in the tertiary care center. At the end of treatment she showed no evidence of tumor in the liver, which had already regenerated to a virtually normal volume for her age and also normal cardiac, auditory, renal and hepatic function and a normal serum α–FP level. Some four months after the end of all treatment she remains well, is developing normally and is on the fiftieth percentiles for both height and weight.

COMMENT

Recent clinical trials have convincingly demonstrated remarkable improvement in the prognosis of children with liver tumors, especially hepatoblastoma. In the SIOPEL 1 study, for instance, relapse-free survival—with a median follow-up of four to five years—was 70-80%. Even children with metastases in SIOPEL 1 had a 30-40% chance of cure. Comparable figures as recently as the late 1970s were 20-30% and <10%, respectively. An article describing the SIOPEL studies—past and present—will appear in a future edition of *Network.* Suffice it to say, for the moment, that the chemotherapy regimes are relatively straightforward and, so long as there is a central venous access device and appropriate monitoring, well tolerated. Radiotherapy is hardly ever needed. The timing of surgery and the choice of surgical center are crucial. These themes will be developed further in the upcoming SIOPEL trials review—so watch this space! ■

-- Jon Pritchard
Jeddah, Saudi Arabia

NEWS

continued from page 5

In Kuwait, Dr Magrath met the Minister of Health, Dr Mohammad Al-Jarallah, and visited the Juma Cancer Center as well as other hospitals. With a high standard of clinical care, Kuwait may have as much to give to the INCTR network as to gain from it. Discussions are continuing as to how best to develop a mutually beneficial relationship. ■

NEW STAFF

INCTR welcomes two new staff members. Renate Smith has joined the Clinical Trials Office as a data manager. Michel Caprasse has joined the administrative staff, and has primary responsibility for the INCTR's new database. ■

PHILIPPINE CHILDREN'S MEDICAL CENTER

The Philippine Children's Medical Center (PCMC) in Quezon City is the country's premier pediatric tertiary care facility. It was created by Presidential Decree in 1979, and is now administratively attached to the Department of Health as its flagship hospital for children.

The hospital offers services in almost all areas of pediatric medicine. Some services—such as pediatric dermatology, pediatric dentistry and perinatology—are either the first in the country or unique to PCMC.

The majority of patients at PCMC have infectious diseases, mainly respiratory and diarrheal illnesses, but cancer cases, especially hematologic malignancies, are the second major cause of hospitalization. Oncology patients account for approximately 17% of inpatient service admissions. This high volume of pediatric patients permits the institution to maintain high quality training and research initiatives. The concentration of subspecialty cases in some pediatric disciplines, e.g. cancer, is seldom duplicated elsewhere in the Philippines.

The ten most commonly seen types of cancer are ALL, AML, non-Hodgkin's lymphoma, germ cell tumors, medulloblastoma, gliomas, neuroblastoma, rhabdomyosarcoma, retinoblastoma and osteosarcoma. There are about 250 in-house interdepartmental referrals each year.

FELLOWSHIP TRAINING

The hospital runs one of only two accredited post-residency fellowship training programs in pediatric hematology-oncology in the country. The three-year program includes clinical rotations in various disciplines during the first two years, with the last year devoted to research. This program started in 1991, and so far has graduated twelve fellows. Seven are already board-certified diplomates of the Philippine Society of Medical Oncology, while the remaining five are board-eligible. All of them are playing important roles in establishing cancer care programs in their hospitals in various parts of the Philippines.

With sophisticated laboratory, imaging and nuclear medicine and well-trained medical and supporting staff, PCMC offers the best pediatric medical care in the country.

HOSPICE CARE

The Hospice Care Service was started in 1995 to provide long-term support to cancer patients and their families, including pain and/or symptom management. Both hospital and home visit teams participate in these services. This multidisciplinary team not only provides the vital link between hospital and home-based care, but also facilitates financial support to patients from various sources.

RESEARCH & DEVELOPMENT

The Research and Development Office, created in 1992, was charged with developing strategies and action plans for building institutional research capability. Under the Office of the Executive Director, it was empowered to formulate policies, rules and regulations necessary to establish the hospital as a research center.

Aside from developing the organizational and operational systems for research, RDO has created an Institutional Review Board and codified all policies, rules and regulations on research activities into a Research Primer. The Office has also designed training programs for researchers; rationalized the allocation of research funds, and instituted a system of fund disbursement and monitoring within the government accounting system.

PCMC adapted the "Essential National Health Research" concept. Consequently, research that results in the provision of tools for decision-making or a guide for policy is particularly encouraged. Areas in which PCMC has demonstrated pre-eminence or sole expertise are particularly emphasized. Priorities include pediatric oncology, pediatric neuroscience, genetics and perinatal medicine. Multidisciplinary collaboration and multi-institutional approaches in research projects are of particular importance.

Research capability building is now focused on three areas: research infrastructure, research manpower training and international linkages.

CANCER RESEARCH

A pediatric cancer registry has been given priority in order to gain baseline clinical epidemiological data upon which both clinicians and researchers can better understand the local behavior of the disease, and guide them in defining future priorities for research and/or interventional educational programs. We hope to gain insights on why patients present in the late stages of their diseases, or why they do not complete their prescribed treatment. In addition, we should be able to compare clinical behavior patterns with western patients in the same histological and treatment groups.

In response to limitations in resources for cancer treatment in a financially challenged country like the Philippines, locally adapted and cost-effective protocols are studied. The main goal is not to rival the cure rates seen in advanced countries (although that is desirable), but to at least improve by 50% our current track record of survival rates. This goal entails not only local treatment protocols but embraces educational programs (under a research framework) that focus on improving cancer early detection, treatment and follow-up, as well as enhancing the competence of the care-givers (focused and rationalized around internationally-funded projects).

Lastly, a tumor tissue bank has been established to provide specimens for future studies, and linked to the database of clinical information gathered under the clinical registry. This will later allow us to understand the genetic aspects of our cancers as they relate to clinical outcomes to better tailor specific cost-effective treatment to specific groups of patients.

LOOKING AHEAD

We will continue to focus on our training program in pediatric hematology-oncology in order to create a critical mass of experts and scientists that are needed to improve our standards of cancer care. The ultimate goal is to distribute this expertise across the country, but link resources more effectively for the sharing of information and synergy of services. This is critical for a country like the Philippines that is composed of many islands, posing geographic barriers to patient access to care.

We will continue to use our own clinical data and those of countries at similar socioeconomic levels to drive our clinical and research initiatives. Lastly, we will link with selected international partners for the long-term. Our goal is developmental. Therefore, we hold the holistic view that treatment protocol projects, for instance, must be brought to a programmatic level where it becomes likewise the nidus for manpower skill, competence development, and mutual transfer of information that will have a lasting impact. This is the framework in which we view our partnership with the INCTR.

Ultimately, working with INCTR, we hope to help create a research-oriented culture among a community of resource-challenged countries like ours, in partnership with advanced countries, and make research the tool for decision-making, with a resultant beneficial impact on outcomes for our patients. ■

--Julius A. Lecciones, M.D.
Chief Research Officer, PCMC

BY THE NUMBERS

Patient Population Per Annum	
Total Outpatients	60,000
Total Inpatient Admissions	9,000
Cancer Outpatients	2,500
Cancer Inpatient Admissions	530
Number of Beds	200
Attending Pediatricians	163
Medical Residents Per Annum	60
Post-Residency Fellows Per Annum	50
Indigent Patients	60%
Paying Patients	40%