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THE PRESIDENT'S MESSAGE

DENIS BURKITT AND THE AFRICAN LYMPHOMA

by Ian Magrath

DISCOVERY OF THE TUMOR

Denis Parsons Burkitt was born in 1911 in Enniskillen, the picturesque county town of Fermanagh, now in Northern Ireland. "Enniskillen" is derived from a Gaelic word meaning Ceithleann's island, the town being situated on an island between two loughs (lakes) connected by the river Erne. According to Irish mythology, Ceithleann was the wife of Balor, the one-eyed king of a race of giants – a mythology that has echoes in Burkitt's life. Sadly, at the age of 11, young Denis suffered an injury that led to the loss of an eye. Although this hampered his eyesight and, to a degree, his subsequent career as a surgeon, it had no effect on his insight. Burkitt doubtless inherited some of his observational skills from his father, James Parsons Burkitt, a civil engineer, but also an amateur ornithologist who was one of the first to use the technique of ringing or banding to recognize individual birds, allowing



Figure 1. Lake Victoria, Uganda. The regions surrounding the lake are high incidence regions for Burkitt lymphoma. Picture from Wikipedia Commons taken by D. Luchetti.

him to meticulously map their territories. James Burkitt's maps must have impressed his elder son, who was later to map the distribution of the "African lymphoma" (Figure 1). Dennis Burkitt, attended the Portara Royal School at Enniskillen, one of five free schools founded by Royal Charter in 1608 by King James I. In this respect he followed in the

footsteps of two Irish literary giants, Oscar Wilde and Samuel Beckett who, like Burkitt, also continued their education at Trinity College, Dublin. Burkitt, without a clear idea of his future, had taken up engineering at Trinity College. He joined the University Christian Society, which gave new meaning to his life; he decided that his calling was to

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become a missionary. This, perhaps coupled to sharing a room with a medical student, led him to give up his engineering studies and instead, take up medicine. After completing his studies he decided to become a surgeon – somewhat surprising, perhaps, in view of his lack of binocular vision – and completed his basic training shortly before the Second World War.

Burkitt took a position as ship's doctor before applying for a post in the colonial medical services. Unfortunately, he was turned down because he had only one eye. After other unsuccessful applications for an overseas posting, he decided to join the Army Medical Corps and, after working in England for a while, was sent to Africa, where he served in Somalia and Kenya. Once, he

spent leave in Uganda and visited the old Mengo Hospital, where the first missionary doctor to Africa, Sir Albert Cook, had worked, as well as the Mulago teaching hospital in Kampala, where he himself would later work. This experience, coupled to his evangelical zeal – and possibly the example of his Uncle Roland, who practiced surgery in Nairobi – convinced him that he was destined to serve in Africa. In 1946, therefore, Burkitt again applied to the British Colonial Office for a post. This time he was accepted and was appointed to the position of District Medical Officer in Lira, a small town in the Northern Lango district of Uganda. While there, he noted a high incidence of hydrocele, caused by mosquito-born filarial worms that block lymphatic vessels, and was able to show that the incidence was much higher in the eastern part of Lango (30% of men) than the western region (1%). This experience, too, must have sensitized him to geographic epidemiology while impressing upon him the important role of arthropod vectors in transmitting disease in Africa – a lesson that served him in good stead in the context of the African lymphoma. Burkitt had been in Lira for only 18 months when he received a telegram summoning him to Mulago Hospital (Figure 2) where Ian McAdam, the only other formally trained surgeon in Uganda at the time, had become ill. McAdam, who subsequently became the head of the Department of Surgery in the University Hospital, was to become a strong supporter of Burkitt's subsequent work.

It was not until 1957 that Burkitt saw his first case of multiple jaw tumors (i.e., bilateral maxillae and



Figure 2. Map of Africa showing the "lymphoma belt" in which Burkitt lymphoma occurs at high incidence. Lower incidence areas (e.g., highlands) within this zone are not shown.

mandibles) in a 5 year-old-boy he was asked to see in the children's ward at Mulago hospital by the pediatrician, Hugh Trowell. A biopsy report described the tumor as a "small round cell sarcoma." Burkitt was unable to offer any advice on treatment, although the gross facial distortions caused by the jaw tumors made a big impression on him. Shortly afterwards he saw a second child, with tumor in all four jaw quadrants, during a regular visit to a hospital in Jinja, a small town situated where the river Nile flows out of Lake Victoria (one of the illusive sources of the Nile sought by the European explorers, Burton and Speke). This second child also had tumors in the abdomen. Like the first, his disease had been diagnosed as a small round cell sarcoma. The coincidence of seeing two children with jaw tumors in quick succession led Burkitt to examine the records of other patients seen in Mulago hospital. He identified 29

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other children who had presented with jaw tumors, although many, like the child in Jinja, had additional disease at other sites, including the orbit and abdomen, salivary glands, nervous system and elsewhere (Figure 3). Most of these tumors were diagnosed as small round cell tumors and variably reported, according to the sites of disease, as sarcoma, retinoblastoma, germinoblastoma, Ewing's sarcoma, Wilms' tumor or neuroblastoma.

Although several European pathologists working in Africa had observed the high incidence of jaw tumors, and of lymphomas in children with cancer many years before Burkitt saw his first case, Burkitt was the first to describe the clinical syndrome. He proposed that all the children with jaw tumors, regardless of other sites of disease, were probably suffering from the same disease. His first paper, entitled "A sarcoma involving the jaws of African Children" was published in the *British Journal of Surgery* in 1958 (vol. 46, 218-213). This aroused little interest, since the disease offered limited scope for surgery. However, unknown to Burkitt, Gregory O'Connor and Jack Davis,

pathologists also working at Mulago Hospital, were in the process of surveying the malignant tumors in children in the Mulago Hospital Registry that had been initiated seven years before. In fact, Davis had earlier observed that approximately half of the childhood tumors were derived from the "reticulo-endothelial system" and O'Connor's and Davis' more extensive review, which included children without jaw tumors, confirmed this. It soon became clear that the tumor described by Burkitt was a lymphoma and, in 1961, Burkitt and O'Connor published additional papers in the journal *Cancer*, bringing it to the attention of cancer specialists. Although it seemed initially that the tumor was confined to Africa, it was subsequently recognized that histologically identical lymphomas occur throughout the world, although at a much lower incidence and with some differences at clinical (Figure 4) and molecular levels from the African lymphoma. The relationship of Burkitt lymphoma to ALL was frequently discussed since the latter disease was rarely seen in Africa. Dalldorf reported in 1962 that ALL, the commonest

childhood malignancy in the USA, was the least common in East Africa, accounting for only 1-3% of childhood cancers in several published series. ALL remains uncommon in Equatorial Africa today – but that is another story.

DISCOVERY OF EPSTEIN-BARR VIRUS

A few months after the publication of Burkitt's first paper, Dr George Oettle, a cancer specialist from South Africa, visited Kampala, and Burkitt was intrigued to learn from him that he had never seen children with a similar clinical syndrome in South Africa. This observation, influenced, perhaps, by his earlier work on hydrocele, led Burkitt to think about the geographical distribution of the tumor. Was it widespread throughout Africa, or confined to certain regions? Burkitt hung a map of Africa on the wall of his office and started to indicate places where children with jaw tumors had been seen. He sent 1,000 brochures to government and mission hospitals throughout Africa and started to plot the "lymphoma belt" shown in figure 1. By now, several research organizations were interested in the tumor and Burkitt was given several grants, totaling £700, which enabled himself and two friends, Ted Williams and Cliff Nelson, both missionary doctors, to undertake a safari to define the southern limit of the high incidence zone on the Eastern side of Africa. Burkitt and his co-researchers set off from Kampala on October 7, 1961 in a 1954 Ford station wagon and returned 10 weeks later, having visited some 57 hospitals in eight countries and travelled 10,000 miles. Although imprecise by today's standards, the



Figure 3. Children with Burkitt lymphoma showing multiple disease sites.

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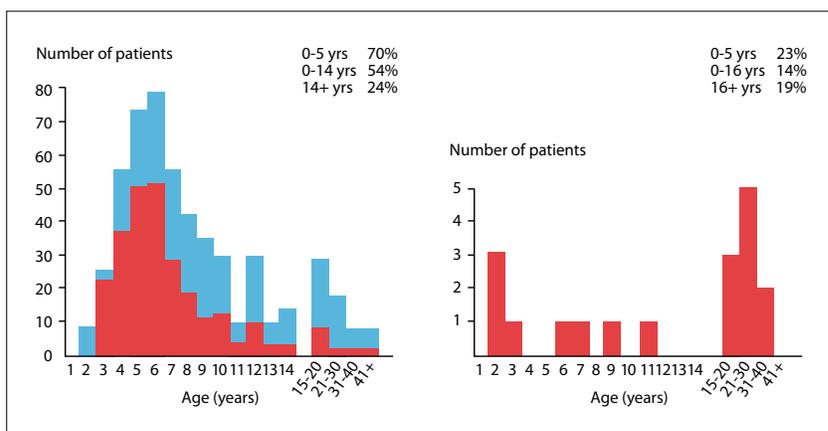


Figure 4. Age distribution of Burkitt lymphoma and fraction of patients (red columns) with jaw tumors. Jaw and orbital tumors are particularly common in young children in African Burkitt lymphoma, but not in Burkitt lymphoma in the USA.

characteristic jaw tumors provided a powerful marker of the occurrence of the tumor, and Burkitt and his friends were able to show that the “tumor belt” extended to Lourenço Marques in southern Mozambique. Having defined in some detail the high incidence regions, it appeared that in East Africa, at least, the barrier to the occurrence of Burkitt lymphoma was altitude. Burkitt discussed this with Alexander Haddow, director of the East African Virus Research Institute in Entebbe. Haddow studied Burkitt’s map and pointed out that the altitude barrier occurred at 5,000 feet at the equator (which passed through Uganda) and became progressively lower with the distance from the equator. This strongly suggested that temperature rather than altitude constituted the true barrier, as had already been shown for a number of insect-borne diseases, particularly those vectored by mosquitoes. Additional visits by air to Rwanda, Burundi, Kinshasa (Leopoldville at the time), Nigeria and Ghana, confirmed the importance of altitude/temperature but also led to the rec-

ognition that low-lying areas where the tumor did not occur were arid regions, such as Kano in southern Nigeria. It seemed that the tumor was common in regions with temperatures that did not fall below 60° Fahrenheit, as long as there were at least 20 inches of rainfall per year – conditions required for mosquitoes to breed.

On seeing Burkitt’s new, improved map, Haddow confirmed that the distribution of the tumor conformed closely to the distribution of number of diseases known to be transmitted by insects, including trypanosomiasis (sleeping sickness), yellow fever, and the recently recognized O’Nyong Nyong. The findings seemed to be consistent with earlier research, particularly in the USA, that had demonstrated that malignancies in animals, particularly sarcomas and leukemias, could be transmitted by viruses, although no one, at that time, had succeeded in identifying a human tumor virus.

Meanwhile, Burkitt had been receiving many invitations to speak. One of his lectures, given at the

Middlesex Hospital in London in March 1961, was attended by a pathologist interested in virology, Michael Anthony Epstein. Impressed with the possibility that the lymphoma could be caused by a mosquito-vectored virus, Epstein approached Burkitt after the lecture and asked him to send some tumor samples to London in order to search by electron microscopy for virus particles in the tumor cells. Initial studies of tumor cells flown in from Uganda were negative, but Epstein and Barr succeeded in developing several continuously growing cell lines from the tumor cells. In the first of these, Epstein Barr-1 (EB1), Epstein and his co-workers, Achong and Barr, were able to identify herpes-like virus particles in a small fraction of the cells. Unable to demonstrate reactivity with sera derived from patients known to be infected with other herpesviruses, it was clear that this was a previously undescribed virus and potentially the first human tumor virus. The report of their discovery was published in 1964 – just a few years after the recognition of the unusual distribution of the African lymphoma.

It has subsequently become clear that all tumor cells (and derived cell lines) in African Burkitt lymphoma contain multiple copies of the EBV genome, although the viral genome is present in only 1-10 per million circulating B lymphocytes (B lymphocytes, which are involved in antibody production, are the cell lineage in which EBV persists throughout life). This alone suggests an important role for EBV, since African Burkitt lymphoma clearly occurs preferentially in the small fraction of EBV-containing cells. It was also demonstrated that EBV can “transform”

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resting B cells into large proliferating cells, suggesting that EBV could be the driving force to the growth of Burkitt lymphoma. This proved to be wrong, however, for although EBV can "immortalize" normal B lymphocytes in vitro and induce them to proliferate, in doing so it expresses 9 viral genes (so-called "latent" genes) whereas only one of these genes, Epstein Barr virus nuclear antigen 1 (EBNA-1), along with some untranslated RNA molecules, are expressed in Burkitt lymphoma. EBNA-1 is known now to be responsible for the replication of the viral genome, and for maintenance of the same number of genome copies in daughter cells. It does not drive proliferation. Actual virus is rarely produced in tumor cells because it is associated with cell disruption (lysis), allowing virus to escape and infect other cells or other people (an essential part of its life cycle). Thus, cell lines or tumors could not survive and the virus would not persist throughout life if all infected cells produced virus. We now have a detailed understanding of the structure and function of various EBV proteins, but the precise mechanism(s) whereby EBV contributes to the development of Burkitt lymphoma remains ill-defined.

A ROLE FOR MALARIA

The geographical studies carried out by Burkitt and others suggested to most that the African lymphoma was a rare manifestation of a common virus infection transmitted by mosquitoes. The subsequent discovery of EBV seemed to confirm this. However, it is now known that EBV is not transmitted by mosquitoes, but via saliva. In societies of low socioeconomic status, there are many opportunities for saliva

exchange, particularly mothers to infants. For example, in the absence of puréed baby foods, mothers often pre-chew the food they give to their infants during the weaning process. Thus, EBV infection, which in any case occurs throughout the world, cannot explain the high frequency zone of Burkitt lymphoma in Africa. Interestingly, in the same year that EBV was discovered (1964), another explanation for the climatically determined distribution of BL was suggested – malaria. This possibility, first expressed in print by Gilbert Dalldorf, a microbiologist from Sloan-Kettering Institute in New York, had been heavily overshadowed by the vectored-virus hypothesis. By now, Burkitt's enquiries had established that the tumor was also common in Papua New Guinea, and Dalldorf, in a detailed epidemiological study, pointed out that malaria was holoendemic in both equatorial Africa and New Guinea, and that repeated infections were nearly universal in the first year of life with variation in the intensity of infection being related to temperature and rainfall, which influence the breeding of mosquito vectors (*Anopheles* species) of malaria. He noted that in Kenya, the highest incidence rates of holoendemic malaria and the African lymphoma occur in identical areas – along the coast of the Indian Ocean and the shores of Lake Victoria. Goma, also in 1964, presented evidence based on extensive surveys in two districts in Uganda that Burkitt lymphoma tends to occur in communities which are very close (within a mile) to permanent or semi-permanent surface water, whether in the form of swamps or lake-edges, where mosquitoes breed. This doubtless explains why

Burkitt lymphoma has a higher frequency in rural regions.

Burkitt and others began to explore the malaria (or "alternative") hypothesis and made a number of tantalizing observations. In the islands of Zanzibar and Pemba off the coast of Tanzania, and Leopoldville (now Kinshasa), intensive malarial eradication programs (directed at mosquitoes) had dramatically reduced the frequency of malaria (from 70% to less than 5%). In each case, in spite of the favorable climatic characteristics, Burkitt lymphoma had not been reported. Since then (in the case of Zanzibar, since 1964), the DDT-based eradication programs have been halted and malaria has returned to these regions – along with Burkitt lymphoma. In a meeting held in 1967, Barnley pointed out that topography also influences the ecology of arthropods. Steep river valley slopes, for example, are not conducive to the persistence of temporary rain pools fully exposed to the heat of the sun, which are the preferred breeding places for *Anopheles gambiae* mosquitoes, and are generally devoid of malaria. He also stated that large bodies of fresh water (such as Lake Victoria) provide the major breeding grounds for *Anopheles funestus*. These findings were consistent with a role for a disease born by anopheline mosquitoes, but did not prove that malaria was the disease in question, although the relationship between the intensity of malarial infection and the occurrence of Burkitt lymphoma has been confirmed by a number of more recent studies in both East and West Africa.

Much later, Geser, Brubaker, de Thé and others conducted clinical

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studies in the North Mara district of Tanzania designed to study the role of malaria directly. In this region, active searching for cases of BL had been ongoing since 1970, permitting the measurement of incidence rates, along with surveys of malaria parasitemia and antibody levels). With this background information in hand, malaria prophylaxis (using a dose of chloroquine every two weeks) was initiated in all children aged 1-10 years for a period of five years (1977-82). The incidence of malaria parasitemia initially fell to the lowest levels ever recorded, and the incidence of Burkitt lymphoma also dropped considerably (from four to one per 100,000 per year) and remained statistically significantly lower throughout the five year period, beginning to rise only after discontinuation of chloroquine prophylaxis (Table 1). However, the drop in incidence appeared to have begun prior to the administration of malaria prophylaxis, although this did not reach statistically significant proportions. This could have been by chance alone, since the relatively small population of people in the North Mara lowlands where the trial took place - approximately 140,000 at the beginning of the study - is likely to result in a somewhat unstable annual incidence rate, although rates as low as those observed during the period of prophylaxis had never previously been seen. In addition, it was found that there were defects in

the system of distribution of chloroquine, which presumably accounted for the increase in parasitemia rates that began after only two years of prophylaxis. Thus, although these results are very suggestive of a role for malaria in the genesis of African Burkitt lymphoma, they are generally not considered to be definitive.

CHARACTERISTIC CHROMOSOMAL TRANSLOCATIONS AND THE DEVELOPMENT OF BURKITT LYMPHOMA

In 1975, a characteristic chromosomal translocation (t8;14) was discovered by Zech and colleagues in Burkitt lymphoma. Subsequent molecular studies in the 1980s demonstrated that this and related "variant" translocations resulted in the juxtaposition of an immunoglobulin gene (the genes responsible for the production of antibodies) to an oncogene called MYC - a gene heavily involved in a variety of critical cellular pathways including growth and programmed cell death (apoptosis). After many years of research, it is now believed that the ectopic (inappropriate) expression of MYC in B cells undergoing an immune response, most often caused by regulatory elements in the adjacent, translocated immunoglobulin gene, is the principle cause of the rapid, uncontrolled growth of Burkitt lymphoma cells.

Overall, the evidence suggests that

at least one mosquito-borne disease, most probably malaria, predisposes to the development of Burkitt lymphoma. Malaria causes profound hyperplasia (overgrowth) of B lymphocytes - the cell lineage from which Burkitt lymphoma is derived. It also results in an increase in the proportion of circulating memory B cells infected by EBV, strongly suggesting that the total body burden of EBV is also increased. This could result in an increased likelihood of the occurrence of the specific chromosomal translocations that are the proximate cause of Burkitt lymphoma. EBV probably also contributes directly to the development of the tumor, perhaps by inhibiting cell death by apoptosis, which would otherwise be induced by the inappropriate expression of MYC.

DISCOVERY OF THE RESPONSE TO CHEMOTHERAPEUTIC AGENTS

While the epidemiological questions raised by the observations made in Africa were intriguing, Burkitt and other clinicians in Africa were faced with the pragmatic problem of managing children with this disease. Surgery was hardly an option - even on the rare occasions when tumor could be entirely removed, regrowth almost always occurred. Radiotherapy was not then available in equatorial Africa (even now, there are very few radiotherapy facilities in this region), but by the late 1950s a number of chemotherapeutic agents had become available and several were known to be particularly active in childhood ALL. It was clearly of considerable interest to know whether Burkitt's lymphoma responded to chemo-

| | 1964-1976 | 1977-1982 | 1983-1987 |
|-----------------------------------|-----------|-----------|-----------|
| Cases (male and female, all ages) | 85 | 15 | 41 |

Table 1. Cases of Burkitt lymphoma recorded in the North Mara District of Tanzania in three sequential time periods. Chloroquine prophylaxis was given in the middle period.

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therapy. Joseph Burchenal, a pioneer chemotherapist working at the (then) Sloan-Kettering Institute for Cancer Research in New York, visited Burkitt in Uganda in 1960 and persuaded him to administer methotrexate – one of the drugs Burchenal had been working on in the context of ALL – to two children with Burkitt lymphoma. In both cases, a single dose induced dramatic tumor regression. This experience encouraged Burkitt to try other drugs, including cyclophosphamide. Subsequently, investigators in Africa, including Burkitt in Uganda, Clifford in Kenya, and Ngu in Nigeria, aided by western experts in chemotherapy, such as Oettgen and Burchenal from the Sloan-Kettering Institute for Cancer Research in New York, and David Galton from the Chester Beatty Institute in London, collaborated in documenting the response of Burkitt's lymphoma to various chemotherapeutic drugs, often donated by the pharmaceutical industry. Although these studies were not conducted in the disciplined way in which clinical trials are carried out today, and a significant fraction of patients was lost to follow-up, they led to the clear demonstration that Burkitt's lymphoma was responsive to a broad range of chemotherapeutic agents. Burkitt, Clifford and Ngu reported some astonishing apparent cures with minimal therapy (several years of disease-free survival after only one or two cycles of therapy). In Burkitt's series of 90 patients with jaw tumors treated at Mulago Hospital, Uganda, 74, or 82%, of the 90 patients had a good response. Complete, durable remissions were observed with all three agents, although response depended upon the tumor size. Burkitt also noted



Figure 5. Staff and patients of the Lymphoma Treatment Center in the Mulago Hospital complex in the early 1970's towards the end of the period of collaboration between Makerere University and the National Cancer Institute, USA.

that recurrent disease, whether at the same or different sites, did not occur after 11 months of remission, i.e., patients free of disease at this time could be considered cured.

These early results laid the foundation for subsequent studies. Notable among these were clinical trials conducted in Uganda as part of a cooperative agreement between the National Cancer Institute of the USA and the University of Makerere in Kampala, Uganda (Figure 5). The emphasis eventually moved to drug combinations based on the most active drugs identified that led to a combination known as COM (cyclophosphamide, vincristine and methotrexate), which is the foundation of INCTR's ongoing studies in the treatment of African Burkitt lymphoma (including AIDS-associated Burkitt lymphoma). In the USA and Europe, much more intensive drug combinations have since been developed, which have resulted in overall

survival rates in the region of 90%.

Burkitt lymphoma has provided a model for the understanding of the epidemiology, the molecular abnormalities that induce tumors, and the treatment of other lymphomas. It is important to remember that the early phases of this work were conducted in Africa where today, unfortunately, the disease usually results in death because of limited resources, even though most children in more developed countries are cured. This must be changed. In addition, it is time to re-explore, with modern techniques, some of the questions that were raised some 50 years ago shortly after Burkitt's first description, as well as new questions that can be asked only in the light of modern understanding of the immune system and the molecular basis of tumor development. The African lymphoma has taught us much, but there is a great deal still to be learned. ■

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PROGRESS REPORT *MY CHILD MATTERS* (MCM) PROGRAM – KENYA

EDUCATION FOR EARLY DETECTION AND TREATMENT OF BURKITT LYMPHOMA AND DETERMINATION OF ENVIRONMENTAL/FAMILIAL FACTORS ASSOCIATED WITH ITS OCCURRENCE.

BACKGROUND

Burkitt lymphoma (BL) is a cancer found mainly in children. It occurs sporadically throughout the world and in endemic pockets in the tropical belt of Africa. In Kenya the disease is seen in Lake Victoria region and the coastal lowlands. This study has so far shown that about 100 cases are reported annually in Western Kenya, which is also known to have widespread poverty. As in other low resource countries, treatment of BL is not readily available in Kenya and outcomes tend to be poor.

OBJECTIVES

The primary objectives of this project are to determine knowledge,

The *My Child Matters* program is a joint endeavor of UICC and sanofi-aventis designed to provide support for institutions or non-governmental organizations working in resource-limited countries in the general area of childhood cancer.

Funding is based on grant proposals submitted to a steering committee from pre-selected countries – more are added each year – on any topic relevant to the care of children with cancer or support for their families.

Each project is assigned a mentor, usually a member of the steering committee to advise on the conduct of the project and assists awardees to achieve their goals.

This unique program was initiated in 2005 and to date 33 grants have been awarded for a broad range of projects in 21 countries.

attitude and practice (KAP) concerning BL among communities living in Nyanza and Western provinces of Kenya and to educate rural communities as well as primary health care providers about signs and symptoms of the disease in order to encourage patients to seek early treatment. This will ensure that health care providers are both familiar with manifestations of the disease and know where to refer patients. In addition, we hope to identify any tendency for the disease to cluster in particular districts and to identify, through a question-

naire, potential risk factors for the disease. This report describes progress made since the project began in April 2007.

ACTIVITIES AND RESULTS TO DATE

CASE RECRUITMENT & COMMUNITY EDUCATION

A total of 156 cases, comprising 81 patients with BL and 75 controls, have, as at the time of this report, been registered on-study. They come from 17 districts in Nyanza and 8 districts in Western Province. Education about the clinical characteristics of the disease has been undertaken by the project team in 75 case neighborhoods in 25 districts in Nyanza and Western provinces. In each of the neighborhoods, selected because of a prior referral of a child with Burkitt lymphoma, 5 to 40 participants have attended the educational sessions. These sessions have been accompanied by pre- and post-assessment of KAP. In this respect, training on data collection for 16 community health workers (CHWs) in Migori District was followed by baseline (pre-education) KAP assessment through the administration of 768 questionnaires in a population of about 335,252 in the last week of



Contributors to *My Child Matters* program, Kenya.

November 2008 in five administrative divisions. Similar training was provided to an additional 16 CHWs from Siaya and Bunyala Districts followed also in late November by baseline KAP assessment through the administration of 720 questionnaires to 180,797 people spread in 12 locations.

WORKSHOPS & EDUCATIONAL TALKS

Education targeting health-workers in Nyanza and Western provinces and aimed at heightening awareness on the need for early detection and treatment of BL has been carried out through workshops and sensitization visits to health facilities. A workshop held in Kisumu on 1st April 2007 was facilitated by the project team and attended by 16 participants from Nyanza and nine from Western Province. A second workshop was held on 4th April, 2008 and attended by 15 participants from Nyanza and 10 from Western Province. Participants for both workshops were invited on the basis of their official positions in the health care service, which is expected to further the objectives of the project.

Educational (sensitization) talks on project activities and distribution of educational materials to health-care workers at their facilities is ongoing and has covered over 64 health facilities to date. This has resulted in heightened awareness among a core group of about 525 health workers of various cadres, including clinicians spread across the study site. With sustained BL awareness, an increasing number of communities is being reached and will eventually be well informed.

A continuing medical education (CME) talk organized in conjunc-

tion with Kenya Medical Association (KMA) in April 08 was attended by 50 doctors, including pediatricians, physicians, pharmacists, general practitioners and other professionals working in public and private health facilities in the region. A talk on BL for all heads of health care facilities in Migori District was held on 9th December, 2008 at Migori and was attended by 67 participants. This was followed by two other CMEs in Nyamira and Homabay District Hospitals (Photo) during the period 27th May, 2009 to 4th June, 2009 and which were attended by 270 health workers. Posters, pamphlets, information leaflets and guidelines for referral of suspected cases of BL were distributed to participants.

In order to maximize the impact of the workshops and other project-related activities, reporters from regional and national news media were invited to cover the events. This resulted in activity reports being featured on national and local radio as well as television and newsprint media.

Post-test data collection for KAP assessment is scheduled for the latter part of 2009 and early 2010 through the administration of 768 questionnaires in the intervention area (Migori District).

EPIDEMIOLOGICAL FINDINGS

A largely even distribution of BL cases in 24 districts of Nyanza and Western Province has been observed, with some seeming clustered cases appearing in a few districts including Migori, Rachuonyo and Siaya, which make up 40% of all cases recruited so far. Of the cases registered, a 2:1 male-female ratio has been noted. The age range is 2.5 – 14.0 years with a mean age of 6.8 years. Both observations are consistent with published

information. There were five ethnic groups among the patients; Luo comprised 71%, followed by Luhya at 19%. The average time between onset of symptoms and visit to first health facility was six days – an important point that suggests that delay is not predominantly related to seeking



Awareness training.

medical advice. However, the average time between the date of admission or out-patient visit to the treatment centre (NNPGH) was three weeks – a relatively long time period for a very rapidly growing tumor, but consistent with referral times for less aggressive cancers. Given the relatively small number of cases registered so far, referral patterns and trends either geographical or temporal, have not yet emerged.

CHALLENGES ENCOUNTERED

A number of challenges were encountered in the course of the project, which led to modifications in size of the anticipated target population to which education was to have been provided. These included:

1. Funding was insufficient to cover the originally anticipated target populations and health care workers. Though initially planned to cover a sizable part of Nyanza and Western Provinces, the target population had to be limited to the BL “cluster” areas/

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The New Nyanza Provincial General Hospital.

districts (i.e., from where 6 – 12 patients have been seen). Efforts are being made to bridge the budget shortfall and allow expansion of the target population to that initially planned.

2. Due to the political unrest experienced in Kenya during the early part of 2008, project activities were delayed for two months because of the country-wide restriction on movement and the unfavorable working environment.

3. Accrual of cases over the last 12 months has been slow due to challenges encountered at New Nyanza Provincial General Hospital, where most cases are referred. This has led to a shift of case recruitment to hospitals in BL cluster-like areas identified from data collected so far.

CONCLUSION

Project oncologists are working closely with pediatricians and physicians in the field on the application of the INCTR BL treatment protocol, which is currently being used at Aga Khan Hospital, Kisumu. The project has applied for further funding from the National Council for Science and Technology to enable us to sustain ongoing project activities and also provide drugs for our cases at selected district hospitals.

The current investment made in creation of awareness on BL among communities and health care workers will take some time before clear dividends are realized. The project started on a promising note but encountered challenges on the way, some entirely beyond our control. In spite of this, we have been able to meet most of the goals and anticipate that by the end of 2009, we will be able to measure the impact of BL education by comparing cases reported prior to and over the study period. Data analysis of environmental/familial factors will be conducted in addition to changes in patient condition (clinical staging) variations at the time of admission over the study period.

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THE UICC MY CHILD MATTERS PROJECT IN TANZANIA

INTRODUCTION

The UICC and the sanofi-aventis Foundation, being aware that most children with cancer in developing countries, such as Tanzania, do not enjoy the same high potential cure



Ocean Road Cancer Institute (ORCI).

rates as children in technologically advanced countries, and mindful of the fact that very little money can make a difference in such resource-poor countries, launched a unique cancer program in 2005 designed to improve the care and support of children with cancer in developing countries (*My Child Matters*). The Director of the Ocean Road Cancer Institute (ORCI) in Tanzania (Dr. Twalib Ngoma) submitted a proposal on Expanding Access to Treatment for Burkitt lymphoma (BL), the predominant childhood cancer in Tanzania, which was selected for funding by the UICC MCM Steering Committee with INCTR acting as mentor.

STATEMENT OF THE PROBLEM

The population of Tanzania, which is in excess of 35 million people, includes 10 million children less than 14 years of age – the peak age for BL unassociated with HIV infection. The estimated average annual incidence of BL in Tanzania is 7 children per

REPORT

100,000, such that it is projected that approximately 700 new cases of BL in Tanzania occur every year. In 2005, it was estimated that only some 145 of these children were treated in various hospitals scattered throughout the country, most of which did not have expertise in the management of this rapidly progressive disease. There were no national guidelines for referral or treatment, and cyclophosphamide, as a single agent, was the most commonly administered therapy in the district hospitals in Tanzania. At ORCI, simple COM therapy (cyclophosphamide, vincristine and methotrexate) without intrathecal treatment (which is required to prevent spread to the central nervous system) – an approach used more than 30 years ago in Uganda, where BL was discovered, was the standard treatment at ORCI. Limited survival information was available because most patients were lost to follow-up after therapy, and throughout the country there can be little doubt that the majority of patients died. This was thought to be due to:

1. Low awareness of BL as a readily treatable form of cancer, leading to more than 80% of children with BL presenting to hospital in very poor general condition and with advanced disease, in which case survival rates are very low. In most instances, because of their poor general condition, it was felt that children would not be able to tolerate combination chemotherapy.
2. Poor referral systems and health infrastructure, with the result that more than 50% of BL patients would not be able to access hospital services and would therefore receive no treatment at all.
3. Delays in performing biopsies or fine needle aspirate procedures for

diagnosis, followed by long delays of up to six months (often well beyond the life expectancy of an untreated patient) before the issue of a report.

4. Assumptions that no news is good news, in the context of poor patient follow-up – whereas the reverse is almost certainly the case.

In August 2004, with these challenges very much in mind, ORCI joined a newly formed multiinstitutional study group coordinated by INCTR to work together on the treatment and characterization of BL in equatorial Africa, and approximately a year later, submitted a proposal to the MCM Steering Committee.

THE MY CHILD MATTERS PROJECT

The primary objective of the project is to expand effective care to as many children with BL as possible in Tanzania, through a coordinated program of public and professional education, the identification of appropriately distributed hospitals capable of treating patients effectively and assisting them to estab-



Child with bilateral jaw tumors before and after treatment.

lish an effective program, and the development of an effective triage system for patients with suspected Burkitt's lymphoma – critically important because of the known higher incidence of this disease in rural regions.

SPECIFIC GOALS

The goals identified for the project in the first year included:

- > To increase the number of BL children in Tanzania who access treatment for BL from 30% to 50%.
- > To reduce the waiting time for biopsy results from six weeks to two weeks.

ACHIEVEMENTS

| | At initiation of Project | End of year 1 (November 2007) | End of Year 2 (November 2008) |
|--|--------------------------|-------------------------------|-------------------------------|
| Number of children diagnosed/per year | 145 | 406 | 650 |
| Average waiting time for biopsy results | 6wks | 2wks | Less than a week |
| Children reporting for treatment in good general condition | 20% | 50% | 60% |
| Follow-up rate | 20% | 85% | 90% |
| Number of centres treating BL countrywide | 4 | 15 | 26 |

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The project team during one of its meetings.

- > To increase the number of children with BL who present to hospital in good general condition and early disease from 20% to 40%.
- > To increase the cure rate of BL in Tanzania from 40% to 60%.
- > To increase the number of children with BL who comply with follow-up appointments from 20% to 40%.

ACTIVITIES CONDUCTED TO DATE

- > Campaigns involving meetings with various stakeholders (pathologists and pediatricians or other specialists treating patients; the general public), training workshops and the media. The campaigns are designed to raise BL awareness in Tanzania - targeted at the general public, health professionals, the families of children with BL (who make excellent advocates in their home village), and policy makers.
- > The formation of BL Working Groups and the facilitation of their meetings.
- > Employment of a pathologist to do FNAC of BL lesions and fast

track BL histology results, at least on behalf of ORCI.

- > The production of information, educational and communication materials (IEC) on BL.
- > The distribution of posters and leaflets to district hospitals.
- > The employment of a "tracking officer" to trace children with BL who had not returned for a scheduled appointment.

SWOT ANALYSIS – PROJECT STRENGTHS

- > Good Mentorship.
- > Dedicated focused project staff.
- > Networking with other groups treating children with BL.
- > Guaranteed funding for planned activities.

SWOT ANALYSIS – PROJECT WEAKNESSES

- > Poor communication/infrastructure.
- > Inadequate and untrained staff in upcountry facilities.

SWOT ANALYSIS – OPPORTUNITIES

- > Formation of nationwide BL network.
- > Further increasing BL awareness and childhood cancers in Tanzania.
- > Catalyzing government policy makers and the media to support the treatment of cancers in children – not just BL.
- > Creating a platform for introducing pediatric oncology into the health agenda in Tanzania.
- > Undertaking additional research and collaboration.

SWOT ANALYSIS – THREATS

- > Lack of funding after completion of the project.
- > Services overwhelmed and stretched to limits due to increased awareness of BL.

LESSONS LEARNED

Even in low-resource countries, with good planning and some funding, it is possible to give good quality treatment to more children and improve their survival outcomes. If we can do well in treating BL, we can also do well in at least some other cancers. ■

*Twalib A. Ngoma,
ORCI and INCTR Tanzania,
Dar-es-Salaam, Tanzania*

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METHOTREXATE-INDUCED SKIN NECROSIS IN A CHILD RECEIVING LOW-DOSE METHOTREXATE

SUMMARY

Methotrexate is an antimetabolite used for treatment of cancer. Although the commonest complications are myelosuppression and orointestinal mucositis, skin necrosis has been reported as a side effect. Most cases of skin necrosis have been reported in persons receiving high dose methotrexate or with underlying skin diseases. A rare case of skin necrosis in a child receiving treatment for Burkitt lymphoma with a drug combination including low-dose methotrexate is reported and the possible risk factors discussed.

INTRODUCTION

Methotrexate is an antimetabolite that inhibits utilization of folic acid by inhibiting dihydrofolate reductase a key enzyme in the generation of reduced folates crucial for the biosynthesis of purines and thymidylic acid.¹ It has been used effectively, most often in drug combinations, for a number of neoplasms such as acute lymphoblastic leukaemia, non-Hodgkin lymphoma and osteosarcoma.² The primary toxic effects of methotrexate are myelosuppression and orointestinal mucositis, which occur 5-14 days after the drug has been administered.² We report the case of a child treated for Burkitt lymphoma with a regimen containing methotrexate who developed skin necrosis within 14 days of commencement of treatment.

CASE REPORT

The patient was a four-year-old girl

who presented at the University College Hospital Ibadan with a month's history of progressive painless bilateral jaw swelling. Five days before presentation, she developed protrusion of both eyes, which soon resulted in bilateral loss of vision. The illness was associated with weight loss and no history of



Pictures showing necrotic lesions described in the text.

swelling of any other part of the body. On examination, the patient looked acutely ill, was mildly pale and had obvious bilateral proptosis with no light perception in either eye. There were bilateral, non-tender swellings of the right mandible with intra oral extension, and bilateral swelling of both maxillae with den-

tal malalignment. Other significant findings were lower motor neuron facial nerve palsy involving the right half of the face and hepatomegaly. An abdominal ultrasound scan revealed an enlarged liver containing a hypoechoic mass; biopsy of the right mandibular mass, showed histological features consistent with Burkitt lymphoma and ophthalmologic assessment revealed features of bilateral optic atrophy. Full blood count at diagnosis revealed a haematocrit of 34%, total white blood cell count of 11,000/mm³ (neutrophils 61%, lymphocytes 36%, monocytes 3%) and a platelet count of 114,000/mm³. Serum electrolytes, urea, creatinine, calcium, phosphate, uric acid and liver function tests were within normal limits. Specific treatment was initiated using COM chemotherapy according to INCTR protocol 03-06C. This consisted of cyclophosphamide 1200mg/m², vincristine 1.4 mg/m² and methotrexate 75mg/m² all given intravenously on day 1. She was also given intrathecal methotrexate, 12 mg, on days 1 and 8 respectively and intrathecal cytarabine, 50mg, on day 4. Cerebrospinal fluid cytology was negative for malignant cells. Four days before commencement of chemotherapy she was started on intravenous ciprofloxacin and amikacin for presumed septicaemia and had become afebrile prior to the initiation of chemotherapy.

On day 13 of the first cycle of chemotherapy, necrotic patches were observed on her labia majora, the skin over the lumpar puncture site, and the medial aspect of the infra-orbital skin of both eyes adjacent to the medial epicanthi. There was also associated bilateral conjunctivitis. A clinical diagnosis of methotrexate toxicity was made and chemother-

NETWORK

apy was stopped. Full blood count performed on the day of appearance of the lesions revealed a haematocrit of 21% (for which she was transfused with blood) and total WBC of 700/mm³ (Neutrophils 78%, lymphocytes 16%, monocytes 6%) and platelet count of 136,000/mm³. Over time, the necrotic patches sloughed off leaving full thickness ulcers at all affected sites and the ulcers adjacent to the medial epicanthi coalesced over the bridge of the nose. The lesions were managed by dressings and healing was almost complete three weeks after. After the Haemogram had returned to normal, chemotherapy was recommenced with methotrexate replaced with Cytarabine. Child remained free of any toxic effect of the new regimen on day 7.

DISCUSSION

There are reports of cutaneous toxicity of methotrexate but most of them have been in adults. Tazi et al³ reported a case of Toxic epidermal necrolysis (TEN) in a nine-year-old child treated for Burkitt lymphoma with a regimen that included high dose methotrexate. Our patient also had Burkitt lymphoma but received low dose methotrexate and had a less extensive but full thickness skin necrosis. Toxic epidermal necrolysis (TEN) is a known cutaneous complication of methotrexate; it is a life-threatening disease characterized by extensive destruction of the epidermis.

Although the ulcers that followed necrosis in our patient were so severe and disfiguring, particularly those of the face, the characteristics of the lesions and non-extensive distribution make TEN an unlikely diagnosis.

Cutaneous ulceration has been reported as a side effect of metho-

trexate therapy in patients with psoriasis. In addition to the rare occurrence of a toxic epidermal necrolysis-like condition, two different patterns of ulcerations have been described in these patients: one type in psoriatic plaques and the other type in skin uninvolved by psoriasis but affected by other cutaneous pathology, such as stasis dermatitis or scars.⁴ Cutaneous ulceration has also been reported to complicate methotrexate usage in patients with erythrodermic mycosis fungoides.⁵

Previous reports on methotrexate-induced skin necrosis have indicated that it is dose dependent and therefore observed usually in patients on high dose MTX or changing drug dosages in patients on prolonged methotrexate use. Others have implicated underlying skin disease as a risk factor; methotrexate-induced cutaneous necrosis is said to be rare in patients without underlying skin disease.^{5, 6}

Our patient does not seem to fit into any the risk groups described above since the dose of methotrexate was not high and there was no underlying skin disease. Methotrexate-induced necrosis has been associated with concomitant administration of drugs that interfere with methotrexate excretion by competing for renal tubular secretion such as ciprofloxacin.² Dalle et al reported cases of methotrexate toxicity following administration of ciprofloxacin but their patients received high dose methotrexate unlike our patient.⁷ Therefore, although ciprofloxacin might have predisposed to the reaction seen in our patient, the chances are low. Concomitant use of Amikacin in our patient may also have been a contributory factor in altering the clearance of methotrex-

ate, even though renal function tests remained normal in our patient.²

CONCLUSION

There is need for clinicians to carefully monitor renal function and consider drug interactions while treating children with methotrexate even when there are no obvious risk factors for toxicity. In African children on treatment for Burkitt lymphoma, cytarabine may be used successfully to substitute for methotrexate in cases of toxicity.⁸ ■

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NNCTR/INCTR NEPAL: THE CANCER PROGRAM IN NEPAL - A BRIEF PROGRESS REPORT JANUARY - OCTOBER 2008

INTRODUCTION

Although the percentage of infectious diseases is decreasing in Nepal, there has been an increase in non-communicable diseases, including heart disease, cancer, diabetes and asthma, which account for an increasing proportion of deaths. The number of new cancer patients per year in Nepal is estimated to be 45,000, and this number is likely to increase. With this in mind, NNCTR/INCTR Nepal, with the support extended by INCTR, and in concert with local government and non-governmental organizations (NGOs), hospitals and communities, has developed several programs related to prevention, treatment and research in the field of cancer in several districts in Nepal.

More than 121,722 people have benefited from the public awareness program conducted by NNCTR/INCTR Nepal in the last six years. During the same period more than 10,250 healthy married women (between 30 and 60 years of age) have been screened for cervical cancer and provided treatment when necessary – including for infectious conditions identified during screening.

More than 1,640 health workers have participated in the Palliative Care Sensitization Program. 355 people, including social workers, technicians and other trainers have been given training appropriate to their role in ongoing programs.

The progress report of NNCTR and planned activities for the period of January 2008 to October 2008 are

presented here. The activities are discussed under the following headings:

1. Cancer education.
2. Cervical and breast cancer screening and prevention.
3. Cervical cancer vaccine program.
4. Palliative care program.
5. Anticipated outcomes.

discussed included patient evaluation, general nursing oncology, cancer surgery, radiotherapy and cancer chemotherapy. In the course of the workshop, nurses were acquainted with breast self-examination, cervical cancer screening by Pap smear and VIA/VILI, lung cancer and smoking, gastrointestinal cancer, psychosocial aspects of care, pain management and palliative care. Field visits were



Nepalese participants in a cancer awareness-raising session.

1. CANCER EDUCATION

1a. WORKSHOP ON NURSING ONCOLOGY – AN UPDATE (6TH JAN - 11TH JAN 2008)

Venue: Nursing in-Service Education Room, Tribhuvan University Teaching Hospital (TUTH) - Participants: 26 Nurses from five Hospitals.

A one-week continuing education program in all aspects of the nursing care of patients with cancer was jointly organized by NNCTR/INCTR Nepal and TUTH with the support of INCTR and the Rural Women's Development and Unity Centre, Nepal. Dr. Yogendra Prasad Singh of TUTH was the principal coordinator of the workshop. Topics dis-

arranged to some centers where relevant activities are ongoing, and nurses' knowledge was tested prior to and after the workshop.

1b. TRAINING THE TRAINERS (TTT) PROGRAMS (20TH TO 24TH APRIL 2008)

Venue: Chetana Kendra Training Centre Budol, Banepa - Participants: 20 persons participated in the training from 13 non-governmental organizations which coordinate their programs with the NNCTR/INCTR Nepal's Cancer Education program.

A five-day TTT program was conducted for persons from seven districts in Nepal (Kaski,

NETWORK

Makawanpur, Mahottari, Sarlahi, Kabhre, Kathmandu and Lalitpur).

1c. CANCER EDUCATION TTT REFRESHER TRAINING (25TH APRIL 2008)

Venue: Chetana Kendra Training Center Budol, Banepa - Participants: 25 cancer educators who are Cancer Education program Local Trainers.

A one-day refresher course was held for cancer educators from five districts. The achievements of the program to date and planned changes were discussed and the important role of the educators emphasized. NNCTR resource persons Dr. Aarati Shah, Dr. Y.P. Singh and Dr. Sudip Shrestha provided the training, organized by NNCTR/INCTR Nepal.

1d. DISTRICT LEVEL COORDINATION MEETING AND NETWORKING (25TH APRIL 2008)

Venue: Chetana Kendra Training Center Budol, Banepa - Participants: 35 representatives of relevant district organizations, local cancer educators/trainees and doctors.

NNCTR/INCTR Nepal held a meeting designed to improve networking

among local governments, NGOs and hospitals working on cancer prevention and early detection at the community level in several districts of Nepal. A network comprising 13 NGO's has already been formed and cancer education programs are in operation in seven districts.

The main objective of the meeting was to discuss the mobilization of local resources and facilities at minimum cost. A review was presented of progress of NNCTR since its establishment to the present, and future plans relating to its collaborative activities with the participating NGOs were discussed.

1e. SCHOOL AND COMMUNITY LEVEL CANCER EDUCATION PROGRAM

During the years of NNCTR/INCTR's operations, more than 16,000 individuals from 95 schools and communities have benefited from its school- and community-based cancer education programs. Concrete achievements can be demonstrated and activities have significantly expanded during this period. There were four handicapped trainees

among them and they in turn educated 82 handicapped (deaf) people for cancer education in two districts. The Federation of Handicapped Association (deaf) of Nepal also collaborated in the cancer education programs.

2. CERVICAL AND BREAST CANCER SCREENING AND PREVENTION

2a. AUSTRALIAN EMBASSY, NEPAL – THE DIRECT AID PROGRAM (DAP)/ SMALL GRANT PROGRAM

In 2007, NNCTR/INCTR Nepal submitted a proposal to the Australian Embassy for a small grant to provide access to 1,500 women for cervical cancer prevention, screening, treatment and follow-up. The Embassy accepted the proposal and signed an agreement with NNCTR/INCTR Nepal on October 29, 2007.

Up to the present, under this program, cervical cancer awareness programs have been organized in 26 centers. More than 2060 women have been screened for cervical cancer; 45% were found to have a genital infections and 20% had uterine prolapse of varying degrees, probably resulting from multiple pregnancies. Patients with cancer were referred for follow-up investigations.

2b. TREATMENT FOR WOMEN WITH UTERINE PROLAPSE

Surgery for prolapse is rather expensive for many women. Accordingly, NNCTR/INCTR Nepal developed an understanding with Scheer Memorial Hospital (SM), Banepa, to provide less expensive treatment, which the majority of women take advantage of. In addition the *Rural Women's Development and Unity Center*, Nepal has agreed to provide funds for the treatment of 52 cases



Cancer education program from (month) 2002 to early 2008.

of prolapse. Although not cancer, many women benefit from the inexpensive care provided for this problem and NNCTR/INCTR Nepal continues to seek additional funding for such services.

2c. CERVICAL AND BREAST CANCER TECHNICAL SKILL TRANSFER WORKSHOP (25TH FEB TO 2ND MARCH 2008)

Venue: Tribhuvan University Teaching Hospital, Kathmandu (TUTH) - Participants: 25 senior nurses from various institutions.

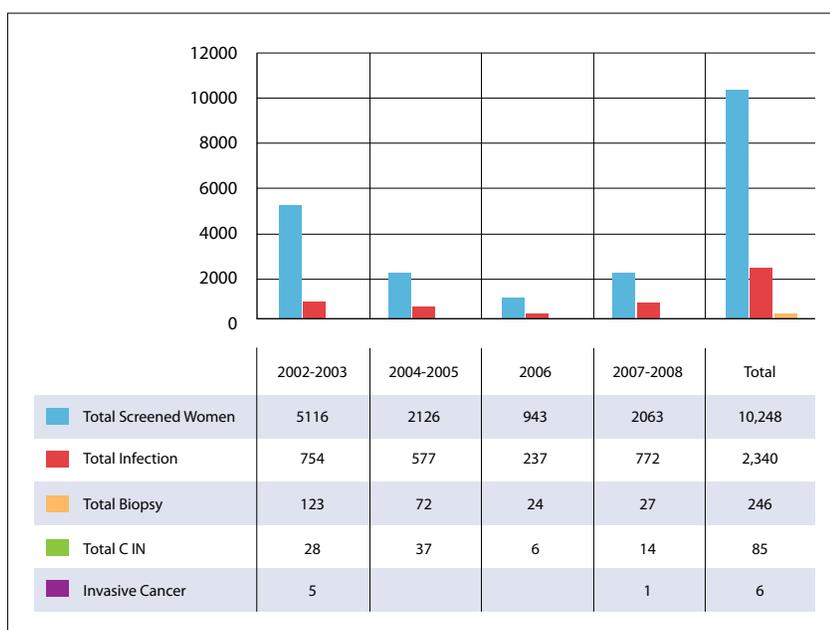
A seven-day refresher course on Cervical and Breast Cancer Screening technical skills was jointly organized under NNCTR/INCTR Nepal and TUTH with the support of INCTR and the Rural Women's Development and Unity Centre, Nepal. The course, again, was coordinated by Dr. Yogendra Prasad Singh of TUTH.

2d. TECHNICAL SKILL TRANSFER WORKSHOP ON CERVICAL CANCER SCREENING, PREVENTION AND TREATMENT FOR MEDICAL DOCTORS AND NURSES

Venue: Eye Centre, Tribhuvan University Teaching Hospital, Kathmandu - Participants: 71 health workers, 14 doctors and seven nurses.

NNCTR/INCTR Nepal, TUTH and Phase Worldwide, UK, jointly organized a four-day technical skills transfer program from 24th to 29th June 2008 at four different centres – TU Teaching Hospital, Chhatrapati Free Clinic, the Maternity Hospital, Kathmandu and Scheer Memorial Hospital, Banepa. Support was provided by INCTR and the Nepal Health Tax Fund, Ministry of Health, Nepal.

On the first day, more than 71 health workers took part in the theory class. On the following three days of practical workshops, 14 doc-



Cervical cancer screening and treatment data.

tors and seven nurses were trained. During the practical workshops 39 patients with positive cases selected from different primary screening camps were referred for further investigation and treatment by colposcopy and cryotherapy. The principal international consultants from Phase Worldwide UK, (an INGO) were obstetricians and gynaecologists Dr. David Nunns, Dr. Rafiat Adekunle, Dr. Sotirios Vimplis and Dr. Gerda Pohl, all from UK. The national faculty was comprised of Dr. Aarati Shah, Dr. Sheela Verma, Dr. Raj Shree Jha and Dr. Meeta Singh. Dr. Meeta of TUTH was the principal coordinator.

The workshop was very successful; all of the participating Nepalese doctors and nurses had a very good opportunity to share skills and knowledge with the International consultants, and doctors from other hospitals have shown a keen interest in joining such workshops in the future. Phase Worldwide UK has agreed to provide support for a six-

week training facility for two doctors every year for three years, beginning in 2007. Four Nepalese doctors have already completed the six-week training program in the UK. The last group is expected to leave for UK early next year.

3. CERVICAL CANCER VACCINE PROGRAM

3a. COOPERATION WITH AUSTRALIAN CERVICAL CANCER FOUNDATION (ACCF)

In 2007, the Australian cervical cancer foundation (ACCF) was formally established in Brisbane, Australia. The main goal of ACCF is to raise funds in cash or in kind for supplying Human Papilloma Virus (HPV) vaccines for protecting women from uterine cervical cancer. Michael T. Wille is the Executive Chairman of ACCF and Dr. Surendra Bade Shrestha, President of NNCTR/INCTR Nepal has been appointed Director of the Nepalese program.

NNCTR/INCTR Nepal and ACCF signed a Memorandum of

NETWORK

Understanding in 2007, according to which NNCTR/INCTR Nepal would be the sole administering agency for the vaccine in Nepal and would mobilize necessary funds for all local expenses for the management of the program. ACCF has set a goal of supplying up to 10,000 courses of HPV vaccine every year, gradually increasing from 100 courses in March 2008. NNCTR/INCTR Nepal

the HPV vaccine, Gardasil, and the ACCF Director, Mrs. Linda Lavarch, former Member of the Queensland Parliament, Australia, visited Nepal for a five-day period. The main purpose of the visit was to share the team's knowledge and experience with Nepalese medical professionals and other stakeholders of the HPV vaccine in Nepal. Many Nepalese doctors took a keen interest in the

iii. On October 4th, a one-day field trip was organized with the entire ACCF team and officials of NNCTR/INCTR Nepal to the Village Development Committee (VDC) in Shankhu village. The purpose of the trip was to administer Gardasil to 80 schoolgirls in grades 7, 8 and 9 in the Shankheswore Malaxmi Vidhyalaya, Shankhu, and Kabhre districts. Prof. Frazer also briefed the press and the community about the importance of the vaccine. Although it was a school holiday, an impressive number of local people and students came to receive the vaccine.



Visitors from ACCF at a welcoming ceremony. Left, Mr. Shama, high school principal. Right, Dr. Bade Shrestha, President of NNCTR/INCTR Nepal.

This was the second visit of the ACCF President and the first for the other board directors. On their first visit, the ACCF team had brought with them 300 doses of Gardasil, sufficient for 100 girls, and on the second, 3000 doses, sufficient for 1000 girls. Many Nepalese people and medical professionals had an opportunity to learn about the HPV vaccine from Prof. Frazer, and knowledge of this advance was also widely disseminated by the media. ACCF President Michael Wille and Prof. Ian Frazer have given assurances that they will be bringing in more and more vaccine to Nepal in order to vaccinate more schoolgirls with the intent of saving the lives of hundreds of women from cervical cancer. This will be no small task – there are estimated to be approximately 140,000 girls aged 11-14 in Nepal. The ACCF team Nepal program was organized and managed by NNCTR/INCTR Nepal with support from the Australian Embassy, the Nepal Oncology Society, TU Teaching Hospital and the ACCF from Brisbane, Australia. A total of 184 girls have been given the HPV vaccine to date.

has received clearance from the Drug Administration Department to use the vaccine in Nepal. The program was formally launched in March 2008 in Nepal at an event hosted by the Australian Embassy.

To date, 100 female students of the 12-14 age group from five schools have been vaccinated.

3b. VISIT BY A TEAM FROM THE AUSTRALIAN CERVICAL CANCER FOUNDATION (ACCF)

A six-member ACCF team, including its Chairman, Michael T. Wille, Deputy Chairman, Lenore Wille, Prof. Ian Frazer, the inventor of

interactive program. The highlights of the program were:

i. On October 2nd, 2008, Prof. Ian Frazer gave a presentation on HPV vaccines at TUTH. 105 medical professionals attended.

ii. On October 3rd, at the premises of Australian Embassy, Prof. Ian Frazer held a "meet the press" program. He briefed the press about HPV vaccine. The same day he gave another presentation at an event held at Hotel Radisson. Many medical professionals from different hospitals and medical institutions attended. A lively question and answer session followed.

4. PALLIATIVE CARE PROGRAM

4a. A TWO-DAY INTERNATIONAL PALLIATIVE CARE WORKSHOP IN NEPAL SUPPORTED BY INCTR AND UICC

(1ST - 2ND FEB. 2008)

Venue: Staff Collage, Jawalakhel, Lalitpur - Participants 1st Feb: 30 (25 doctors & five government officials). Participants 2nd Feb: 38 (nurses and social workers from 12 hospitals, four government offices and 11 social organizations).

NNCTR/INCTR Nepal organized a two-day workshop on "The Challenges of Palliative Care Development in Nepal," which was aimed at developing and strengthening palliative care in Nepal. The first day was devoted to the education of doctors, the second to nurses. The workshop was inaugurated by Dr. Bishnu Prasad Pandit, Secretary of Health and Population Ministry of the Nepali Government. Dr. Surendra Bahadur Bade Shrestha, President of NNCTR/INCTR Nepal, welcomed the international and national participants and made a brief presentation in which he described the work of NNCTR/INCTR Nepal in cancer prevention, treatment and research, and its involvement in the development of palliative care in Nepal. The

objectives of the workshop were:

- 1) To discuss the challenges of developing palliative care in Nepal.
- 2) To acquire an understanding of the challenges in developing accessible and affordable palliative care in Nepal.



Dr. Yogendra Prasad Singh teaching at NISH College.

The focus of this workshop was to provide information about the goals and methods used in the delivery of palliative care as well as teaching methods for various health care providers. Special attention was given to the need for a multidisciplinary approach.

5. ANTICIPATED OUTCOMES

The organizers anticipate two major outcomes of this workshop, as follows:

1. Immediate impact:

In the course of the workshop, efforts were made to explore the present status and the urgent need for palliative care in Nepal. It sensitized the policymakers and various stakeholders

to the need for the formulation of a national policy as an urgent priority, and the need to base the policy on a thorough understanding of the present situation and the challenges faced in moving forward.

2. Long Term Impact:

This workshop will

contribute to the development of an efficient palliative care system in Nepal in both service and educational sectors and to increased public awareness for the need of palliative care for cancer and non-malignant diseases. The goal is to ensure that all those who need palliative care receive it. The workshop also indicates the need for well-trained and self-motivated health care providers. Short term palliative care training (non-credit courses) will soon begin in the Nepal Institute of Health Science (NIHS) in a joint venture with NNCTR/INCTR Nepal to order to rapidly develop human resources for palliative care, at least at a basic level.

ACKNOWLEDGEMENT

NNCTR/INCTR Nepal is grateful for support from its parent organization, INCTR, and also from ACCF, the Australian Embassy – DAP Program Team, Scheer Memorial Hospital and other hospitals, NGOs and individuals who have supported or participated in the development and operation of these programs. ■

Surendra B. Bade Shrestha,
NNCTR/INCTR Nepal,
Banepa, Nepal



School girls after receiving HPV vaccine.

NETWORK

NCI'S OFFICE OF INTERNATIONAL AFFAIRS ADDRESSES GLOBAL BURDEN OF CANCER

The U.S. National Cancer Institute (NCI) is the largest cancer research entity in the world. Positioned within the U.S. Government's Department of Health and Human Services and representing the largest institute of the National Institutes of Health, NCI managed a budget of \$4.8 billion in 2008. NCI has both an Intramural Research Program with laboratories in Bethesda and Frederick, Maryland, and an Extramural Research Program that funds cancer research at nearly 650 universities, hospitals and other sites in the U.S. and abroad. The scope of NCI-funded cancer research includes basic science, epidemiology and clinical research that spans the cancer continuum from prevention to end-of-life care.

The U.S. Congress passed the National Cancer Act of 1971. This and subsequent legislation specifically emphasize an international presence in directing that NCI supports:

- a) research in the cancer field outside the United States by highly qualified foreign nationals;
- b) collaborative research involving American and foreign participants;
- c) the training of American scientists abroad and foreign scientists in the United States.

This legislative language reflects the idea that cancer research undertaken anywhere can benefit people everywhere; a position that underpins NCI's international activities. NCI's Office of International Affairs (OIA) is administratively located within the office of NCI Director, Dr. John Niederhuber, who has expressed his strong personal support for NCI's international



Dr. Joe Harford at INCTR's Cancer Control Meeting.

engagement. OIA seeks to track NCI's international activities and manages certain projects. OIA has been directed since 2002 by Dr. Joe Harford.

"Cancer does not recognize geopolitical borders, and already more than 90% of cancer cases and deaths are outside the U.S.," notes Dr. Harford. "For the NCI, the international burden of cancer not only represents an opportunity to assist, by sharing our existing knowledge in helping to build capacity for cancer research and care, but it also provides a broad range of opportunities to add to that base of knowledge through collaborative research."

OIA seeks to build capacity in cancer research where that is currently lacking and, in this regard, shares the vision of INCTR. Indeed, OIA is a major supporter of INCTR activities through core funding of the organization and additional funding for selected educational and training activities.

OIA's training activities extend around the globe. One example is

the sponsorship of participants in the NCI's Summer Curriculum in Cancer Prevention. Courses on Principles of Cancer Prevention and Molecular Prevention are offered in Bethesda each July and August. Although the Summer Curriculum began as a U.S. domestic activity, over the years it has become progressively international with more than half of the participants in the last two years being from outside the U.S.

This international representation has added richness to the courses with an "international day" becoming a feature. On this day, participants from around the world share the situation regarding cancer prevention in their home countries. OIA has been supporting the attendance of participants from low- and middle-income countries for a number of years. In the last two years, OIA has partnered with the International Atomic Energy Agency (IAEA) in bringing participants to the Summer Curriculum. The IAEA's Programme of Action for Cancer Therapy nominates participants who are then reviewed and supported by NCI through OIA.

Among his many duties, Dr. Joe Harford serves on the executive steering committee on NCI's Breast Health Global Initiative, which endeavors to develop economic-based, culturally appropriate guidelines for developing countries.

Forty-seven participants from 22 countries have been thus supported over the past two years. OIA has also provided scholarships to 37 other participants from low- and middle-income countries outside the IAEA collaboration. In addition to the Summer

Each year, the NCI supports nearly 1,000 international health professionals who come to the Bethesda campus for four-year post-doctoral training or shorter-term positions. Nearly half represent four countries: Japan, China, Korea and India.

Curriculum in Cancer Prevention, OIA assists individual scientists with short- to medium-term visits to the U.S. in the context of collaborative research involving NCI intramural scientists or NCI grantees.

OIA also provides support for thematic workshops and conferences held around the world. The INCTR's own meetings represent a major commitment on the part of OIA/NCI via the provision of sponsorship of participants from low- and middle-income countries. Another recurring meeting that has had OIA support for many years is that of the African Organization for Research and Training in Cancer (AORTIC). OIA has also participated in numerous thematic workshops that overlap with the interests of INCTR, including, for example, two that took place in 2008 - one on breast cancer in Morocco and another on Burkitt's lymphoma in Uganda.

OIA also engages in projects that have been termed "health diplomacy." For example, the Middle East Cancer Consortium (MECC) has as its members Cyprus, Egypt, Israel, Jordan, Turkey and the Palestinian Authority - countries with a history of conflict. Launched in 1996 with assistance from the NCI, MECC has sought over this 12-year period to bring together cancer researchers and health care workers from these countries to work together for the good of all people in the region. The flagship project of MECC is a joint cancer registry project that supports population-based cancer registries in each of the membership juris-

dictions. In 2006, NCI published a monograph comparing cancer incidence in Cyprus, Egypt, Israel, Jordan and the U.S. SEER registries.

A second MECC project involves palliative care. Arguably, says Dr. Harford, the three most important features of cancer in the Middle East are "late presentation, late presentation and late presentation." When cancer is detected late, curability drops dramatically, and often palliation is the only remaining option. Too many people experience poor-quality deaths with pain and other symptoms going unrelieved. The MECC palliative care project involves training and equipping of health care workers from the MECC membership in the principles and practice of palliative care. Among other resources, the *INCTR Palliative Care Handbook* is utilized in MECC-sponsored training activities.

Research on palliative care is also being encouraged. In 2008, NCI published an inventory of palliative care services in the region represented by MECC that was commissioned by OIA and conducted by the Observatory on End-of-Life Care of Lancaster, UK. Both the MECC monograph on cancer incidence data and the MECC monograph on palliative care can be seen along with other MECC-related publications on the Web site maintained by OIA (<http://www.mecc.cancer.gov/publications.html#pc>).

In 2007, the Arab Medical Association Against Cancer recognized Dr. Harford for his role in MECC as well as other work in the Arab world. The award cited his "significant contributions

to enhance the status of cancer care and cancer research in the region and unwavering efforts to support needed infrastructure and create opportunities in cancer education, training and capacity building to help cancer patients and their families throughout the Arab world."

Dr. Harford serves as the NCI liaison to a number of global organizations, including the International Agency for Research on Cancer (IARC) and the International Union Against Cancer (UICC). He has also been instrumental in the encouragement of U.S.-based entities to extend their reach around the globe. He serves on the International Affairs Committee of the American Association for Cancer Research (AACR) and works closely with colleagues from the American Society for Clinical Oncology (ASCO), the Oncology Nursing Society (ONS) and the American Cancer Society (ACS), to name but a few.

NCI's support of INCTR is a means by which the agency can reach researchers around the world. Within NCI's mission, INCTR is a conduit to build capacity for cancer research in resource-constrained settings.

"It is clear that the world has gotten smaller in terms of our ability to communicate and to do business globally," says Dr. Harford. "However, dealing with the burden of cancer that exists now and that is growing is a very big job. No single entity is equipped to address all of the issues, and so cooperation is not optional but essential." ■

Marcia Landskroener for INCTR

NETWORK

ImPACT FOLLOW-UP MISSION TO YEMEN

Dr. Stuart Brown, Director of INCTR's Palliative Care Program, PAX, participated in a ImPACT follow-up mission to Yemen from June 23-25th to discuss progress made in developing a palliative care program as part of the overall cancer control plan for Yemen. Yemen is one of the six model countries selected by the International Atomic Energy Agency's (IAEA) Program of Action against Cancer (PACT). ■

CHALLENGE FUND TRUSTEE'S MEETING

The second meeting of the new Board of Trustees of the Challenge Fund, a charity registered in the UK that will work closely with INCTR, was held on June 26th in London. Dr. Max Parkin, a well-known epidemiologist, was elected Chairman of the Board. Discussions were primarily focused on the objectives of the Trust, the present financial situation and fund raising. Mr Niblett, one of the trustees, presented a check for £2000 to be used for the treatment of Burkitt lymphoma in Africa – one of INCTR's ongoing projects. ■

WHO IAEA COLLABORATION

INCTR was invited to participate in a meeting that included representation from WHO, IAEA PACT, the NCI and the International Agency for Research on Cancer (IARC). The meeting, which took place on 2-4th July, at WHO headquarters in Geneva, was primarily directed towards discussion of a joint WHO IAEA program on cancer control. INCTR was invited to attend since it works with both WHO and PACT on cancer control projects. ■

FOLLOW-UP MEETING ON LYMPHOMAS IN DEVELOPING COUNTRIES

During the European Association for Haematopathology meeting that took place in Bordeaux from September 20-25th further discussions were held in follow up to the Lugano Workshop on lymphomas in developing countries (see the last edition of NETWORK). The discussion topics included opportunities for epidemiological studies and the need for training and education of pathologists in developing countries. An additional meeting was held in Paris on October 10th. ■

11TH INTERNATIONAL CONFERENCE ON MALIGNANCIES IN AIDS

Dr. Magrath attended a meeting on AIDS-related malignancies in Bethesda (October 6-7th) to present a lecture on Burkitt lymphoma on the 50th anniversary of Burkitt's first paper, and also attended a meeting of the USA AIDS Malignancy Consortium (AMC) in order to initiate discussions on the possibility of collaboration between INCTR and AMC. ■

PEDIATRIC ONCOLOGY MEETING

Some 35 pediatric oncologists from 12 countries assembled in Brussels from 3-6th November to discuss three topics: an international treatment study on Wilms' tumor, collaborative studies in childhood nasopharyngeal cancer (NPC) and the further development of an INCTR Handbook on supportive care for children undergoing cancer therapy. It was agreed that Dr. Bakhshi from AIIMS, New Delhi, would prepare a draft protocol for

Wilms' tumor. The group also decided to develop a questionnaire relating to the reasons for late presentation of NPC and to examine consanguinity as a risk factor for NPC. In the last two days of the meeting, participants broke up into small groups to write sections of the supportive care handbook. This is now some 70% complete. The meeting was supported by the Office of International Affairs (OIA), NCI (NPC component) and by Eli Lilly. ■

INCTR BREAST CANCER REVIEW STEERING COMMITTEE

This committee met by teleconference on November 10th to discuss the creation of a bibliography of breast cancer studies conducted in developing countries. This project is sponsored by OIA. ■

TRAIN THE TRAINERS WORKSHOP

INCTR's French branch, AMCC held a "train the trainers" workshop in Bobo-Dioulasso, Burkina Faso from 11-15th November on palliative care. 45 doctors and head nurses from five African countries attended the workshop. ■

JOINT EMRO-INCTR-ALSC

A meeting in Cairo took place from 15-18th December to launch the WHO Eastern-Mediterranean region cancer control strategy (which INCTR assisted in developing). Two days of the meeting were devoted to a workshop on breast cancer control (breast cancer is the commonest malignancy in the region) which INCTR organized. The report of the workshop is available on INCTR's Cancer Control "wiki" site. The workshop was partially supported by OIA. ■

COMITÉ HÉRAULTAIS DE LA LIGUE CONTRE LE CANCER

The French League Against Cancer, a charitable organization founded after World War I, is a major player in the fight against cancer. The League's goal is to come to the aid



Dr. Henri Pujol.

of cancer patients, their family and friends. Since its founding in 1918, the League has developed into a strong network that leads the fight on several fronts: research, information and prevention, and psychosocial assistance for patients.

France offers its citizens a national health system. Over the past decade, with cancer incidence on the rise, the government has demonstrated a renewed interest in coordinating the management of cancer prevention, treatment and research. As a federation of 102 departmental committees that works to relay to the public the mission of the administrative council and the national scientific council, the League is one of two non-governmental organizations (NGOs) supporting France's fight against cancer.

At its helm, until 2007, was one of the country's most experienced cancer experts. Henri Pujol, the president of the National Federation Against Cancer from 1983 to 1997 and president of the League Against Cancer from 1998-2007, now directs the League's Hérault Committee located within Languedoc Roussillon, a winemaking region in the south of France.

Even in this lovely part of the world, cancer incidence is on the rise. Since 2002, cancer has become the primary cause of death in France, usurping that dubious distinction from coronary heart disease. "More and more people are cured, but at the same time more and more people develop cancer because of the aging population," notes Dr. Pujol. "Today, one death in three in France is caused by cancer. These statistics led the government to develop several action plans to fight cancer."

With input from Dr. Pujol, the first of these plans was launched by Dominique Gillot, then Secretary of State for Health, in 2000. Three years later, President Jacques Chirac launched a second action plan, and France's current president, Nicolas Sarkozy, has a third plan in development. With nearly two million French people affected by this disease, cancer is not just a medical problem, says Dr. Pujol, but a social one as well. The citizens of France are demanding action.

"Any successful national plan must emphasize the importance of prevention, treatment and research," says Dr. Pujol. "Jacques Chirac said publicly that people with cancer don't just want to be cared for; they want to be cured." That pragmatic approach resonates with Dr. Pujol, who sees the League playing a key role in educating

the people of France about the dangers of tobacco use and the importance of cancer screening — steps that improve patient outcomes.

While the French government funds screening programs for breast, lung and colo-rectal cancers, there is no standardized screening program in place for prostate cancer — even though Dr. Pujol notes that the incidence of prostate cancer now surpasses all other types of cancer in France.

The League is in a good position to mount its own public awareness campaign about prostate cancer, since it enjoys excellent relationships with hospitals and cancer centers throughout the country. The organization distributes several publications related to cancer prevention and treatment. Its flagship enterprise is the creation of patient welcome centers within hospitals, known as *Espaces Rencontres Informations* (ERI).

The League also enjoys an excellent relationship with *Alliance Mondiale Contre le Cancer* (AMCC), providing office space in Montpellier and working together with INCTR's partner to answer the needs of professionals and volunteers fighting cancer in French-speaking developing countries.

In 2004, the National League against Cancer was the principal partner in AMCC's efforts to bring solutions to French-speaking African nations. For the past two years, the local committee has supported AMCC's public awareness event, *Cancer Day* for French-speaking countries.

"There is real collaboration and trust between the League and AMCC," he says. ■

Marcia Landskroener for INCTR

NETWORK

PROFILE IN CANCER MEDICINE

SAVING EYES, SAVING LIVES

Retinoblastoma (RB) has one of the best cure rates of all pediatric cancers - if it is diagnosed early. For the past two decades, Dr. Carlos Leal has been a leading proponent of early detection and treatment of this rare tumor in young patients throughout Mexico.

An oncologist practicing at the Instituto Nacional de Pediatría in Mexico City, where he took his medical training, Dr. Leal enjoys the benefits of well-equipped facilities dedicated exclusively to clinical treatments and research in pediatrics. The government-supported teaching hospital sets the national standards of patient care and, in training the next generation of medical professionals, seeks to remedy the shortage of pediatric oncologists throughout the country.

With the help of the National Academy of Medicine and the support of Dr. Roberto Rivera-Luna and the INCTR, Dr. Leal created the first collaborative group for pediatric oncology in his country. The Mexican Retinoblastoma Group (RTBMex), a team of pediatric ophthalmologists established in 2003, has developed a national protocol that has been accepted by the National Seguro Popular health insurance program. Only 50% of the Mexican population is covered by other forms of health insurance, but the national insurance program provides medical coverage for all uninsured children with cancer.

This is a tremendous accomplishment, given the group's initial findings in 2003. In a retrospective review of 500 RB cases diagnosed at 16 institutions over a six-year span, a large number of patients presented in advanced stages and treatment schemes varied widely. From this study, Dr. Leal says, it was clear that the group needed



Dr. Carlos Leal co-chairs INCTR's retinoblastoma subcommittee.

to work collaboratively to develop a national early detection program as well as a treatment protocol.

With the participation of 27 centers, the group created a National Retinoblastoma Registry. Early diagnosis and education were priorities. Under Dr. Leal's leadership, the group also developed a national treatment protocol with guidelines for the management of retinoblastoma. Today, all Mexican children, from Tijuana to Cancun, receive the same high quality treatment.

Dr. Leal also serves as co-chair of INCTR's subcommittee on retinoblastoma, endeavoring to share his knowledge and experience in treating patients with RB with colleagues in developing countries.

"One of the principal problems in developing countries is late diagnosis, which leads to a high mortality rate," says Dr. Leal. "Early diagnosis is an important modality we can put into practice cheaply and easily to avoid the critical problems we experience when diagnosis is late. We have been able to bring about a huge change in the retinoblastoma field in my coun-

try through the work of the Mexican Retinoblastoma Group and the development of the national treatment protocol," he says.

To help educate the public about Rb, Dr. Leal's group launched a program that placed posters in childhood vaccination clinics frequented by young parents.

As part of his work with INCTR, Dr. Leal has been involved with a study designed to identify the causes of late presentation in RB in 10 countries with limited resources. He has also contributed to RB programs throughout Latin America. With public outreach programs in São Paulo, Buenos Aires and Lima, doctors are saving eyes through early diagnosis. Supported by St. Jude Children's Hospital, trained ophthalmologists from Latin America countries are traveling to remote regions of central Guatemala and Honduras to provide training in the diagnosis and treatment of young patients with RB, effectively saving the lives of hundreds of children.

"The most important thing is to make a prompt diagnosis so we can save the eyes," notes Dr. Leal. "In poor countries, the general rule is to perform enucleation, or removal of the diseased eye. In Mexico and in other Latin American countries, earlier diagnosis makes it possible to have a target of performing enucleation in only half of our patients."

The gold standard for Rb diagnosis is the Ret Cam, a sophisticated camera that allows the physician to photograph the inside of the eye and pinpoint the areas that require treatment. With this \$100,000 piece of equipment, Dr. Leal says, they could save another 50 eyes each year. A small price to pay - but developing the necessary funding is not easy. ■

Marcia Landskroener for INCTR