N E T W O R K

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THE PRESIDENT'S MESSAGE

A PLAGUE FROM WITHIN[1]

by Ian Magrath

.....in the midst of a scourge, there is more to admire in the actions of men than to despise.....

--Albert Camus, *La Peste*

A Dickensian Antiphony

In the course of the last century, humanity has sunk to its greatest depths and risen, by some measures, to its greatest heights. The world has been consumed by two world wars that resulted in 50 million civilian deaths in Europe and the Soviet Union alone. Unfortunately, war appears to be a perennial affliction of the human race. More than 60 major armed conflicts have begun since 1945, approximately 50 of which continue to the present day in some shape or form. Violence not infrequently reaches the level of mass slaughter or even genocide—more than 800,000 people were killed in Rwanda, for example, in 1994. The majority of these conflicts are in developing countries (the Balkans are the exception), such that the deaths, serious injuries and societal disruption have a greater impact than they would in societies with more advanced infrastructure. Moreover, they create millions of refugees, many of whom flee to countries barely able to provide for their own populations, such that death rates from starvation and disease among the refugees are high. The recent attacks in the USA caused the deaths of more than 5,000 civilians who came from 80 countries. Future terrorist acts as well as counter-terrorist measures will inevitably result in the deaths of even more innocent people. The INCTR extends its sincerest condolences to the families, friends and fellow countrymen of all of the innocent victims of the various heinous acts that have littered recent history and which will, unfortunately, almost cer-

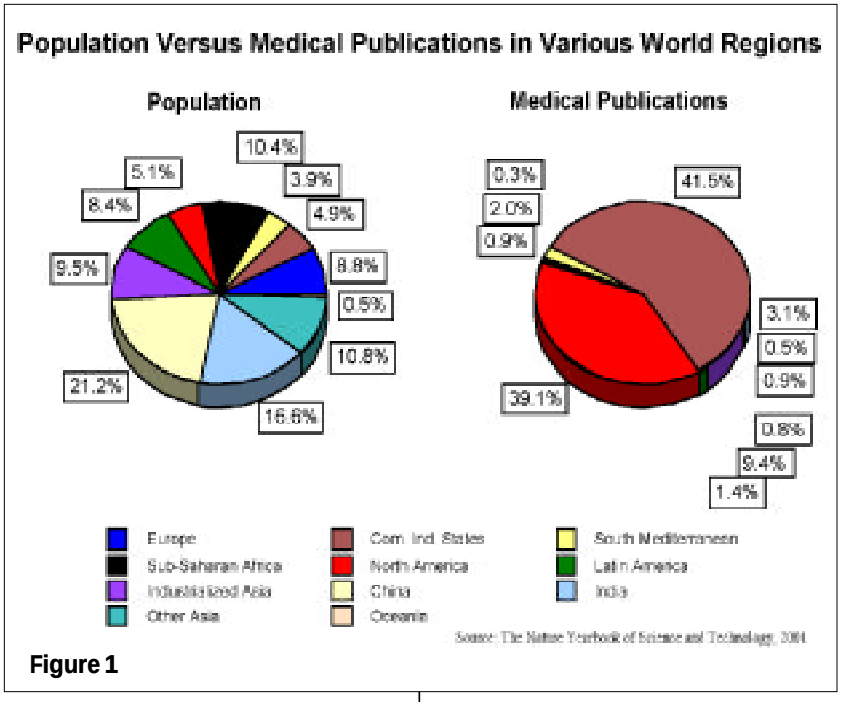

Figure 1

[1]*Plague is believed to have caused the deaths of some 50 million Europeans between 1347 and 1771 and worldwide, perhaps 200 million people. Modern risks to human health come primarily from antibiotic-resistant strains and the potential use of the plague bacillus as an agent of biological warfare. Its genome has recently been fully sequenced.*

tainly continue into the foreseeable future.

Yet while host to internecine struggles of cataclysmic proportion, the last century has also witnessed unprecedented advances in science and technology, without which, ironically, neither the recent attacks in the USA nor the almost instantaneous transmission of the devastating images of death and destruction to every corner of the globe (a result clearly desired by the perpetrators) would have been possible. We live in an era in which the secrets of quarks and bosons, the elementary particles of matter, are being unraveled, space probes are sent to the furthest reaches of the solar system, and more than 90% of the human genome has been sequenced. Many of us are fortunate enough to be able to enjoy, first-hand, the cultures of many other countries and peoples, as well as the artifacts, literature and music of other ages. More than 500 million people now have immediate access to enormous quantities of information through the Internet.

A FAUSTIAN DILEMMA

Paradoxically, despite the enormous strides made in the fields of science and technology, ignorance and poverty still engulf a large proportion of the human race, and diseases, old and new, continue to ravage populations. Average life expectancy has greatly improved, but socioeconomic inequity is increasing. Today, more than one billion people drink unsafe water and 2.4 billion are without adequate sanitation. Approximately 3.4 million people, mostly children, die each year of water-related diseases, over a million from malaria alone. In 1999, there were 5.4 million new cases of AIDS (4 million of whom were living in sub-Saharan Africa) and 8.4 million new cases of tuberculosis, while in the year 2000 there were 10 million new cases of cancer. The sheer scale of the human misery caused by these diseases, which is predicted to increase dramatically with time (cancer cases will reach an estimated 20 million by 2020) is incomprehensible. One may, I hope, be forgiven for asking whether this is indeed a paradox, or simply a consequence of human nature and the laws of mathematics. But whatever its cause, the profound Dickensian contrasts of the twentieth century confront us with a major challenge for the twenty-first century. How can we bring the benefits of science and technology to the huge fraction of the world's population that presently has little or no access to them? And at the same time, how can we avoid the misuse of technology—in the words of Faust, the false path arising from the fact that so much poison is hidden in the cure?

E PLURIBUS UNUM

The recent terrorist acts in the USA have galvanized the world into action against the threat of future attacks, for aggression of such magnitude and consequence against the richest, most powerful, most influential and most visible country on earth unequivocally demonstrates universal vulnerability and has huge potential global reverberations (doubtless, critical elements in the choice of the targets). To control terrorism—the perpetrators of which can hide amidst the general population, are succored by multiple resources wittingly or unwittingly provided, move easily from one country to another, and can turn the accouterments of everyday life into weapons against innocent

EXTRACTS FROM THE UNIVERSAL DECLARATION OF HUMAN RIGHTS

Article 25

(1) Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services.

Article 26

(1) Everyone has the right to education. Education shall be free, at least in the elementary and fundamental stages. Technical and professional education shall be made generally available and higher education shall be equally accessible to all on the basis of merit.

(2) Education shall be directed to the full development of the human personality and to the strengthening of respect for human rights and fundamental freedoms. It shall promote understanding, tolerance and friendship among all nations, racial or religious groups, and shall further the activities of the United Nations for the maintenance of peace.

Article 27

(1) Everyone has the right freely to participate in the cultural life of the community, to enjoy the arts and to share in scientific advancement and its benefits.

people—broadly-based global cooperation is essential. We can but hope that September 11 will become not only a day of remembrance for the victims of terrorism, but also a day on which to celebrate the beginning of a new world order—a day that catalyzed the nations of the earth to unite to a previously unprecedented degree in combating not only terrorism, but all common enemies. If so, the deaths and suffering will not have been in vain.

It is only in the twentieth century that wars on a global scale have been seen, and as a reaction to their previously unimaginable horrors we have witnessed the emergence of international organizations whose members are nation states, such as the United Nations (including the World Health Organization and the International Court of Justice), the World Trade Organization and the World Bank. While there is perennial debate about the efficiency and success of such organizations, the fact of their existence, combined with such instruments as the Universal Declaration of Human Rights (see panel opposite), signifies that the human race is moving into an era in which international interactions are increasingly subject to the rule of law and independent arbitration rather than to the ancient formula of "might is right." There is, of course, a considerable distance to travel along this path pitted with land mines, and many nations will be wary of subjecting their present freedom of action to international consensus, particularly when such consensus must be reached by countries with broadly different cultures, economies, interests and sensibilities.

But whereas political commonality may be difficult or impossible to reach, there is a surprising degree of agreement on universal human rights. Perhaps too, there can be consensus on universal threats, for there can be no more potent unifying force. International terrorism, the enhanced power of which in this technological era has been so starkly demonstrated, is on center stage at the moment, but other, more widespread problems such as ignorance, poverty and disease affect vastly greater numbers of people and also carry major and more sustained socio-political consequences. Concerted action is surely the most effective means of dealing with these problems, and ought also to be particularly achievable in the context of disease, since the latter is less susceptible (although not immune) to differing political or religious perspectives. The eradication of smallpox stands is an example of successful international action in this area. Moreover, improving the lives of people is likely to be a potent means of increasing national and international security.

In an era in which tools capable of changing our biological nature have emerged (to be greeted, quite naturally, with clamorous debate), alongside the ability to annihilate the human race, perhaps the time has come to seek to match these technical marvels with political and organizational structures of equivalent virtuosity. Probing the mysteries of fundamental particles or the human genome may be likened to pushing the accelerator of progress, but by the same token, the interwoven blights of ignorance, poverty and disease are huge burdens which act as brakes, both by reducing the intellectual potential of the human race and, perhaps worse, by predisposing populations to crime, social unrest, political instability and ultimately, armed conflict. Poverty and ignorance provide a breeding ground, if not for the architects of terror, at least for those susceptible to its propaganda.

MINIMIZING HARM

The versions of terrorism are many and varied. Consequently, effective control is dependent upon the gathering of "intelligence" about the locations of terrorists, their means of support and the acts they plan to commit. The eradication of terrorism, based on such intelligence, must be carried out with a minimum of harm to innocent people—whether physical or at the level of societal freedoms. Research into the origins of terrorism is also essential if we are to prevent it. This will entail much soul-searching and greater attention to the long-term results of political or military actions.

Strong parallels exist with disease control, perhaps because terrorism is, in effect, a plague from within, a cancer that attacks the innocent and unsuspecting. Cancer, like terrorism, has definable causes which will need to be identified through research for intervention to be successful. While a major element of prevention must be socio-political, immediate action is necessary to minimize the suffering of present victims. In order for appropriate authorities or donors to commit the needed resources to disease control, scientists and physicians must be responsible for providing evidence (intelligence?) concerning cancer patterns in various world regions, for the causes of individual cancers, and for the effectiveness of preventative or therapeutic measures. Sometimes, disease prevention can be accomplished by a simple act.

Hand washing with soap and water can reduce the incidence of diarrhea by 35%, and smoking cessation dramatically reduces the mortality from several cancers and many other diseases. Of course, modifying human behavior associated with a significant psychological, political or economic impact is never easy. Reducing smoking rates, for example, is not simply a question of dealing with addiction to nicotine, but also involves addressing the competing influences of different sectors of society, some of which stand to profit enormously from encouraging the smoking habit. Consequently, Richard Peto has estimated that there were 71 million tobacco-related deaths between 1930 and 1999 in industrial nations alone, and the World Health Organization estimates that there are presently 3 million deaths a year worldwide from tobacco, almost a third of which occur in developing countries.

Europe and North America account for 15% of the world's population, and 75% of its total output of scientific papers. Industrialized Asia accounts for 10.8% and all other nations, 4%.

Where prevention fails, it is essential to confirm the diagnosis of cancer. Missing the diagnosis may have fatal consequences, and an incorrect diagnosis may lead to unnecessary psychological anxiety as well as to time-consuming, expensive and potentially risky treatment. Treatment should be no more than is necessary (proportionate?), and adjusting treatment to risk is a difficult task that entails identifying the locations of cancer throughout the body. The collections of cancer "cells" (a word recently co-opted to refer also to terrorist groups), are particularly difficult to eliminate when scattered throughout the body since "collateral damage" to normal cells must be kept to a minimum, although it is difficult or impossible to avoid altogether.

AN EQUAL MUSIC

Fighting cancer, like terrorism, is not a single process and requires application of a broad range of approaches to its prevention and treatment. These, in turn, must be managed by highly trained, dedicated teams of professionals—underpinned, of course, by the political will to commit the required resources. Because of its cost, it attracts little attention as a health problem in the poorest, heavily indebted nations, which must sometimes focus all of their available resources on providing clean water and helping their infants to survive beyond the age of five. Similarly, international organizations, for many reasons, tend to focus primarily on these grass roots problems even though many developing countries have undergone significant epidemiological transitions such that mortality rates from chronic diseases, including cancer, are increasing and represent a health challenge of ever increasing importance. But research in fundamental physics, space technology and sophisticated biotechnology is conducted in nations whose average wealth is high, but in which poverty has yet to be eliminated. Whilst priorities in government spending will always be hotly contested, some of this research is conducted by non-governmental organizations, and in any event, the greater good is probably better served by including significant expenditure on fundamental research whilst simultaneously addressing the alleviation of poverty and ignorance—indeed, the former may, sooner or later, have a significant impact on the latter.

By the same token, given that cancer is a global problem, all nations must address it at some level, although there must, of necessity, also be quantitative and qualitative differences in national emphasis. Enhanced international cooperation is likely to have a synergistic effect on efforts to control cancer although, as with other global coalitions, individual countries will contribute in different ways or to different degrees whether with respect to the provision of financial support, experts, or simply helping to take advantage of opportunities to better understand one or more aspects of cancer. At present, a tiny fraction of global research, including medical research, takes place outside North America, Europe, Japan and Australasia (Figure 1), yet the developing countries provide an immensely rich source of potential knowledge about cancer, as well as numerous, largely untapped opportunities for the conduct of research into its prevention and treatment—research that would help both the local populations as well as people everywhere. These opportunities are currently being largely overlooked, partly because of the mal-distribution of global resources, but also because many western researchers are not

aware of the possibilities that exist for effective collaboration. Changing this situation should be given a much higher priority.

In 1971, Richard Nixon, then President of the United States of America, announced a war on cancer. The consequent boost in resources has been of tremendous benefit to understanding and controlling cancer, but almost all of these benefits have been reaped by the rich countries. Cancer, like terrorism, is a scourge which merits exceptional action on the part of the international community. In this United Nations *Year of Dialogue Among Civilizations*, might not cancer be elevated, along with other common ills, to the rank of a global problem that, like terrorism, requires global action? And should not developing countries, home to the major part of human suffering, be involved more fully in the struggle against it? ■

REGIONAL NEWS

CHINA

The INCTR is supporting the development of a cooperative group for pediatric lymphomas in Eastern China. With INCTR funds, a computer and printer were purchased, a data manager was employed, and a meeting was supported - a joint National Lymphoma Collaboration meeting associated with a National Training Course for Pediatric Oncologists. The meeting lasted 10 days and included approximately 25 people. ■

INDIA

INCTR is supporting the development of the Indian Cooperative Group for the Study of Leukemia (ICGSL), including support for data management. Data regarding treatment of patients with acute lymphoblastic leukemia with protocol MCP841 collected between 1990 and 1997 from these centers is in the process of being analyzed. This data will then be prepared as a joint publication of these three centers, which presently form the core of the ICGSL. A new group protocol is being developed, the design of which will draw heavily upon information obtained in the course of conducting previous protocols.

Investigations into the molecular profile of acute lymphoblastic leukemia (ALL) in India in comparison to that in other world regions are underway. Early findings suggest significant differences, for example, a paucity of ALL with a 12:21 translocation in India. This information has relevance to treatment approaches and outcome, since prognosis varies in ALL with different translocations (patients with 12;21 translocations generally have an excellent prognosis). These studies are being done in a collaboration between the All India Insitute for Medical Sciences and Dr Kishor Bhatia's laboratory at the King Fahad Children's Medical Center in Saudi Arabia. The findings will be presented at the annual meeting of the American Society of Hematology in December. ■

SUB-SAHARAN AFRICA

Dr Chitsike in Harare, Zimbabwe, will participate in the collection of data regarding the reasons for late presentation of retinoblastoma. ■

With the support of INCTR, Chinese oncologists met in Shanghai to discuss pediatric lymphomas.

COURAGEOUS FIGHT BY A PATIENT WITH BURKITT'S LYMPHOMA IN TANZANIA

WARNING SIGNS

The case presented here is that of a nine-year-old girl who developed a jaw swelling in April 1994. This was initially attributed, by her parents, to a recent tooth extraction.

The swelling progressively increased in size. When the parents noticed that their daughter was sitting on the sand by herself and looked very very tired while all the other children were playing in the playground, they developed an unsettled feeling which made them to take her to the nearby district hospital right away.

After examining the patient, the doctor – a medical assistant at the district hospital - suspected that the patient might have Burkitt's lymphoma but had no facilities to perform tests to confirm the diagnosis. The clinical diagnosis was conveyed to the parents. When the word cancer was mentioned, the parents were overcome with shock, fear and denial. The doctor recommended that the patient be referred to the Consultant Hospital in Dar es salaam, which is 1,000 km from the district hospital. Since at that time it was the rainy season and most of the roads were not easily passable, it took about ten days for the family to arrive at the Consultant Hospital.

THE DIAGNOSIS

The patient and her parents had a horrible trip to Dar es Salaam. She developed malaria on the way. The deterioration in her health only emphasized the seriousness of the situation. The parents were physically and financially exhausted and could only watch in utter despair as the staff at the casualty department of the Consultant Hospital whisked their daughter off to the pediatric ward for supportive care and work-up to establish the diagnosis. The investigations included a full blood count, chest X ray, ultrasound of the abdomen and pelvis, spinal fluid examination, touch imprint and tissue biopsy. The diagnosis of Burkitt's lymphoma was confirmed in the third week of her stay at

the Consultant Hospital. During the weekly Tumor Board meeting in her fourth week stay at the consultant hospital, the Tumor Board recommended that the patient be transferred to the Ocean Road Cancer Institute where she was to receive her chemotherapy.

THE TREATMENT

Burkitt's lymphoma is a very aggressive cancer but it is also exquisitely sensitive to chemotherapy. This patient's prognosis was extremely good. At the Ocean Road Cancer Institute the expected cure rate for a patient with her stage of disease is 85%. Although cytotoxic drugs are usually not affordable to most Tanzanians due to their high costs, at the Ocean Road Cancer Institute (ORCI) we have a policy of supporting all pediatric oncology patients with free chemotherapy treatment. Therefore the patient was assured of receiving the ORCI recommended combination chemotherapy despite the fact that her family could not afford to pay for the treatment.

THE WIN

In July 1994 the patient was started on Cyclophosphamide 30mg/kg i.v bolus, Vincristine 1.4mg/m^2, Methotrexate 15mg/m^2 and allopurinol 100mg three times a day – repeated at two weekly intervals. After four cycles the tumour had melted away. Throughout the grueling ordeal the patient gained weight and emerged as a strong survivor. We advised the patient to continue with chemotherapy for another two cycles to ensure that the cancer did not come back. In October 1994 the patient was finally free – free from intravenous fluid administration, free from the raid of cytotoxic drugs on her body, and free from disease. The mother was ecstatic. As for the patient, all she could really think about was school, home and her friends.

THE PATIENT IN THE YEAR 2001

The patient is well and attending secondary school. When asked what she plans to do with her life – a life she so nearly lost - she says that she intends to become a doctor. ■

submitted by
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Dar es Salaam, Tanzania

A BURKITT'S LYMPHOMA CASE FROM NIGERIA

O.B. is an 11-year-old boy referred from a private clinic to the Department of Pediatrics, University College Hospital (UCH), Ibadan, Nigeria, with a month history of swelling of the left jaw. The left upper first premolar tooth was lost a week prior to presentation. Because the gum was bleeding so easily, the patient had changed from using a toothbrush to foam for cleaning his teeth. There was no weight loss.

Mother had been applying 'Robb' liniment and hot fomentation to the swelling because she perceived it was due to trauma. However, the swelling continued to increase rapidly in size. Out of frustration, the mother visited a 'native' doctor who made scarification marks on the swelling to ward off the evil spirit thought to be responsible for the illness. In addition to this, native herbs (name unknown) were applied to the swelling.

As there was no improvement, the patient was taken subsequently to two private hospitals. He was given an intramuscular injection for five days in the first hospital, while on reaching the second hospital, he was promptly referred to UCH, Ibadan.

AT THE HOSPITAL

The patient was the first of four children in a monogamous family of low socioeconomic status. Physical examination revealed a malnourished boy, weight 25kg (70% of weight for age). There was a smooth mass over the left maxilla and mandible, measuring 9 x 8 cm in the transverse and longitudinal diameter, respectively. The swelling was hard and many scarification marks were visible. There was no intra-oral extension of the mass. The first left upper premolar was missing, but no other tooth was loose. Mild dental mal-alignment was noted. A diagnosis of Burkitt's lymphoma, stage B was made.

Results of investigations that could be done were: PCV =40%; WBC, 26,600/mm3 (neutrophils 53%, lymphocytes 30%, monocytes 7%); and platelets199,000/mm3.

Jaw radiograph showed loss of the dental lamina dura (a hard layer of bone surrounding the tooth) and marked displacement of teeth. Fine needle aspiration cytology was suggestive of a non-Hodgkin's lymphoma, Burkitt's type. On the 16th day of admission, and with the help of the social worker, some of the required cytotoxic drugs were purchased. However, the patient had deteriorated as shown by increased liver size (5cm) and the presence of meningism, suggesting involvement of the cerebrospinal fluid. A spinal tap was done, and the cerebrospinal fluid (CSF) was shown to have a low glucose level with elevated protein (140mg/dl) but no tumor cells were observed. The chemotherapeutic regimen included: subcutaneous cytosine arabinoside at 50mg/m2 (45mg), 12 hourly for 6 doses, intrathecal cytosar (delivered by spinal tap), 36mg/m2 (35mg) on days 1 and 5, intravenous (i.v.) cyclosphophamide 1000mg/m2 (960mg) on day 1, i.v. oncovin 1.5mg m2 (1.4mg) on day 1, and oral prednisolone 40mg daily for (COAP). Allopurinol, at a dose of 100mg thrice daily and liberal oral fluids (3L/day) were administered.

By the fifth day of the first course of chemotherapy, the meningism had resolved. The electrolyte and urea, calcium and phosphate, creatinine and uric acid values were normal except for a low serum sodium level of 126mmol/L. Between the 23rd and the 31st day of admission the patient developed headache, blurring of vision and occasional dizziness with a left facial nerve palsy and left hemiparesis. Repeat CSF cytology showed clusters of large lymphoblastic cells, indicative of central nervous system involvement by Burkitt's lymphoma. There was also papillodema, suggesting raised intracranial pressure. The patient became confused on the 31st day of admission. With further financial support provided by the social worker, the second course of treatment was started and 20% mannitol 1gm/kg / dose 6 hourly was given on three occasions in an attempt to control the elevated intracranial pressure. It is interesting to note that the jaw swelling had become reduced in size.

THE LOSS

On the 37th day of admission the patient had a tonic-clonic seizure lasting about two minutes. The electrolytes were normal. However, the papilloedema had not resolved, suggesting that the raised intracranial pressure caused the seizure. Further siezures ensued, which failed to respond to paraldehyde and phenobarbitone. The patient went into coma after four days and died the following day.

Post mortem showed multiple tumor nodules in both kidneys, leptomeningeal (coverings of the brain and spinal cord) infiltration by the tumor with evidence of cerebral oedema and left testicular involvement. ■

submitted by
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BURKITT'S LYMPHOMA - A CLINICAL PERSPECTIVE

Burkitt's lymphoma was first recognized in Africa as a tumor of the jaw occurring in high frequency in children. Although it is believed that Burkitt's lymphoma has existed in Africa for thousands of years, the earliest documentation of this tumor can only be traced to the beginning of the twentieth century when its unusual and prominent features were observed and recorded by European missionary doctors. Hospital records from the first missionary hospital in Uganda dating from 1897 to 1956 revealed a high frequency of tumors of the jaw and orbit in children seen there in this period, and analysis of these records suggest strongly that over 50% of the cases of childhood cancer were what we would now call Burkitt's lymphoma - a figure very similar to more recent estimates of the incidence of Burkitt's lymphoma in Uganda. During the 1950s and '60s, in-depth clinical and pathological descriptions of the features of this tumor were made by Dennis Burkitt, Greg O'Conor, Dennis Wright (the author of the accompanying article on page 10) and others. Another of the many contributions made by Burkitt and his colleagues (see also Professor Wright's article) was to delineate the geographical distribution of this tumor in Africa. The findings of their survey suggested that this disease had a high incidence in an area that is approximately 15 degrees north and south of the equator with a prolongation southward in the eastern side of the African continent. This was shown to be a consequence of climatic factors and led to the hypothesis, likely, but still unproven, that malaria predisposes to Burkitt's lymphoma. It also led to the discovery of Epstein Barr virus, based on an earlier and subsequently disproved hypothesis that the disease might be caused by a virus vectored by a mosquito.

Shortly after the descriptions of the African lymphoma were published, pathologists recognized that some childhood lymphomas occurring in the US and Europe at low incidence ("sporadically") were identical to African Burkitt's lymphoma, whose incidence was considered high enough for the disease to be referred to as "endemic." In equatorial African countries, the average annual incidence is four to ten per 100,000 children under the age of 16 years whereas in western countries it accounts for a few percent all childhood cancers and has an annual incidence rate of 0.2 per 100,000. The clinical distribution of disease, and differences in the frequency of involvement of various sites in different world regions, as well as in HIV associated BL (particularly with respect to jaw involvement) is described in the accompanying article. Clinical staging is based on the extent of disease, and total tumor volume appears to be a major determinant of prognosis. Patients with central nervous system (CNS) involvement tend to have the worst prognosis in patients outside Africa, where CNS disease is usually associated with extensive disease elsewhere, particularly in the bone marrow. In Africa, however, CNS disease is often isolated, or associated with minimal disease elsewhere, and bone marrow involvement is uncommon (less than 10% of patients, even after relapse).

Many lessons have been learned from the study of African Burkitt's lymphoma, one of the most important being that it was one of the first tumors shown to be curable by chemotherapy alone. The investigation of the efficacy of chemotherapy in the treatment of this disease was a logical approach since traditional approaches to cancer management - radiotherapy and surgery - were not feasible. Radiotherapy was by and large not available in Africa and complete surgical resections of tumor masses, particularly those in the facial region or large masses in the abdomen, were not possible. Furthermore, rapid recurrence usually occurred in patients who underwent surgical resection of localized disease. A number of drugs were shown to be active in the treatment of Burkitt's lymphoma, most notably cyclophosphamide (CTX), vincristine (VCR) and methotrexate (MTX). Chemotherapy with CTX alone, even one or two doses, resulted in some cures. However, combination chemotherapy regimens using CTX, VCR and MTX (COM), coupled with intrathecal chemoprophylaxis with MTX, appeared to improve the overall survival rates. Results achieved in studies conducted during the 1970s resulted in the cure of 40 to 50% of patients. The treatment regimens used were not expensive, were relatively simple to administer, and toxicities were manageable in the African setting. Since then, attempts have been made to improve upon the results achieved by employing more complex treatment regimens, for example, based on the French LMB regimens. Although effective, these regimens are more toxic and expensive, and for these reasons cyclophosphamide alone or simple COM or COM-like regimens are still widely used for the treatment of Afri-

NEWS OF INCTR STRATEGY GROUPS

RETINOBLASTOMA STRATEGY GROUP

The treatment sub-committee of the Retinoblastoma Strategy Group met in July to design and develop treatment protocols for advanced retinoblastoma. Two protocols were proposed: one for the treatment of patients with extraocular disease without overt signs of metastatic disease at presentation, and another for the treatment of patients with metastatic disease at first diagnosis. Protocol objectives, patient eligibility criteria, treatment and evaluation parameters were agreed upon for both studies. It is anticipated that draft versions of the two protocols will be completed by early 2002.

The INCTR Ethical Review Committee has reviewed and approved the survey study, "Understanding Problems Faced by Parents of Children with Retinoblastoma Prior to Treatment." This questionnaire was designed at the January meeting of the Strategy Group. Early feedback from investigators participating in this study has been informative. They say that parents are very willing to share their stories and that the process of obtaining information required for the questionnaire also provides an opportunity to educate parents about the disease.

INCTR is presently working with Retinoblastoma International in the preparation of a public service announcement relating to the early detection of retinoblastoma. The announcement will be linked to a popular television series called "The Bold and the Beautiful," starring Hunter Tylo. ■

OSTEOSARCOMA STRATEGY GROUP

Progress has been made in approving the new protocol for the treatment of metastatic osteosarcoma in participating centers. So far the protocol has been approved in three centers: the Kingh Fahad Children's Medical Center, the Philippines Children's Medical Center and the Shanghai Children's Medical Center. Protocol accrual will commence imminently. ■

LEUKEMIA STRATEGY GROUP

In follow-up to the January meeting among investigators participating in the leukemia study group in India that took place in Hyderabad, Dr Banavali visited INCTR with an outline of a new protocol to be used by the major Indian centers participating in this group. The protocol was discussed in detail and a draft protocol document will be prepared for review by the Leukemia Strategy Group early next year. ■

can Burkitt's lymphoma, although there is rather limited documentation of results obtained.

The observation that there was no difference between the histological appearance of African Burkitt's lymphoma and Burkitt's lymphoma observed in the US and Europe led investigators in the US to employ the same treatment regimens used in Africa for American patients. From early studies conducted in the US, it appeared that there was no difference in response or survival rates achieved compared to those achieved in African patients, and a study conducted by the Children's Cancer Study Group using a "COMP" regimen, which included prednisone and local radiation for 18 months, gave a survival rate of approximately 50%. Since this time, considerable progress has been made in the treatment of Burkitt's lymphoma in the industrialized nations. The development of newer, more intensive combination chemotherapy regimens along with considerable improvements in supportive care have made this disease curable in 90% of patients. Unfortunately, current treatment results for children with African Burkitt's lymphoma continue to remain the same as those achieved in the 1970s.

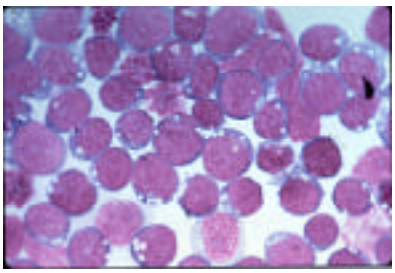
In summary, much was learned and continues to be learned from African Burkitt's lymphoma. This knowledge has resulted in benefits not only to the medical and scientific community, but also to many cancer survivors. It is an important goal of the INCTR to develop strategies to improve the outcome of children with African Burkitt's lymphoma. The INCTR would be pleased to hear from investigators in Africa interesting in participating in studies of Burkitt's lymphoma. ■

--submitted by Melissa Adde , INCTR

BURKITT'S LYMPHOMA – A PATHOLOGIST'S PERSPECTIVE

Denis Burkitt wrote his first paper on the lymphoma that bears his name in 1958. The feature that drew his attention to the tumor was the characteristic, and often dramatic, involvement of the jaws. The first of his many contributions to the study of this tumor was to show that patients with jaw tumor also had visceral tumors and that similar visceral tumors were seen in patients without jaw involvement. Burkitt's lymphoma (BL) has a characteristic cytomorphology. Labeling tumor cells *in vitro* with tritiated thymidine showed a proliferation rate of 100%, a figure subsequently confirmed by labeling with proliferation markers such as Ki67. An international meeting of haematopathologists in 1969, sponsored by the World Health Organization and the International Agency for Research on Cancer, expressed a majority view that BL should be defined on the basis of its cytomorphology. Two members of the group, however, were of the opinion that the tumor should be defined on the basis of its clinico-pathological features and they rejected the view that BL exists in a specific histological and cytological sense. Over 30 years later, it is apparent that the minority group were at least partly correct, insofar that Burkitt's lymphoma has different clinical features in different world regions, is also predisposed by immuodeficiency syndromes and HIV infection, and may, in fact, be a family of closely related tumors.

BL, as defined by cytology and histology, falls into at least three categories. Endemic BL, as described by Burkitt, shows age-related jaw tumors and visceral tumors involving the kidneys, liver, endocrine organs, gonads, breasts and gastro-intestinal system. Involvement of peripheral lymph nodes is unusual. The tumor occurs in children, with a peak age incidence of seven years, and occasionally in young adults. Sporadic BL, as seen in Europe and the USA, typically involves the abdomen, and has a particular penchant for the terminal ileum and ascending colon. A number of patients present with massive intra-abdominal tumors and the exact origin of these tumors may be difficult to ascertain. Peripheral lymph node involvement is more common, and bone marrow involvement not infrequent, particularly at relapse. This is often referred to as acute B cell leukemia, but patients with marrow involvement respond well to the same therapy used for BL and poorly to acute lymphoblastic leukemia therapy. Burkitt's lymphoma is the commonest non-Hodgkin lymphoma of children in the developed world. A third category of BL is AIDS-related BL, a tumor that occurs in HIV-positive individuals, usually early in the course of their disease, prior to significant immuo-suppression, that most commonly presents with peripheral lymphadenopathy. Interestingly, in spite of the high prevalence of HIV in Africa, there is no evidence that this has influenced the incidence of BL. In contrast, the incidence of Kaposi's sarcoma has been dramatically increased. It can be seen that the eponymous title BL has been applied to two tumors that are clinically different from the tumors described by Denis Burkitt in Africa. The reason why these tumors are morphologically identical is presumably because they have translocations involving one of the immunoglobulin genes and the c-myc oncogene that results in c-myc deregulation. Deregulation of this transcription factor results in unrestrained cell proliferation without differentiation. The resulting B-blasts therefore look identical.



Cytological appearance of Burkitt's lymphoma. These tumor cells were obtained from a simple fine-needled aspirate of a jaw tumor in an African child. The white spots are tiny fat globules, or "lipid vacuoles," which are characteristic of this tumor.

The Epstein-Barr virus status of the three varieties of BL is also different. Endemic BL is 100% EBV positive; rare EBV negative cases have been described from Africa but it is not clear whether these are endemic cases. The EBV status of sporadic BL varies with the childhood prevalence of EBV infection in the community from which the cases are derived. In Europe and North America, where EBV infection occurs later in childhood, it is in the region of 20%, in north Africa and Iran, where EBV infection occurs earlier, it is between 70-90%. Paradoxically, only 20 to 30% of AIDS-related BL are EBV associated, although almost all patients have antibodies against EBV. The terms endemic and sporadic BL are not entirely appropriate since rare cases with the typical clinical features of endemic BL are seen in in Europe and the USA, and it is possible that a

small fraction of African cases correspond to sporadic BL. In addition, it is not clear how these terms should be applied in other world regions which sometimes have clinical patterns intermediate between the two (e.g. some parts of South America and Turkey). Basing distinctions on clinical features alone is imprecise at best.

The different features of the subtypes of BL probably reflect origins from different types of B-cells and possibly differences in the pathogenesis of the tumors. Studies of cases of BL from the American BL Registry, mainly of sporadic type, showed a transition between reactive follicles and tumor, suggesting an origin from follicle centre cells. This author has suggested that endemic BL may be derived from marginal zone B-cell and therefore is a type of MALT lymphoma. The evidence for this is circumstantial in that the tumor frequently involves mucosal sites, does not usually affect peripheral lymph nodes and shows relative sparing of the bone marrow and spleen. Mucosal B-lymphocytes migrate to the breasts during late pregnancy and lactation, which might provide an explanation for why massive breast involvement by tumor is seen in young women who present with endemic BL during pregnancy and lactation. Denis Burkitt recorded cases in which there was spontaneous regression of breast tumors on cessation of lactation.

If endemic BL is derived from mucosal lymphocytes, how can we account for the jaw tumors that are such a characteristic feature of this tumor? Involvement of the jaws greatly exceeds involvement of any other part of the skeleton. Jaw tumors are age-related. All children aged three with BL seen in Uganda in the 1960s had jaw tumors, whereas by the age of 15 only 10% had jaw involvement. The age incidence of jaw tumors coincides with the period of maximum dental development. It also coincides with the presence of cellular bone marrow in the mandible. Recent studies using magnetic resonance imaging have shown that cellular marrow in the mandible retreats toward the condyle and is largely replaced by fatty marrow in late childhood.

Jaw tumors in endemic BL usually involve more than one quadrant of the jaw and involvement of all four quadrants is not uncommon. The tumors are clonally related, precluding independent origin in each quadrant, and suggesting that the tumor cells specifically home to and proliferate at this site. A few years ago Dr Jayola Thomas and I conducted a histological study on segments of mandible obtained at post-mortem examination on children from Ibadan, Nigeria. Most of these children had died of infection or trauma. We identified lymphoid aggregates in relation to the unerupted teeth, at the site where the earliest jaw tumors are detected by radiology. This finding raises many questions. Are these aggregates of mucosal lymphoid tissue? The dental epithelium is a downgrowth from the oral epithelium and therefore of mucosal origin. Is this lymphoid tissue physiological or is it induced by an infectious agent, possibly EBV? Unfortunately the jaw marrow is not the easiest tissue to study but it would be of interest to know whether this lymphoid tissue is found in the jaws of children from other areas of the world. It is intriguing to consider that if these lymphoid aggregates are caused by an infectious agent much more common in African children, and if they also account for the high frequency of jaw involvement in Africa, then environmental factors, like host factors (e.g. the lactating breast), may have a role in determining the clinical sites of disease. ■

submitted by Dennis Wright
Professor of Pathology Emeritus
The University of Southampton

NEWS BRIEFS

VOLUNTEERS

INCTR is very pleased to have a number of volunteers helping in the Brussels office. These include Sandra Jackson, who is assisting in the administration of the INCTR's new Education Program, Janet King, who is providing overall administrative support, and Hilary Wallace, who is providing assistance in INCTR's Public Relations efforts. ■

VISIT TO IARC AND UICC

INCTR staff visited the International Agency for Research in Cancer and the International Union Against Cancer in July. The purpose was to discuss collaboration in the area of cancer control, particularly with respect to activities in Nepal in conjunction with the Nepalese Cancer Relief Society. It was agreed with IARC to explore the possibility of establishing a project relating to the early detection of cervical cancer, and possibly to establish a cancer registry in at least one region in Nepal. The UICC also expressed an interest in collaborating in cancer control projects, and will further explore specific possibilities with INCTR in the context of Nepal. ■

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

THE PHILIPPINE CHILDREN'S MEDICAL CENTER

by Dr Julius A. Lecciones
Chief Research Officer

The Philippine Children's Medical Center (PCMC) is the country's premier pediatric tertiary-care facility. Created by Presidential Decree in 1979, it is the Department of Health's flagship hospital for children.

The hospital is envisioned to be a leader in specialty care of the unborn child, neonates, children and adolescents. In order to attain this national preeminence, the institutional mission encompasses a three-fold objective of service, training and research.

FACILITY AND STAFF

The hospital has modern equipment suited for tertiary level of specialty care, including sophisticated laboratory, imaging and nuclear medicine departments. It also has a full complement of general pediatric, and subspecialty medical, surgical and diagnostic services. The hospital is host to 163 attending pediatricians and medical consultants who are the preeminent experts in the country. About 60 residents and 50 post-residency fellows per year complement this medical manpower. Supporting the medical staff are pediatric nurses, medical technologists and allied-medical technologists who are among the best in the country.

PCMC is located in a suburban city east of Manila. It is a 200-bed hospital for indigents and paying patients in a ratio of 60:40, respectively.

PATIENT POPULATION

An average of 60,000 outpatients are seen each year with more than 9,000 average annual inpatient service and pay patient admissions. There is an upward trend in the number of admissions and consultations. This increasing trend is most noticeable in cancer patients. 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, and the growing reputation of the hospital has led to it providing a nationwide referral service.

The majority of patients have infectious diseases, mainly respiratory and diarrheal illnesses, but second to infectious diseases are cancer cases, especially hematologic malignancies. Oncology patients account for 17% of inpatient service admissions.

HEMATOLOGY ONCOLOGY SERVICE

The Pediatric Hematology-Oncology Section includes both in-patient and outpatient services. In addition to the multidisciplinary cancer team, pediatric surgery, radiology, pathology and child psychiatry are also part of the core team.

There are seven consultants and attending oncologists in the section itself, complemented by four post-residency clinical fellows, and two tothree pediatric residents on rotation at any given time. Patient follow-up, some chemotherapy and diagnostic procedures are performed in the outpatient clinic. There is always at least one consultant/attending physician assigned to each in-patient and outpatient service.

An average of 2,500 outpatients are seen or treated annually. The average in-patient admissions total 530 per annum. 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 inter-departmental referrals each year.

Aside from bedside and outpatient teaching rounds, other activities include the tumor board conferences, hospice care meetings, monthly case audits, mortality/morbidity reviews, weekly journal clubs, pathology rounds and slide reviews, morphology sessions, case management, blood transfusion committee meetings and histology committee meetings.

FELLOWSHIP TRAINING PROGRAM

The hospital runs one of only two accredited post-residency fellowship training programs in pediatric hematology-oncology in the country. It is a three-year program that includes clinical rotations in various disciplines during the first two years, with the last year devoted to research. This program started in 1991, and 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 hospitals in various parts of the Philippines.

HOSPICE CARE PROGRAM

The Hospice Care Service was started in 1995 to provide long-term support (psychosocial, psychological and spiritual) 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 AND DEVELOPMENT OFFICE

The Research and Development Office, created in 1992, was charged with developing strategies and action plans for institutional research capability building. It was empowered to formulate policies, rules and regulations necessary in realizing the goals of establishing the hospital as a research center.

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

PCMC adapted the "Essential National Health Research" concept in the rationalization of its research thrusts. Consequently, research that results in the provision of tools for decision-making or a guide for policy is particularly encouraged. Areas in which PCMC had demonstrated preeminence 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 focused on three areas: research infrastructure (clinical epidemiology and data management unit, research laboratory, information center, medical records modernization project and audio-visual unit), research manpower training and international linkages.

CANCER RESEARCH ACTIVITIES

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. Insights can be gained on why patients present in late stages of their diseases, or why they do not complete their prescribed treatment. In addition, we should be able to compare clinical behaviour patterns with western patients in the same histological and treatment groups.

Secondly, locally adapted and cost-effective protocols are studied in order to best respond to limitations in resources for cancer treatment in a financially challenged country like the Philippines. 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 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. ■

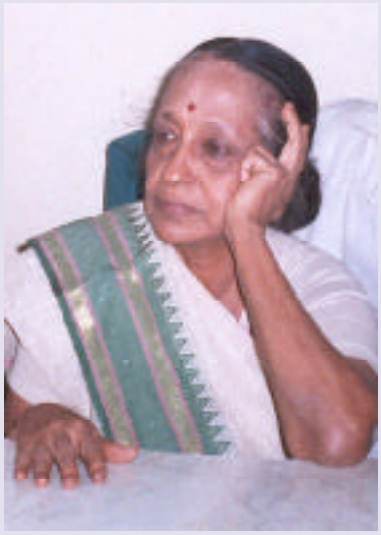
PROFILES IN CANCER MEDICINE

BUILDING HOPE IN INDIA

She went to medical school at a time when most Indian women did not pursue professional careers. She never married or raised a family, devoting her life instead to medicine. Independent and idealistic, she sought to help the sick and dying people she saw languishing on city streets, with nowhere to turn for help. She took up the fight against cancer under difficult circumstances and sought to bring hope and healing to the most unfortunate inhabitants of her country. Today, Dr V Shanta looks back on a career spanning 50 years, a career during which she helped to build one of the largest, most comprehensive cancer centers in India. The Cancer Institute's mission was in its earliest beginnings the same as it is today: to bring to the poorest of the poor the most refined scientific technology and the best patient care possible.

Shanta went to work for India's first female medical graduate, Muthalakshmi Reddy, in a 12-bed thatch-roofed hospital where she and a single colleague worked in 12-hour shifts. Much of what she learned about cancer treatment she taught herself. Her earliest patients came to the hospital in dire straits. "Everyone was in dismal condition," Shanta recalls. "There were very few we could cure. The treatment we could offer was inadequate and most were in advanced stages of cancer."

"Today, we do see many patients being cured," says Shanta. "That is one satisfaction. It is also satisfying to know that we have trained so many dedicated professionals. But the road is never-ending. Still we are working with very limited resources. In the grand scheme, we have done so little, and there is still so much to be done."



Dr V Shanta is executive chairman of The Cancer Institute in Chennai.

Shanta believes that the key to success in cancer treatment in her country lies with the people of India who are trained in medicine—many of whom are working abroad. "We have to provide the conditions for them to come back," Shanta says. "That is what we are trying to do at the Cancer Institute. We have asked for support for visiting professors to come and train our staff in sophisticated areas such as molecular techniques and cytogenetics, which we can use for routine diagnoses. We would like to have visiting professors train and evaluate our medical staff. Together, we can make good progress." - *MCL*

EDITOR'S NOTE

This is a Special Edition of *NETWORK*, with expansive coverage of news from the 2001 Annual Meeting and a new feature, "Profiles in Cancer Medicine," that we plan to continue with each issue. Because of space limitations, we dispensed with our normal Case Report coverage in this issue. Look for a report and an article on Burkitt's Lymphoma in the next edition. We welcome letters and case reports from our readers on any topic related to cancer in countries with limited resources. Please send your submissions to:

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INCTR ANNUAL MEETING SET FOR SPRING 2002

Planning is underway for the next INCTR Annual Meeting, which will take place in Brussels between 29 May and 1 June. Based on suggestions made by participants of the 2001 meeting, a poster session and special lectures by individuals who have made major contributions to cancer treatment in developing countries will be included. Further information will be provided in the next edition of *NETWORK*. ■