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Volume 2, Number 4, Summer 2002 — **Inside**: Breast Cancer Review - **5** Case Report - **6** NNCTR Project Report - **9** Letters - **12** News - **15** Partner Profile: Bhaktapur Cancer Care Center - **18** Profile in Cancer Medicine - **20**

THE PRESIDENT'S MESSAGE

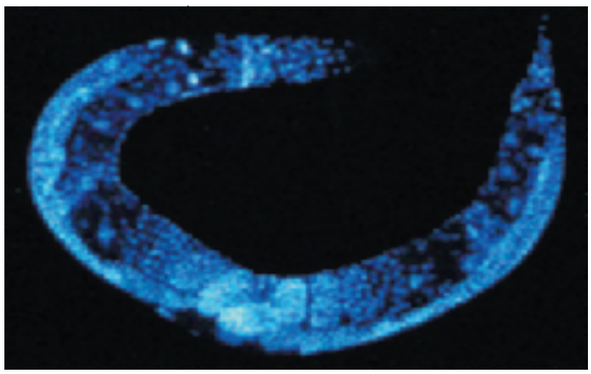
BALANCING RISK: THE FAUSTIAN DILEMMA OF CANCER CHEMOTHERAPY

by Ian Magrath

Es ist so schwer, den falschen Weg zu meiden,
Es liegt in ihr so viel verborgnes Gift. —Goethe

Cancer chemotherapy, as patients and those who care for them are only too well aware, can be a double-edged sword. This is perhaps not surprising for a treatment modality whose existence owes much to a substance developed for belligerent rather than benevolent purposes—mustard gas. Initially used in World War I, it was considered to be an advance over chlorine as a weapon of mass destruction because of its devastating effects on exposed body parts, and its ability to penetrate the protective clothing and gas masks available in 1917. Although it was soon observed that non-fatal victims rapidly developed low blood cell counts, it was an event in World War II that gave major impetus to the notion that a substance developed as a weapon might be used to combat human disease.

In 1943, American munitions ships and tankers berthed in Bari Harbor in southeastern Italy were bombed. Sixteen were sunk. Hundreds of oil-soaked men were rescued from the water and were soon observed to be suffering from unexpected symptoms. Eighty-three died. The cause of their demise was traced to contamination of the oily water with nitrogen mustard—one of the ships, the *Liberty*, had been carrying 100 tons of mustard munitions. Low blood counts were again observed among the exposed military personnel and autopsies in 53 of the victims revealed marked involution of lymphoid tissue. Studies at Yale University showed that this effect could be reproduced in mice and in 1946 Goodman and colleagues reported beneficial effects on lymphoid neoplasms in people. Nitrogen mustard is still used in the treatment of Hodgkin's lymphoma, although medical staff who handle or administer the drug must not only ensure that it is injected cleanly into a vein, with no leakage into subcutaneous tissues, but must also take steps to avoid inhalation of its vapors and to prevent it from coming into contact with their own skin. Although many chemotherapeutic agents have been developed since World War II, the vast majority of these, while generally not injurious to tissues on direct contact, have the potential to damage or destroy normal cells as well as cancer cells. They are, in effect, poisons whose dosage and administration must be carefully controlled if susceptible cancers are to be eradicated without causing irreparable harm to patients. Such potentially harmful agents must only be given under expert supervision.



Photomicrograph of the "Elegant" nematode worm, *Caenorhabditis elegans*, which provided a model for the understanding of apoptotic processes in embryonic development (see panel on page 3), and led to the discovery of the first "death proteins" involved in apoptotic pathways. Picture published with the kind permission of James McCarter and Tim Schedl, Washington University.

NETWORK

Shedding Cancer Cells

Cancer cells are malignant by virtue of their capacity for unlimited expansion and their potential to spread to parts of the body beyond their sites of origin. Most conventional anti-cancer drugs are particularly toxic to dividing cells, and in all cancers, a fraction of the cell population must be capable of undergoing replication, since otherwise the cancer could not grow. In general, the higher the replicating fraction, the greater the likelihood that the cancer will be curable by chemotherapy (at least, by those drugs that primarily affect dividing cells). But many normal cell populations in the body are in a dynamic state of equilibrium between the production of new cells and the death of old or spent cells, such that, like cancer cells, some are also continuously dividing. Cell populations in which the turnover rate is high, such as blood-forming cells and lymphocytes (as observed in the victims of exposure to poison gas), cells of the hair follicles, and the lining cells of the mouth and gastrointestinal tract are particularly susceptible to anti-cancer drugs. Perhaps the most common side effect observed with the majority of drugs in use today is the increased risk of potentially life-threatening infections as a consequence of diminished numbers of white cells, which are responsible for protecting against infection and which, given their high turnover rates (sometimes higher than those of tumor cells), are particularly susceptible to chemotherapy. The reason that conventional anti-cancer drugs predominantly affect dividing cells is that the majority of them interfere either with DNA replication (duplicating the genetic material is an essential first step in cell division), or with the physical process of the separation of daughter cells. Cells die when something goes wrong with this process because of the existence of a "quality control" mechanism, whereby irreparable damage to the genetic material, or other disturbances which might lead to imperfect replicas of the parent cells, switch on a molecular pathway that induces suicide through the activation of enzymes that literally digest the cells' component parts. This process, which is active (i.e., consumes energy) and, unlike other kinds of cell death does not excite inflammation, is known as *programmed cell death* or *apoptosis*. The latter is a Greek word which refers to any process of shedding, such as the falling of leaves from trees in autumn (which itself involves apoptosis). The word apoptosis was suggested by a Greek scholar, James Cormack, of Aberdeen University, to the discoverers of programmed cell death, Kerr, Wyllie and Currie, as a fitting term for the "cellular dropout" they had described in 1972.

***Vinca rosea*, the plant from which a frequently used chemotherapy agent, vincristine, is derived. Many drugs used in cancer chemotherapy today are natural products.**

Poison in the Cure

Drugs that cause damage to replicating cells (and often have other side effects too) can cause severe toxicity, or, as demonstrated on the battle fields of Flanders and in Bari Harbor, even death, if given in too high a dose. The goal of cancer chemotherapy is to give enough of a drug, or a combination of drugs, to eradicate cancer, but not enough to induce severe or irreversible toxicity. Medical oncologists have spent a good part of the second half of the last century learning, through empirical clinical trials, where the dividing line between acceptable and unacceptable toxicity lies. The line is not fixed, and indeed, varies from one patient to another, so that one can only deal in probabilities in the context of populations (cohorts) of patients - i.e., the percentage of patients who will develop toxicity of a given degree with a given dose of drug. Greater risks are warranted when the stakes are high, i.e., when the likelihood of curing the patient is considered low and the disease is one which progresses rapidly.

The *therapeutic ratio* (the risk-benefit ratio) can be altered in favor of the patient by the combined use of several chemotherapeutic drugs active in the disease, because each will have a somewhat different range of toxic side effects, if often overlapping; several relatively minor side effects are more tolerable than a single major toxicity. Drug combinations are also more efficient therapeutically, since each drug damages the tumor cell in a different way, making it more difficult to survive the cumulative damage or to develop resistance to subsequent treatment (one treatment administration is rarely enough). Resistance arises because of the presence of mutations which, through any of a broad range of mechanisms, negate the effects of the drug. Combination therapy has been remarkably effective in some types of cancer, even when advanced, e.g., in leukemias and lymphomas, childhood

Developing Worms Elucidate Cancer Pathways

The protein components of the molecular pathways leading to apoptosis were first identified in the nematode worm, *Caenorhabditis elegans*, by Horvitz, after Sulston and Brenner had shown that apoptosis is critical to organ development, and to determining the number of cells (959) in the adult worm. The work of all three was recognized this year by the award of a Nobel prize. The nematode proteins have their counterparts in a wide range of multicellular organisms, including humans, indicating that apoptosis is a fundamental biological process. Indeed, apoptosis is, in essence, a regulator of the numbers of cells in a variety of cell populations, and as such is a critical element not only in sculpting the form (and in the case of the nervous system, the neurological connections) of the developing embryo, but also in the control of numerous physiological processes. In mammals, apoptosis is involved in the shedding of cells from inner lining surfaces, such as those of the gastrointestinal tract and endometrium, as well as in the regulation of the expansion of immunologically competent cells participating in an immune response. Virus-infected cells can be killed through the activation of apoptotic pathways. The induction of programmed cell death in cells in which the genetic material is damaged, or in which normal replication is hindered, is particularly relevant to tumor cells, since genetic abnormalities are the immediate cause of neoplasia. In order for genetically modified cells to survive, one or more of the apoptotic pathways must be inactivated by the genetic abnormalities themselves. The tumor cells are then able to pass the *check points* of cell division and differentiation where abnormalities are detected and sufficiently damaged cells diverted into an apoptotic pathway. Interestingly, tumor cells sometimes mimic immunologically competent cells and develop the capability of activating apoptotic pathways in normal cells, for example, lymphocytes that would otherwise destroy the tumor cells. There are many paths that lead to apoptosis, and while some may be damaged in tumor cells, others are activated by chemotherapeutic agents to which the tumor is sensitive, or by radiation therapy.

cancers, testicular cancers and choriocarcinoma, although in many other cancers, chemotherapy has limited benefit or is able to control the disease temporarily, but not to eradicate it, i.e., there is inherent resistance to available chemotherapeutic drugs—perhaps due to a general resistance to apoptosis.

Balancing Risk

The success of chemotherapy depends upon three main factors. The particular drug combination used, the sensitivity of the cancer itself (which varies according to the extent of disease and the biochemical attributes of individual cells) and various patient characteristics which influence the amount of active drug that finally reaches the cancer cell. Most drugs are chemically modified (metabolized) in the body before the active element is formed and are also converted into inactive elements. The drug and its derivatives (metabolites) are eliminated from the body, each with its own time frame. Inherited genetic factors influence the efficiency of the various enzymes involved in drug activation and detoxification, as well as the ability to repair damage done by the drug to both normal and tumor cells. Both are relevant to the outcome of therapy and the degree of toxicity encountered. Genetic variability in both tumors and patients provides an explanation for the inability to predict outcome in individual patients. Interestingly, some of the inherited characteristics which influence the efficacy of treatment and the degree of toxicity are also relevant to the impact of environmental toxins (carcinogens) that cause or predispose to cancer.

Estimates of the likelihood of therapeutic benefit can be significantly refined by defining *risk factors*. These are characteristics of the cancer (e.g., its size, degree of spread, or molecular genetic abnormalities) or of the patient (e.g., age, sex, general state of health, or inherited ability to metabolize a drug or repair genetic damage) that are known to affect outcome with a given treatment regimen. Risk factors are of considerable value in determining the most appropriate therapy for the patient, for risk in medicine, as in all walks of life, must be consonant with potential benefit—the greater the likelihood of treatment failure (and, therefore, death) the greater the acceptable risk of significant toxicity. This is the premise on which the principle of *risk adaptation* of therapy is based—patients with a low risk of dying (i.e., who respond well to a given treatment

regimen) can be successfully treated with less intensive, less toxic (and less expensive) therapy while patients at high risk (i.e., much less likely to respond to a given treatment regimen) may appropriately be given more intensive and therefore more toxic therapy.

It is important that therapy is not reduced to sub-optimal doses in low risk patients, or made sufficiently intensive that the likelihood of severe toxicity is unacceptable even in high risk patients. Drug doses or scheduling may have to be modified in individual patients who encounter excessive toxicity. Balancing therapeutic effect with toxic risk is not easy, but in the more readily treatable diseases, e.g., childhood malignant lymphoma, successive clinical trials with increasingly intensive regimens for higher risk patients have resulted in survival rates of approximately 90% in both high- and low-risk patients, although the therapy given to each group differs markedly in intensity. Of course, whether a patient succumbs to a life-threatening toxicity is, to a significant degree, dependent upon the quality of the medical care received, particularly the immediate administration of antibiotics to treat or prevent an infection arising in a patient with a low white blood count. Skilled supportive care is critical to the success of chemotherapy regimens associated with a significant risk of toxicity.

Geographical Variation in Risk

While the principles of chemotherapy outlined above apply to patients anywhere in the world, in developing countries the balance between therapeutic benefit and toxicity may differ greatly from that in countries with greater resources. The response of tumors to chemotherapy in different world regions may vary because of differences in the pattern of genetic abnormalities present in tumors; because of differences in factors that modify drug metabolism or tolerance, including genetic variability in different populations (sometimes enhanced by higher rates of consanguinity); and because of co-morbidities, i.e., the presence of unrelated health problems (e.g., malnutrition, malaria, hepatitis or tuberculosis). Excessive toxicity may dictate modifications in dose, schedule or even discontinuation of individual drugs or the entire treatment program. Treatment may also be compromised because of prohibitive cost, the quality of supportive care, or the ability or willingness to adhere to the planned therapy (on the part of doctor or patient).

In developing countries, cancers are generally much more extensive at the time of presentation because of delays in diagnosis or limited access to appropriate therapeutic facilities, such that a greater proportion of patients fall into a high risk category—requiring, if still potentially curable, more toxic and more expensive therapy. Radiotherapy or surgery alone is rarely curative in patients with disseminated tumors. Thus, the lack of resources creates a vicious cycle—limited resources result in poor access to care and consequently more advanced tumors, which in turn require more resources for their management. The INCTR's mission is, in essence, to help to demonstrate that this vicious cycle can be broken—by ensuring, through professional and public education, and, where appropriate, screening programs, that more patients reach appropriate treatment facilities early in the course of their disease, while at the same time enhancing the capacity to deliver appropriate therapy safely, such that potentially curable patients receive the care they need. Patients for whom cure is not an option should be given palliative care—another area where limited resources lead to suffering which could frequently be easily ameliorated. Prevention, including education about behavior that increases cancer risk and screening high-risk populations for accessible, simply treated pre-malignant lesions (e.g, cervical and oral cancers) will, if successful, help to slow the rise in the burden of cancer resulting from increasing population size, aging, higher tobacco consumption and dietary changes. Clearly, the need for augmentation of resources, and for simultaneous efforts on multiple fronts will require effective, coordinated collaboration with many institutions and organizations.

The Future - Targeting Drugs at the Lesions Responsible for Cancer

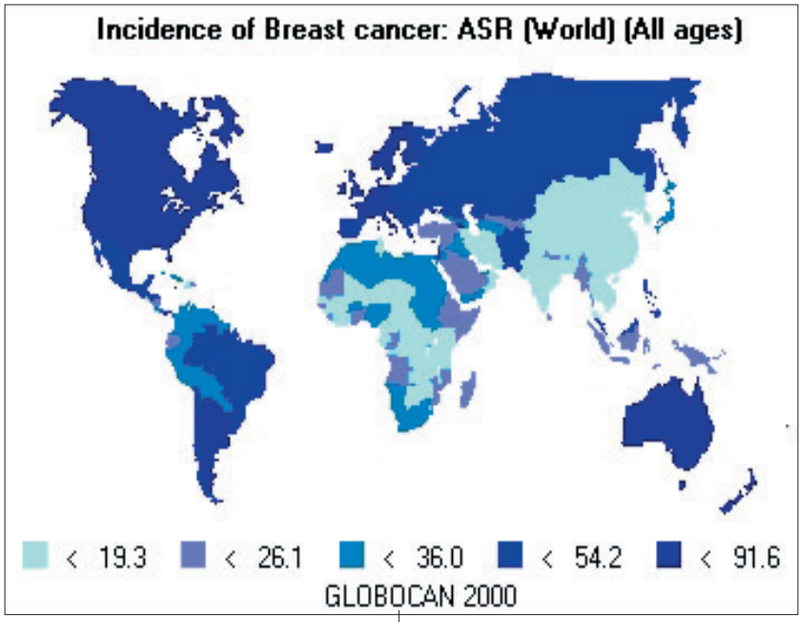
Advances in the understanding of the molecular genetic lesions that are the immediate cause of cancer provide promise that the next generation of chemotherapeutic drugs will be much less toxic. These genetic lesions provide an "Achilles heel" which is, in essence, specific to cancer cells, such that drugs targeted at them should be equally specific. Doubtless, combinations of such drugs will be required, since cancer cells contain multiple genetic lesions and are adept at developing drug resistance. Targeted drugs, which are likely to have the relatively low toxicity rates of the order of magnitude seen with present antibiotics,

(continued on page 15)

BREAST CANCER IN BRIEF

Breast cancer is the most common cancer in women in the world. According to the GLOBOCAN database of the International Agency for Research on Cancer (IARC), there were over a million new cases in the world in the year 2000, 579,285 occurring in more developed countries and 471,063 in the less developed countries. The highest rates in the world (>90 per 100,000) are in the USA and the Netherlands; the lowest (<6 per 100,000) are in Haiti and the Gambia. Since many more women live in less developed countries, however, the annual incidence rate of breast cancer is almost three times as high in the more developed countries (63 per 100,000 females, age standardized rate (world), versus 23 per 100,0000 in the less developed countries). Within developing countries, breast cancer has a higher incidence in upper social classes than in lower, in which cancer of the uterine cervix is more common. Breast cancer affects approximately 1 in 8 to 10 women in western nations.

Breast cancer is predominantly a hormone-dependent cancer, the risk of development being in part related to the duration of estrogen exposure during a woman's lifetime (and, in fact, to higher blood estrogen levels). Early menarche (younger than 12 years in western countries) and late menopause (over 55 years) increase the risk, as does a late (over 30 years of age) first pregnancy, while more pregnancies, and possibly the total duration of lactation, are associated with a lower risk. Increasing age, a family history in an immediate relative (particularly if young), previous history of breast cancer (or premalignant breast disease) or of certain other cancers,



especially other conditions in which radiation has been given to the chest, such as Hodgkin's lymphoma or thyroid cancer, greatly increase the risk of developing breast cancer. Other potential risk factors such as smoking, alcohol and fat consumption may be relevant, but remain controversial. Although there is a close correlation between national per capita dietary fat intake and the incidence rate of breast cancer, fat consumption could be a surrogate marker for other aspects of a more affluent lifestyles. Of interest in this regard, however, are the low rates in wealthy South Korea (12.5 per 100,000) and Japan (31.3 per 100,000). Mutations in certain genes, particularly p53, BRCA1 and BRCA2, are associated with a markedly increased risk of developing the disease (which tends to occur at a much younger age), but mutations in these genes do not account for all familial cases, suggesting that other predisposing genes remain to be discovered. The relative importance of these various risk factors has not been well studied in developing countries, but higher pregnancy rates and dietary differences could well be relevant to the lower incidence. It should also be stated that in most women with breast cancer, a specific risk factor cannot be identified.

There are a number of subtypes of breast cancer. Most arise from ductal epithelium (i.e., the lining of the duct carrying milk from the cells which produce it). Intraductal lesions, including papillary carcinomas, arise from large ducts and in some cases do not penetrate the ductal basement membrane which lies beneath the lining cells of the ducts. Such cancers are not, then, invasive, and can be considered premalignant lesions (ductal carcinoma in situ, or DCIS). They are readily cured by surgical excision. Lobular carcinoma arises from the small end-ducts of the breast tissue and, like DCIS, may not penetrate the basement membrane of the lobules— so-called lobular carcinoma in situ. The most common invasive breast cancers in western countries,

accounting for approximately 70% of breast cancers, are ductal carcinomas. The majority have no additional characteristic features, but subtypes, e.g., medullary, tubular and mucinous varieties, are occasionally observed. Lobular carcinomas account for some 10% of breast cancers. Paget's disease of the breast, which presents with eczematoid changes in the nipple with an underlying carcinoma (either intraductal or invasive), occurs in less than 5% of cases. Inflammatory breast cancer is characterized by dermal lymphatic invasion by cancer cells and redness and warmth of the skin. This may occur either at initial diagnosis or at the time of recurrence. Inflammatory breast cancer appears to be more common in North Africa (see next article), and may or may not represent a separate pathological entity. Rare breast cancers include adenocystic carcinoma, carcinosarcoma, squamous cell carcinoma or metaplastic carcinomas (with bony or cartilaginous elements). The advent of mammography in more affluent countries has revealed a broad range of premalignant lesions and breast hyperplasias (benign growths) that require considerable pathological expertise for their diagnosis. Many of these lesions may not become malignant in the lifetime of the woman, such that clinical decisions regarding treatment are not always easy.

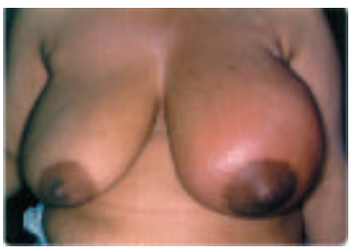


Figure 1: A patient with inflammatory breast cancer generally presents with a tender, firm and enlarged breast, rather than a discernable mass. This patient was diagnosed with acute mastitis carcinomatosa involving the entire breast.

Breast cancer is highly curable if detected early, and since the majority of breast cancers are first noticed by the patient (as a lump in the breast), public and professional education may be the single most important factors in increasing the rate of early detection. Unfortunately, in developing countries, the majority of patients—often as many as 80%, which is the inverse of the fraction in affluent nations—have advanced disease. Simply reducing the size of this problem would improve survival rates. Mammography has been widely accepted as being valuable in reducing mortality from breast cancer in women aged 50-69, but recent results from some countries have created some controversy in this regard.

Treatment may involve any of the primary cancer treatment modalities, including surgery, radiotherapy, chemotherapy and hormonal therapy, or a combination of these, depending upon the size of the lesion, the presence of lymphatic or distant spread, the estrogen (and progestogen) receptor status of the tumor, as well as the patient's menopausal status. Lumpectomy (removal of the tumor with preservation of the remainder of the breast) and radiation have been shown to be as effective as removal of the entire breast (mastectomy) in women with operable disease. Both chemotherapy and hormonal therapy (tamoxifen) have been shown to decrease the likelihood of recurrence after local therapy, tamoxifen, which blocks the binding of estrogen, being used in estrogen receptor positive cancers (sometimes in addition to chemotherapy). The role of antibodies directed against tumor cells, although active in patients with metastatic disease, is still under study in patients with less advanced disease. Results depend upon the extent of the disease as well, of course, as the therapy given. Recurrence or spread can occur many years after primary treatment. In more developed countries, mortality rates are about a third of incidence rates, but a much higher—although not precisely known—proportion of women with breast cancer die from their disease in less developed countries.

—Ian Magrath, INCTR

INFLAMMATORY BREAST CANCER

Inflammatory breast cancer (IBC) is one of the most aggressive types of locally advanced breast cancer. It was first described by Lee and Tannenbaum in 1924[1]. The designation "inflammatory" stems from the clinical appearance, which mimics an acute inflammation of the breast (Fig. 1). This type of cancer has been considered to be a special clinico-pathological entity but there is not general agreement on this. The typical patient presents with pain and a tender, firm and enlarged breast characterized by diffuse brawny induration of the skin with an erysipeloid edge. In the earliest phase, a mass may not be palpable. These signs and symptoms are characteristically rapidly progressive with a median duration before diagnosis of less than two months.

IBC represents 1% - 6% of all breast cancers [2]. A strikingly high incidence of this form of breast cancer has been reported in North Africa, especially in Tunisia and Egypt. It is unclear, however, whether this

clinical presentation is related to differences in the biologic characteristics of the disease or variability in diagnostic criteria. Two types are usually distinguished: (1) a primary type in which inflammatory changes appear simultaneously with the carcinoma, and (2) a secondary type in which the inflammatory manifestations appear in a breast with longstanding carcinoma.

Pathologically, IBC is highly angiogenic and angioinvasive. Although it is not a specific histologic subtype of mammary carcinoma, the presence of numerous ectatic and dilated dermal lymphatics clogged by malignant cells constitutes the histologic hallmark that is associated with the clinical picture. Tumor emboli eventally give rise to metastases [3]. Primary IBC is often of ductal type, with prominent angio-lymphatic invasion (Fig. 2). It usually has a high histologic grade with pleomorphic tumor cells and highly atypical mitotic figures. In contrast to secondary IBC, invasion of the dermis outside the lymphatic vessels is uncommon. The skin within and outside the zone of erythema appears histologically identical, with tumor emboli frequently present in areas that are clinically unremarkable.

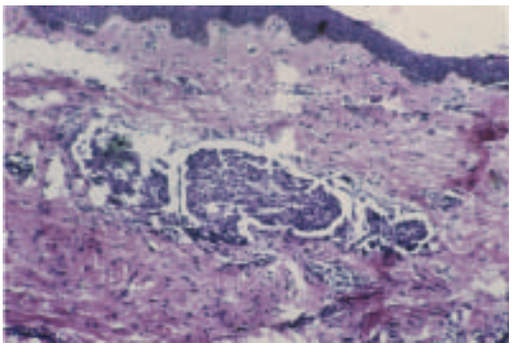


Figure 2: Primary inflammatory breast cancer is often of ductal type, with prominent angio-lymphatic invasion.

Although the histologic features of IBC have been well described, the molecular basis of the disease has been only recently investigated. This work has led to the identification of genes that are involved in the development and progression of the disease [4]. The majority of IBC tumors are estrogen receptor (ER) and progestogen receptor (PgR) negative, epidermal growth factor receptor (EGFR) and c-erb2 positive, and have a rapid growth rate. Genetic concomitants of the IBC phenotype are being evaluated and include p53 mutations [5], expression of RhoC GTPase and LIBC genes [6], and high levels of vascular endothelial growth factor (VEGF), basic fibroblast growth factor, IL-6, and IL-8. The latter are secreted by the tumor cells. Recently IBC cell lines such as SUM149, SUM198[7], and a unique xenograft model [8] have been developed.

Evolutionary Phase	No. of Patients	Survival
PEV0	233	46.0%
PEV1	56	26.0%
PEV2	65	18.5%
PEV3	14	21.4%
Total	368	

Table 1. Relation between evolutionary phase and five-year relapse-free survival (p<0.001)

Staging

The TNM classification system first adopted by the UICC in 1972 is the most commonly used system for the staging of breast cancer patients. However, this classification does not distinguish inflammatory breast cancer, whose clinical behavior differs irrespective of the original tumor measurements or apparent nodal involvement. Consequently, an adjunctive system of classification was adopted by investigators at Gustave-Roussy Cancer Institute in France. In this system inflammatory tumors are classified according to their evolutionary phase (Phase Evolutive).

Two elements, signs of inflammation and the growth rate, were used to distinguish the three degrees of evolution.

PEV3—These are the worst cases, which correspond to the classical acute inflammatory type of breast cancer. The entire breast is hot, red

and presents with diffuse edema of the dermis and subcutaneous tissues. There is almost always a collateral circulation and greatly enlarged lymph nodes are hidden in the edematous tissues, i.e. the picture of acute mastitis carcinomatosa involving the entire breast (see page 6).

PEV2—These are the cases of moderate severity, which correspond to the sub-acute pseudo-inflammatory form which involves only a part of the breast. However, peritumoral and cutaneous edema is more often to be found beyond the limits of the tumor, even though at times it is difficult to precisely demarcate. The enlarged lymph nodes are often matted together and attached to the tumor by an indurated cord of "neoplastic lymphangitis."

PEV1—These are the cases which are apparently the least serious but also the most difficult to define. They are differentiated from the usual "chronic" type of breast cancer by one essential and unique characteristic: the rapid rate of growth.

PEV0—These are the cases which correspond to the classic "chronic" type of breast cancer but they lack the previously mentioned signs of inflammation.

Any tumor which has apparently doubled in size in six months is considered to be in evolution (progressive). The determination of this characteristic is based on questioning of the patient and thus is subjective. Clearly classifying the phase of evolution is impossible for recently discovered tumors. However, a skin biopsy for demonstrating involvement of skin lymphatics by tumor cells is a more reliable method of assessing the stage of evolution.

In a study of 73 patients classified according to this staging system and conducted at the NCI, Cairo in the 1980s, 48 cases were diagnosed as inflammatory (PEV2 and PEV3), and 25 were non-inflammatory (PEV0 and PEV1). Histpathological examination of 45 cases revealed 35 primary and 10 secondary types. Twenty-nine per cent of the inflammatory cases were postmenopausal. The median age was 42 years with a peak incidence in the fifth decade of life. Bilateral breast involvement was encountered in four cases. All inflammatory breast cancer cases had lymph node involvement at presentation; 75% had axillary, and 25% had both axillary and supraclavicular nodes. A large number of cases occurred during pregnancy (27%). A bigger tumor size at presentation (mean: 7.2 cm) was also observed. The majority of inflammatory breast cases were ER negative (73%). The relation between evolutionary phase and five-year relapse-free survival is presented in Table 1.

Treatment

Until the introduction of combined modality therapy, fewer than 5% of patients with IBC survived five years[9]. While radiotherapy alone yielded five-year survival rates of 12%-38% in various series, a combination of surgery and radiotherapy has slightly improved five-year survival rates in some studies [10]. This discouraging outcome, and the hypothesis that virtually all patients with IBC have disseminated micrometastases at presentation, led to the use of neoadjuvant chemotherapy before and after surgery and/or radiation. Several studies have been published from the Harvard Joint Center for radiation therapy, the Milan group, and the MD Anderson Cancer Center [11-13]. The largest series of patients was reported by Rouesse et al [14] who studied 230 patients who received either radiotherapy alone or three cycles of neoadjuvant chemotherapy followed by alternating cycles of radiation and chemotherapy, as well as maintenance therapy. Two different drug combinations were administered, one with more drugs and more prolonged maintenance therapy. All patients had hormonal treatment as well. The four-year disease-free and overall survival rates were significantly better for those who received additional drugs and more prolonged chemotherapy, reaching 46% and 66% respectively. Both chemotherapy regimens gave superior results to radiation alone without chemotherapy.

These studies were followed by other studies that were based on the concept of prolonged neoadjuvant anthracycline-containing chemotherapy to the point of maximal objective clinical response followed by local/regional treatment and consolidation chemotherapy [15]. This has led to both improved disease-free and overall survival rates. This approach now constitutes the mainstream of current treatment for patients with IBC. However, improving our understanding of the molecular basis of IBC, and the use of novel targets for future interventions in the diagnosis and treatment of this type of malignancy, are clearly needed. ■

Submitted by Sherif Omar and Hussein Khaled, National Cancer Institute, Cairo, Egypt.

Editor's Note: References for this article are available from INCTR upon request.

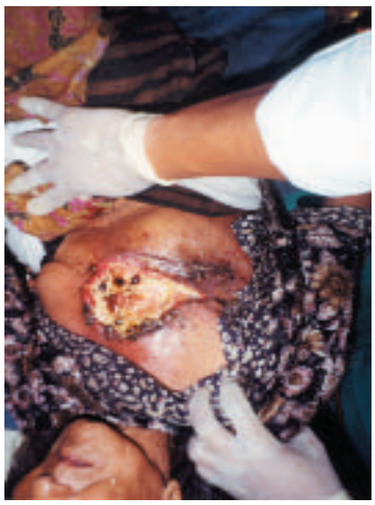
THE PRICE OF NEGLECT IN BREAST CANCER

Summary

A case is presented of a breast cancer associated with a maggot-infested wound in an elderly Nepalese woman who received no care for six months.

Case Report

A 70-year-old nulliparous widow from rural Nepal was brought to our referral-level hospital with a six-month history of a non-healing wound of the right breast. She had suffered from a progressive lump in the breast, which later ulcerated, for the last year. Her relatives noticed some maggots in the wound. Menarche and menopause were at the ages of 13 and 49 years, respectively. Her husband died a few months after their marriage, when she was 14 years old. Since then she had become a heavy smoker and consumed homemade alcohol regularly. She stopped these habits five months ago when her neighbors explained that this wound would not heal unless she gave up alcohol and smoking. She had been staying alone in a small house for almost 40 years.



She had never sought modern medical advice. Her past medical and family history were not contributory to the present illness. She was brought to the hospital only because her relatives found that the ulcerated foul-smelling wound was not getting better with local herbal treatment. Moreover, the presence of maggots in the wound provoked them into taking her to a medical center. She was unaware of the malignant nature of her disease. On clinical examination, she was a thin-built, moderately nourished elderly female who was very concerned about being examined in the outpatient clinic. On local examination, there was a large irregular ulcerative growth (10 by 12 cm) with a necrotic base and many maggots in the right breast which had essentially undergone auto-amputation (Fig. 1). There were three fixed axillary lymph nodes and the arm was swollen on the same side. The left breast and axilla were normal. Incisional biopsy revealed infiltrating ductal carcinoma. Thorough wound debridement was done. One course of broad-spectrum antibiotics and tamoxifen (20 mg/day) was prescribed and advice given on regular dressing of the wound at the local health center. After two months, the patient was much better with a smaller wound now free of maggots. She has continued to take tamoxifen and is being followed up regularly.

Discussion

Many breast cancer patients in Nepal do not attend health care services because of ignorance of health issues in general. In addition, social taboo plays an important role in prohibiting women from seeking medical advice, especially in rural Nepal. A female with a breast lump or other abnormality will usually refuse to visit a doctor due to the taboo connected with examination by a male doctor. Our recent review of breast cancer cases reveals that patients were not aware of the disease for a mean duration of 8.3 months[1]. This could be one of the main reasons why the majority of the female breast cancer patients present with advanced stage disease. In the present case, the patient did not try to share her trauma with others, even after progressive changes in the breast for a long time. Only after auto-amputation of the breast and evolution of the foul-smelling wound was she brought to the hospital. By this time, the wound was putrefying and infested with maggots.

Fortunately the presence of maggots in the wound compelled her relatives to bring her to the hospital. Interestingly, maggots provide debridement of necrotic tissue and have been used therapeutically in this way. Although the therapeutic use of maggots has declined since the advent of aseptic wound management and antibiotics, maggots may have a role in the debridement of certain complex wounds[2]. Maggots secrete proteolytic enzymes and antibacterial substances, both of which aid in wound debridement.

Figure 1: Right auto-amputated breast cancer with maggot-infested wound.

Conclusion

Cancer education may be the most important remedy for breast cancer in developing countries at the socio-economic level of Nepal. ■

Submitted by Yogendra Singh and Pukar Maskey, Department of Surgery, Tribhuvan University Teaching Hospital, Kathmandu, Nepal. References available upon request from INCTR.

NNCTR EDUCATES HEALTH WORKERS AND CHILDREN ABOUT CANCER IN NEPAL

Nearly a year ago, with the assistance and support of INCTR, NNCTR was established as its representative in Nepal. NNCTR is located in a small building provided by Sheer Memorial Hospital at Banepa, Nepal. Banepa is a small town situated 26 kilometers east of Kathmandu, the capital of Nepal. One of the prestigious universities of Nepal, Kathmandu University (KU) is in the Banepa valley and the KU Medical School (KUMS) is also functioning on the premises of the Sheer Memorial Hospital.

One of the objectives of NNCTR is to work in close cooperation with INCTR to improve the access of the common people in Nepal to cancer care. To do this, NNCTR is determined to work with other organizations and personnel dedicated to cancer care activities, particularly the Nepal Cancer Relief Society (NCRS) and its district organizations. We have selected 11 district organizations in which to initiate cancer education programs.

Many community health care workers attended the cancer awareness program sponsored by NNCTR.

NNCTR operates its cancer education and prevention activities from this facility in Banepa, Nepal.

Things have been going well. We held a one-week workshop to "train the trainers" from these 11 districts and we hope to have some follow-up programs. NNCTR is not currently in a position to serve all of these districts, but we will will select a few of them, depending upon their interest and commitment, for future activities.

NNCTR/INCTR (Nepal), with its principle of collaboration, has established working relations with Scheer Memorial Hospital (SMH), KUMS, Bhaktapur Cancer Care Center (BCCC), TU Teaching Hospital, Bir Hospital, Banepa Municipality, the District Health Office, Kabhre and many other organizations. We have initiated community education programs. With the assistance of INCTR, NNCTR has signed an agreement with IARC/WHO in Lyon, France, for a cervical cancer screening program (CCSP) in Banepa. IARC has provided the necessary financial and other assistance for training medical personnel for the program. The one-year screening pro-

Above and below: By reaching school-aged children of Nepal, NNCTR hopes to raise cancer awareness and increase opportunities for prevention and early detection.

gram is intended to reach 5,000 women. Similar programs are being established at Bhaktapur and Bharatpur Cancer Hospital. SMH is providing the necessary technical and other support for the screening program at Banepa. KUMS medical students are interested in extending voluntary services to the screening program. In this way, NNCTR/INCTR (Nepal) is developing a healthy network of cancer care activities in Nepal.

At this stage, NNCTR is working primarily to develop a suitable education program in Nepal. We are also developing education materials for awareness and manpower development. With the awareness program we are reaching community health workers as well as schoolchildren of adolescent age (grades 7-10) for cancer education. Educating this age group will promote healthier lifestyles which may result in cancer prevention. We have completed education programs in 22 schools in Kabhre District and in 10 schools in 10 other districts, reaching 6,000-7,000 students altogether. We also organized a one-day workshop for 40 community-level health workers in Kabhre District. The District Health Officer was very impressed with the program. We are receiving many requests for conducting similar programs from different community organizations.

Several medical schools and institutions are being established in Nepal. If the cancer education module under consideration for KUMS medical students (to be developed in conjunction with INCTR) is successful, we could establish working relations with other medical schools. That will ultimately help to minimize the problems of trained manpower at all levels.

NNCTR, with the close cooperation of Dr. Y.P. Singh of Tribhuvan University Teaching Hospital, is also conducting a workshop entitled "Nursing Oncology Update" at his hospital. Depending upon its success we may undertake similar workshops in other hospitals and medical institutions.

Our one-year performance clearly indicates that NNCTR/INCTR (Nepal) is "on the move" and we have every intent of continuing on this trajectory. ■

Submitted by Dr. Surendra B. Bade Shrestha, National Coordinator, NNCTR / INCTR Nepal

NETWORK

LA INVESTIGACIÓN CLÍNICA EN AMÉRICA LATINA

La investigación Clínica en Cáncer es uno de los pilares a partir del cual se ha desarrollado la Oncología Médica en el mundo.

El método científico aplicado a la investigación biomédica ha permitido conocer los beneficios que los distintos tratamientos oncológicos proveen a los pacientes, sus eventuales toxicidades y su uso en la estrategia terapéutica curativa o paliativa del cáncer humano.

La enorme mayoría de los datos en la literatura mundial provienen de unos pocos países centrales, mayoritariamente los Estados Unidos y Europa junto a Japón y Canadá.

Uno de los problemas a resolver es si estas conclusiones que se obtienen y que son aceptadas como válidas son extrapolables a todas las regiones del mundo y a sus diferentes poblaciones.

La investigación Clínica en Cáncer en América Latina tiene más de 30 años de experiencia con especial actividad en algunos países y centros seleccionados.

Uno de los primeros antecedentes de actividades conjuntas fue, en la década del 70, el proyecto CCTRP (Collaborative Cancer Research Treatment Program) que reunía diversos centros de América Latina (Argentina, Brasil, Perú, Uruguay, México y Venezuela) junto a Instituciones de relevancia de los Estados Unidos (*Memorial Sloan Kettering* de New York, *M.D. Anderson Institute* de Houston, *Lombardi Cancer Center* de Washington, *Roswell Park Memorial Institute* de Búfalo, *y Mount Sinai* en Miami) en proyectos de investigación bilaterales con el apoyo del *National Cancer Institute* (USA) y la Oficina Sanitaria Panamericana (OPS).

Este proyecto, que publicó numerosos trabajos con importantes conclusiones en la literatura internacional, fue lamentablemente finalizado por limitaciones de las leyes americanas al apoyo económico para la investigación fuera de los EEUU.

Sin embargo, durante su desarrollo, una enorme cantidad de experiencia y enseñanza mejoró notablemente la Investigación Clínica en la región.

Otros grupos también actuaron en forma cooperativa, uno fue el Grupo Latinoamericano de Tratamiento de Hemopatías (GATLHEM), que realizó importantes estudios en enfermedades oncohematológicas reuniendo la colaboración de diversos países (Argentina, Uruguay, Brasil, Cuba y Costa Rica).

Más recientemente, el Grupo Oncológico Latinoamericano (GOL) con la participación de investigadores de Argentina, Chile, México, Perú, Brasil, Colombia, Ecuador, Venezuela y Uruguay realiza protocolos de investigación en cáncer de cervix y su trabajo fue aceptado para presentación en la última reunión de ASCO 2002.

Es indudable que la situación actual presenta un contexto diferente a los de los años anteriores: aun cuando los recursos económicos y tecnológicos están en los países desarrollados, una enorme cantidad de pacientes están disponibles en los países del tercer mundo. Si podemos conciliar las buenas prácticas de la investigación y una adecuada metodología, los países de Ásia, África y América Latina podrían desarrollar un enorme potencial para estudios clínicos que mostrarán los resultados que serían aplicables a una gran mayoría de la población mundial.

Dentro de este encuadre, el INCTR podría ser una herramienta fundamental para el desarrollo de la Investigación Clínica en el tercer mundo actuando como:

1- Nexo entre los países centrales y las naciones en desarrollo.

2- Brindando apoyo y asesoramiento en las distintas áreas de la investigación.

3- Actuando como facilitador entre los Investigadores y centros de los países en desarrollo, y Institutos, Compañías Farmacéuticas y Organismos Internacionales que podrían apoyar o cooperar en estos proyectos.

Estos objetivos son totalmente coincidentes con la misión del INCTR A pesar de las enormes dificultades de las naciones en desarrollo existe una innegable potencialidad que, con el correspondiente apoyo, puede adquirir un enorme desarrollo con el consiguiente beneficio para los pacientes de todas las regiones del globo. ■

—Eduardo Cazap, MD
Buenos Aires, Argentina

SUMMARY

Clinical cancer research is a basic component of medical oncology. The vast majority of data in the literature arise from studies done in the more developed countries. One of the unanswered questions is whether these data are valid in the developing countries.

Clinical cancer research in Latin America has been in progress for more than 30 years in some selected centers. One of the first joint undertakings, in the 1970s, was the CCRTP (Collaborative Cancer Research Treatment Program) in which several centers in the USA worked with various Latin American institutions on bilateral projects. This program was supported by the National Cancer Institute, USA, and the Pan American Health Office.

Other experiences were the GATLHEM, a cooperative group for hematologic malignancies, and more recently, the GOL group working in cervical cancer. These earlier collaborative efforts, which involved centers and investigators from several Latin American countries, resulted in a number of publications.

Today, although economic resources and tehnology are more readily available in the industrial nations, there are large numbers of patients in developing countries. This situation creates a mutually beneficial climate for collaborative research. In this respect, INCTR could play an important role in the evolution of clinical research in developing countries—through encouraging the development of networks of investigators, through the provision of advice and support in the conduct of studies, and through acting as facilitator between investigators and institutions in developing countries, and at counterpart institutions, pharmaceutical companies and international organizations in more developed nations who may be interested in supporting or participating in clinical projects. Such a role is entirely consistent with the INCTR's mission and would help, in spite of the enormous difficulties they face, to permit the developing countries to realize their enormous potential to contribute to our understanding of cancer and its treatment throughout the world. ■

JOIN THE CHALLENGE FUND

The Challenge Fund started as an initiative taken by a group of physicians concerned by the rising incidence of cancer in the developing world and the disproportionate availability of information and resources available in the developed world. The European School of Oncology provided financial sponsorship of the initiative. The first formal meeting, held at Djerba, Tunisia, with five experts from different countries, produced the Djerba Statement. The principal components of the statement are as follows:

1 Research in the creation of simple and relevant recommendations to increase cancer awareness among health professionals and the general public;

2 Research in early detection, prevention and treatment in the common cancers, and

3 The definition of appropriate mechanisms to involve all possible partners in developing innovative public health research in cancer.

The Djerba Statement was published in major oncological journals. At the second meeting in Cairo, the objectives of the Challenge Fund were expanded to include a promotion of information exchange between countries of the developing world.

In January 2001, 80 participants from 17 countries took part in a stimulating interaction in Rome. The next meeting will take place at Abu Dhabi, 15–16 December 2002.

One of the major initiatives of the Challenge Fund has been a breast cancer screening programme in Cairo. In its pilot stage, the program reached 5,000 women who were screened by trained health workers. A larger randomized trial is proposed to correspond to a similar study currently underway in Mumbai. It is expected that other appropriate projects which could be sponsored by the Challenge Fund will emerge from the Abu Dhabi meeting.

To support the Challenge Fund, contact Dr Indraneel Mittra at imittra@vsnl.com. ■

Photo: Steve Holt

SAVE THIRD WORLD COUNTRIES FROM AGGRESSIVE TOBACCO PROMOTION

The WHO, Tech Report 695 of 1983 observed that *"25-35% of males between the ages of 18-20 yrs are already addicted to cigarette smoking in the world's most populous nations of India and China".*

The richer western nations are bringing pressure to bear on tobacco companies through strong and tough legislations and heavy fines. Indeed, tobacco companies are selling fewer cigarettes in their home bases. The September issue of the *British Medical Journal* (*BMJ* 2002; 325:616), confirmed the approval of "*tougher restrictions on the manufacture, presentation, and sale of cigarettes"* by the European Court in Luxembourg against

the world's largest tobacco companies.

It is disappointing to note that the British-American Tobacco Company, one of the largest tobacco companies in the world, has recently opened the largest tobacco factory in Africa's most populous nation, Nigeria!

It is already established that tobacco use is responsible for over 95% of lung cancer in the world. Could anyone imagine what will happen in another 20-25 years when the current millions of newly recruited smokers in the so-called third world countries of Africa, Asia and Latin America develop tobacco-related cancers and other diseases?

—Dr. MA Durosinmi
Consultant Haematologist
Obafemi Awolowo University
Teaching Hospital
Ile-Ife, Nigeria

Prof Ama Rohatiner (center) displays the award given for her lecture at a meeting organized by the Dokuz Eylül University Institute of Oncology, Izmir, Turkey, in September. With her are Riza Çetingöz, a Radiation Oncologist in Turkey, and Jean-Marie Andrieu, a Hematologist from Georges Pompidou European Hospital in Paris.

Pictured at the INCTR stand at a meeting in Turkey are (from left): Mukaddes Gümütekin, MD, Pharmacologist, Oktay Tarhan, MD, Fellow in Medical Oncology, Ihan Öztop, MD, Assistant Prof. in Medical Oncology, Kamer Uysal, MD, Associate Prof. in Pediatric Oncology, Riza Çetingöz, MD, Associate Prof. in Radiation Oncology, and Nur Olgun, MD, Prof. in Pediatric Oncology, Head of the Institute of Oncology in Dokuz Eylül University.

INCTR IN TURKEY

I am pleased to inform you that we had the INCTR stand during the September meeting and the participants showed great interest. Nearly 100-150 participants had been expected, however the number reached 230 on the second day. Most of them were medical oncologists, hematologists and oncologic surgeons. Several pharmaceutical company stands as well as an EORTC stand were erected during the meeting. Participants demonstrated a real interest in the INCTR stand, and most of them were hearing about the INCTR for the first time. I tried to give information about the structure, mission and projects of the organization. During the sessions, when I was not at the stand, one of our interns (a medical student) looked after the stand and referred visitors to me. Prof Ama Rohatiner also made herself available to answer some of the questions. Most of the visitors were happy to take the published material available at the stand, but only a few left their names and addresses. At the middle of day two, we had distributed all but two of 54 folders.

Thank you so much for giving us this opportunity which was exciting and rewarding. Now, more physicians and nurses working on the field of cancer in Turkey know about this unique and dedicated organization and we hope this event may serve as another beginning for further collaborations.

—Kamer Uysal, MD
Dokuz Eylül University
Inst. Oncology, Dept. Ped. ONone

DES RENCONTRES EN FAVEUR DU DÉVELOPPEMENT DE LA LUTTE CONTRE LE CANCER POUR LE CONTINENT AFRICAIN

Grâce aux progrès mesurables de la situation sanitaire globale des pays en voie de développement au cours de ces dix dernières années, nous assistons à l'émergence progressive des données sur les pathologies liées aux cancers qui, sans être les premières causes de mortalité et morbidité en Afrique, n'en demeurent pas moins préoccupantes.

Le réseau de l'INCTR se met en place depuis quelques années et des rencontres fructueuses avec le milieu médical Africain se sont produites au bénéfice du développement de la Lutte Contre le Cancer. En voici un exemple concret.

En 2001, j'ai été invitée[1] à assister à la réunion annuelle de l'INCTR. A cette occasion, j'ai rencontré le président du GFAOP[2] (Groupe Franco-Africain d'Oncologie Pédiatrique) et nous avons pu évoquer la problématique du manque de moyens et de formations pour le personnel soignant en Afrique. Comme il évoquait sa recherche de financement pour des formations d'infirmières d'Afrique francophone, j'ai pu l'informer de l'existence de bourses offertes par l'UICC pour les infirmier(e)s. Par ailleurs, l'IONF (*International Oncology Nursing Fellowships*), qui était réservées jusqu'à présent aux anglophones, s'ouvrait aux francophones pour la première année. Fin 2001, nous avons eu le plaisir de sélectionner trois candidatures pour des formations pertinentes dans des services d'oncologie pédiatrique français.

En 2002, les contacts avec les médecins africains, venus en plus grand nombre, ont permis de mieux analyser l'émergence de problèmes nouveaux (le tabagisme par exemple) et de cerner leurs besoins prioritaires pour une lutte efficace contre le cancer.

La formation des équipes médicales est pour tous une des priorités, en particulier pour les infirmières et les techniciens de laboratoires. En Afrique Sub-Saharienne, le personnel de santé est limité en nombre, spécialement en zone rurale. Les médecins exercent majoritairement en ville, laissant donc aux infirmiers et sages-femmes un rôle et une tâche importante, tant dans le privé que dans le public. La formation continue de ces professionnels, principalement en oncologie, est souvent aléatoire et de toute manière dépendante de financements internationaux comme c'est le cas au Burkina Faso avec l'IARC (Dr R. Sankaranarayanan). C'est donc sur cette nécessité de mettre en place une offre de soins de qualité, tant pour les médecins que pour les patients, que nous nous devons tous de collaborer pour améliorer la prise en charge des cancers en Afrique. ■

—Sabine Perrier-Bonnet
UICC, Nursing Committee et
Comité français

Echange de point de vue sur la problématique africaine du cancer lors de la confér-ence annuelle de l'INCTR 2002 entre Madame Perrier-Bonnet et le Dr Garba Cisse du département de gynécologie et d'obstétrique de la polyclinique Le Lac Tele au Mali.

[1] Membre du Nursing Committee et du Comité Français de l'UICC (Union Internationale Contre le Cancer)

[2] Pr. Jean Lemerle, IGR Paris.

continued from page 4

will be particularly valuable in developing countries, where toxicity is less readily managed. While likely to be expensive, savings on the management of side effects, and higher cure rates, will at least partially offset increased cost. This development in combating cancer is analogous to the tendency in human warfare to use targeted "smart weapons" in order to limit damage to civilian populations. Warfare, however, is a tragedy of the human condition, and it is small consolation that weapons developed to kill people have, on occasion, been effectively directed against diseases that kill people. ■

NETWORK

NEWS BRIEFS

UICC Meeting

INCTR had a stand at the UICC Cancer Congress last June in Oslo, Norway. Many of the participants stopped by to hear about INCTR's work, and many of them expressed an interest in becoming associate members or participating in INCTR activities.

AMCC Governing Council

A meeting of the Governing Council of the AMCC-INCTR's branch in France took place July 17, 2002 at the INCTR Offices in Brussels. The members of the Governing Council are: Guy de Thé, President; Jean Content, Vice President; Louis Schoofs, Treasurer; and Ian Magrath, General Secretary. The AMCC will focus its efforts on cancers in women and children in developing countries, particularly in Africa.

ACCP Meeting

At the July 2002 Steering Committee meeting held in Lyon, France, the Alliance for Cervical Cancer Prevention invited several outside organizations to participate in discussion on the work they were doing together and to suggest ways in which their collaborative work could be extended. Paul Van Look outlined various areas in which ACCP could collaborate with WHO in studies, writing papers, and sponsoring meetings. Helène Sancho-Garnier emphasized that UICC would like to be kept informed of ACCP's work. Ian Magrath suggested ACCP could work more in parallel with the INCTR. Indeed, a fruitful collaboration is underway between the International Associations for Cancer Research and the INCTR in the field of cervical cancer prevention. Projects have been initiated at three sites in Nepal and a fourth site is shortly to be established in Tanzania.

INCTR's Palliative Care Initiative

Initial discussions took place on this topic at the INCTR annual meeting in Brussels in May. Taking advantage of several members of that initial group being present in London on holiday in August, INCTR called a subsequent meeting at St. Bartholomew's Hospital. Robert Twycross, Emeritus Clinical Reader in Palliative Medicine at Oxford University, was kind enough to attend and give advice. Dr Twycross agreed that INCTR was in a unique position to promote palliative care through its numerous collaborating sites.

INCTR's major role would be to assist in the establishment of palliative care programs through the provision of education and training of local medical and nursing staff and other health workers. Hence, the program would be coordinated through a subcommittee of the Education Committee to be chaired by Dr Stuart Brown. After considerable discussion it was decided that, as a first step, the cancer centers in Nepal should be contacted and the possibilities of such an initiative explored. An exploratory visit is being planned.

Mark Your Calendars

The Annual Meeting of the INCTR is planned for May 29–31, 2003, to be held at the Hilton Hotel in Brussels. The program will include the INCTR Award Lectures, Leukemias and Lymphomas, Late Effects and New Technologies. There will be a poster session accompanied by brief oral presentations on selected posters.

The call for abstracts for the Poster and Oral Presentation Session will be announced in November 2002.

For the most current information about Annual Meeting 2003, visit our web site at www.inctr.org, or e-mail edupont@inctr.be or bene@inctr.be.

Thanks To Staff Volunteers

INCTR is grateful for the valuable help provided by our team of volunteers. Caroline Houard is in charge of mailing our Network Newsletter. The last edition was sent to 400 recipients around the world. Sandra Jackson has assisted in the organization of exchange visits—a component of INCTR's educational programme. Hilary Wallace has provided help in updating our fundraising database. Lorena Jimenez joined us for a short period in the Clinical Trials Office whilst Mieke Gees, a secretarial student, worked in the main office helping to reorganize archives and files during her summer break. Thanks to all of them!

INCTR OPENS IN LONDON

A new branch of the INCTR has just been established in London at St. Bartholomew's Hospital, a mediaeval institution founded in the 12th century for the 'sick poor' of the city.

The hospital has a long tradition of excellence in treating patients with cancer and in all aspects of cancer research. 'Barts' is also one of the medical schools of the University of London. It is therefore very appropriate as a location for the London branch, which, whilst strongly linked to all existing INCTR programmes, will focus on developing the Education Program. It will also participate in some of INCTR's research projects.

Education has always been central to INCTR strategy. Training programmes for both health care personnel and scientific staff are vital. Thus, workshops and education sessions are planned, not only for nurses and doctors but also for scientists, laboratory technical staff, data managers and pharmacists in developing countries. The INCTR's Visiting Expert programme will complement such formal training by providing practical help 'on the ground.'

Research is also fundamental to all aspects of cancer control, prevention and treatment. The London branch will therefore help to develop and coordinate collaborative research projects between specialist centres in the Western world and university departments in developing countries.

Prof. Ama Rohatiner and Margaret Cresswell in London look forward to hearing from you! Contact them at ama.rohatiner@cancer.org.uk. ■

INCTR SENDS VISITING EXPERT TO MEXICO

Dr Linn Murphree visited the Instituto National de Pediatria (INP) in Mexico City as a visiting expert in retinoblastoma for one week in early July. His host was Dr Carlos Leal, who is in charge of the retinoblastoma program at the INP. Dr Murphree is an opthalmologist who directs the Retinoblastoma Center in Children's Hospital of Los Angeles.

Both doctors considered the trip very successful. Dr Murphree felt that the standard of care for children with retinoblastoma at INP was of a high level. He was dismayed, however, by the overwhelming problem of delayed diagnosis. During the week he spent at the INP, three new patients were seen—two with orbital and brain extension and one with an eye completely filled with tumor.

Dr Murphree also visited the other major hospital in Mexico City, Hospital Infantil de Mexico, where he met with Dr Rodriguez-Almarez, an opthalmologist. Dr Murphree strongly advocated the development of a coordinated program for the treatment of retinoblastoma in Mexico as well as the development of additional professional and public educational programs. Dr Leal has already formed a national retinoblastoma study group which will meet in January. INCTR representatives will participate in this meeting. ■

INCTR SUPPORTS RETINOBLASTOMA EXCHANGE PROGRAM

Dr Maria Raquel Bravo received funding from INCTR to spend two weeks in August at the Instituto Nacional de Pediatria (INP), Mexico City, where she worked to improve her knowledge of the management of patients with retinoblastoma. She profited greatly from the opportunity to observe the integrated approach to management. The INP team includes a pediatric oncologist, a pediatric ophthalmologist, a radiotherapist and a psychologist. Dr Bravo hopes to develop a similar program in her own institution, El Instituto Oncologico Del Oriente Boliviano, with a particular emphasis on public and non-specialist education directed towards diminishing the problem of late diagnosis. ■

NETWORK

BHAKTAPUR CANCER CARE CENTER

Nepal is a small landlocked country between India and the Tibetan Autonomic Region of the Republic of China and is one of the ten poorest countries in the world—a result of centuries of feudal autocratic regimes in a country completely isolated from the rest of the world by the high Himalayan Mountains.

Since its liberation into the modern age in 1951, Nepal has been spending its health care budget on the prevention of communicable diseases. Only recently has Nepal been able to take interest in cancer prevention and treatment.

In 1992 the Nepal Cancer Relief Society (NCRS) opened the Bhaktapur Cancer Care Center (BCCC) in an old building at Bhaktapur, one of the cities in the Kathmandu Valley. It provided treatment with surgery and chemotherapy only, but lacked radiotherapy services because of the prohibitive initial costs.

In 1995, The Rotary Club of Mansfield in the United Kingdom initiated a project to establish a radiotherapy department at BCCC at the request of NCRS through the Rotary Club in Nepal. The Rotary Foundation contributed almost $400,000 to buy a CIRUS Cobalt 60 radiotherapy machine from France and the Nepalese government's Ministry of Health provided 70% of the building costs. NCRS raised the rest from the public and various institutions and societies in Bhaktapur.

The Rotary Club of Mansfield sent two volunteers to Bhaktapur in 1998 to train six Nepalese graduates as medical physicists and therapy radiographers for the initial commissioning of the radiotherapy services. In 1999, King Birendra of Nepal, accompanied by Queen Aishwarya Rajya Laxmi Devi Shah, ceremoniously inaugurated the new Center. The new BCCC was a supreme example of how NGOs like NCRS and the Rotary International, in collaboration with His Majesty's Government (HMG) of Nepal, the public, and various institutions and societies in Bhaktapur, could successfully work together to provide much-needed radiotherapy services for cancer patients. More than 100 destitute patients have since benefited from radiotherapy treatment.

Diwakar Rajkarnikar, president of the Nepal Cancer Relief Society (left), and a resident oncologist welcome patients to the Bhaktapur Cancer Hospital. The INCTR is supporting its cervical cancer screening program.

Mansfield Rotary Club also established a pilot clinic for screening women for cervical cancer by pap smear; cervical cancer in Nepal is one of the biggest killers of women. The Club also established the first cancer library in Nepal at BCCC.

Since that time, the Rotary Club has provided two Ambassadorial Scholarships to BCCC for postgraduate studies at Nottingham University for one academic year each, and recently funded a new laboratory to provide haematology and histopathology services. BCCC is twinned with the Department of Oncology at Aberdeen Royal Infirmary, where the Head of the Department is David Hurman, who acts as technical advisor to BCCC.

An autonomous management committee runs the BCCC voluntarily with a partial grant from HMG. The remainder of the cost is met through patient fees; there are no free health services in Nepal. In a very short period of time, BCCC has proven to be a formidable cancer institute serving the Kathmandu Valley (population 1 million). But BCCC still lacks much essential equipment that would normally be found in a modern cancer

hospital, the most important of which is a treatment simulator.

Patients are referred to BCCC from other tertiary centers in the region for opinion and treatment. Presently, BCCC operates 25 beds for chemotherapy, palliative care and pain management services. About 1,000 new cancer patients, both children and adults, are seen each year. Doctors treat cancers of the lung, cervix, breast and ovary, as well as leukemias. In addition to the hospital's well-woman clinic for cervical cancer screening and breast self-examination, BCCC takes education programs and screening camps to the outskirts of the municipal region. Nepal Cancer Relief Society is taking a lead in preventive programs as well. Thirty-two of the 75 districts in Nepal are served.

Partnering With INCTR

INCTR has proven to be a vital partner for developing cancer services in Nepal. INCTR has supported BCCC's initiatives to undertake a more comprehensive cervical cancer screening program (based on direct visualisation with acetic acid, rather than pap smears) in the Bhaktapur District, in collaboration with the IARC. The IARC has already provided a colposcope, cryotherapy and LEEP (loop electrosurgical exision procedure) equipment for the treatment of pre-malignant lesions, and has trained doctors, nurses and staff in screening methods and colpscopy practices. As we continue, we hope to develop additional modern methods to fight cancer. We consider INCTR our "big brother by our side," as we strive to bridge the gap between developing and developed countries in the fight against cancer.

INCTR's keen interest in improving cancer services in developing countries and its goal to send help where it is needed most will prove beneficial for our country. Its additional objective to facilitate research activities will certainly help countries like ours in the days to come. ■

Dr Aarati Shah, Medical Director, and Dr Bibek Padhan, Chairman, Nepal Cancer Project, The Rotary Club of Mansfield, UK, contributed to this article.

Detailed Statistics of Bhaktapur Cancer Care Center

Facilities – Inpatient and Outpatient service to cancer patients.

Number of Hospital Beds – Twenty-five (with plans to add eight beds in near future)

Doctors – Eleven including oncologists, surgeons, anaesthetists

Nurses – Thirteen

Medical Physicists – Three

Therapy Radiographers – Four

Laboratory Technicians – Two

Total Staff – Forty-five including administrative and ancillary services

New Patients attending OPD – Approximately 3,200 per year

New Radiotherapy Patients per year – Approximately 450 per year.

Women attending Cervical Smear Clinic – Approximately 600 per year

Field Work – BCCC conducts several health camps for cancer awareness and screening work.

STAY IN TOUCH

We welcome your letters and submissions to Network, the INCTR Newsletter, and encourage you to stay in touch.

To help us keep you informed, please convey your new address, e-mail, fax and telephone numbers to us at:

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NETWORK

PROFILES IN CANCER MEDICINE

PREPARING A NEW GENERATION OF CANCER SURGEONS

Dr Manohar Lal Shrestha has particular expertise in general and cancer surgery. He has demonstrated considerable leadership in national and international medical affairs, but the essence of his character as a physician in Nepal is demonstrated by his outreach to youngsters and the succession of doctors and healthcare workers who are following in his footsteps.

Working through a branch of the Nepal Cancer Society, he meets personally with about 200 adolescent boys each year, educating them about cancer—what can cause cancer, the importance of early detection, and what can be done to prevent and treat the disease. Through programs in the schools, students learn how they can become responsible citizens and advocates for good health.

"In any developing country, there is an enormous health burden," he says. "If you want to build up the nation as a productive society, the health of the individual must come first. In my country, it is a question of developing manpower and building medical teams that will take up this challenge."

It is not an easy challenge where basic facilities, physicians and properly trained health workers are in short supply. Dr Manohar is director of the Bir Hospital in Kathmandu, a government teaching hospital in Nepal where medical oncologists and oncological nurses are available to care for patients. Unfortunately, he says, patients too often present with cancer in severely advanced stages.

"My mission is to reorient our approach to medical care, to make local health workers competent, to integrate the medical profession into the communities," he says. "Illiteracy of the population is a huge problem. So is poverty. We have to train people to take care of themselves in their own communities."

Dr Manohar Lal Shrestha (center, with Dr Y Singh and Dr Surendra Shrestha) serves on the advisory board of INCTR .

The frequency of cancer in Nepal is increasing as a result of changing environmental and dietary factors, he notes. The Ministry of Health in Nepal is directing more funds to support cancer treatment. Recognizing the health risks associated with smoking, the government has directed that taxes collected from the sales of cigarettes be used for healthcare programs.

Yet cancer awareness is on the rise as well. "People are becoming more aware; our facilities in rural areas are being used more. People are asking questions and seeking answers. This is because of our efforts to make people aware of what cancer is, how it can be treated, and how a healthy life can be ensured."

The Nepal Cancer Relief Society, of which Dr Manohar is a founding member, is endeavoring to improve education and cancer screening facilities in the villages of Nepal. The national breast screening program has attracted 1.5 million women between the ages of 19 and 60 to local facilities. Another government initiative has trained 2,400 village workers who now are sharing their newfound knowledge about cancer, AIDS and tuberculosis with their communities.

"These are the individuals who are carrying the message to each and every corner of the country. I believe one person *can* make a difference. There are sincere people working in the field, and it gives me a great deal of satisfaction to know that I am governing a program that will reduce the disease burden in my country and that will make people happier."

Affiliated with the Nepal Medical College, of which he is a founding member, and as a surgical tutor and examiner at the Royal College of Surgeons of Edinburgh, UK, and College of Physicians and Surgeons of Pakistan, Dr Manohar has played an important role in training and educating young surgeons. He still is involved in post-graduate teaching (PGMECC, Nepal), striving to share his surgical knowledge and skills with a new generation of health care professionals. A more personal contribution to the medical advances in his country are his two sons, both of whom are doctors, and both of whom are members of the Nepal Cancer Relief Society. One wants to be a surgeon, the other a radiologist, he says.