N E T W O R K

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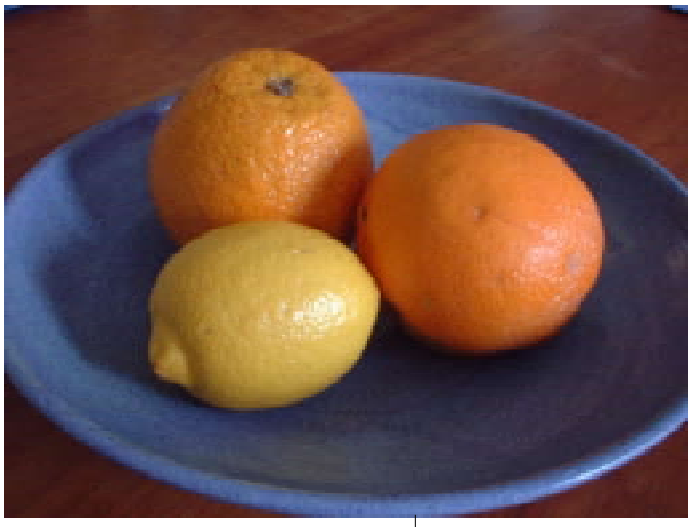
THE PRESIDENT'S MESSAGE

THE RISE OF SCIENCE AND CONSCIENCE

by Ian Magrath

Sir James Frazer, in his pioneering work on magic, mythology and religion, has much to say on the thought processes of early human communities. In *The Golden Bough*, he refers to the "primitive" magical reasoning that led to a broad range of ritual practices that enable humans to survive in the face of odds weighted heavily in favor of the natural forces that threatened them. Primitive or not, and fallacious or not, the fruits of this formative era of human culture continue to have a remarkable influence on our lives. A second type of reasoning, which we may refer to as scientific, has played an increasingly dominant role in human society; there are few corners of the world that have not been touched by its practical application, even though most of the world's population has had little scientific training. It would be pointless to discuss the pros and cons of each type of reasoning since both are part of the human condition, although it is surely correct to state that in the absence of scientific reasoning, humans would not have evolved beyond the stage of hunter-gatherers. Yet scientific reasoning alone provides an insufficient basis for the management of human affairs, since it does not involve emotion, conscience or morality. We may, then, surmise that human society results from a compromise between these two thought processes, just as it also depends upon a compromise between the needs of the community and those of the individual. Throughout human history, these closely related dualities have vied for supremacy.



James Lind, in the first modern controlled trial, demonstrated the ability of oranges and lemons to cure scurvy.

In medicine, the threads of scientific reason have existed since the beginning of time, although buried for much of human history under the weight of magical thinking, or by tomes of medical wisdom, sacred or otherwise, inherited from the past. Any hint of a departure from tradition has been given short shrift. Paracelsus, for example, who rejected the notion that medical knowledge must be garnered from ancient texts, was barred from the university and in 1528 lost his position as Physician to the city of Basle. His holistic approach to medicine was roundly rejected in Europe for at least 400 years. In the 21st century, science is, at last, taking an increasingly prominent role as the basis for medical practice, but the hard edges of science must be blunted by compassion. For at its heart, it derives from individualism - that aspect of "Western civilization" which surged to center stage in the Renais-

sance era. But in this same era private conscience also emerged, leading to passionate discussions of the conflicting interests of individuals and society, and so to human liberty and human rights. Such ideas were alien to the primitive communities described by Frazer, who considered the individual as a *representative* rather than a member of society.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

—Declaration of Helsinki, 2000

KILLING AND EATING GODS

In his chapter "Eating the God," Frazer describes how among the Acagchemem native American Indians of California, "The notion of the life of a species as distinct from that of an individual, easy and obvious as it seems to us, appears to be one which (they) ....cannot grasp." He describes how the life of a species of animal cannot be conceived of as "anything other than an individual life, and therefore exposed to the same dangers and calamities which menace and finally destroy the life of the individual." The Acagchemem worshiped the wild buzzard, and every year, at the feast of *Panes*, sacrificed one of these birds in order to preserve the species - for according to their rationale, killing a young healthy animal liberated the life force, which would then be reborn in another, equally vigorous bird. Not to kill, at intervals, one of these sacred animals at the peak of its health would result in the gradual loss of the vitality of the entire species, and eventually its extinction - with serious consequences for those who held it sacred. When the sacred animal or plant was also a critical dietary element (e.g., corn, or the bison) the link between the animals' well-being and the salvation of the community was direct.

Sometimes the vitality of the people and their world were closely allied to their King, who usually also enjoyed divine status. His enfeeblement and death must therefore be avoided at all costs - by killing whilst still in his prime, in order to ensure that his still vigorous soul would be passed on to a younger successor. Plants, animals, or people were often used as surrogates, particularly as gods became more supernatural. Frazer records that "Twice a year, in May and December, an image of the great Mexican god Huitzilopochtli or Vitzilipuztli was made of dough, then broken in pieces, and solemnly eaten by his worshippers....." The Aztecs believed that by consecrating bread their priests could turn it into the very body of their god, "so that all who thereupon partook of the consecrated bread entered into a mystic communion with the deity by receiving a portion of his divine substance into themselves." In this, the Aztecs were entirely at one with their Spanish conquerors.

SCIENCE VERSUS TRADITION AND MAGIC

Frazer's enormous scholarship and accumulation of volumes of evidence from all over the world had widespread implications for psychology, anthropology, mythology and religion. The primacy of magical thinking in meeting the needs of the community with respect to survival, accounts for the slow emergence of science, which required a degree of individual genius on the one hand, and tolerance by dominant society forces (invariably threatened by new ideas) on the other. Moreover, in the absence of logical precepts, glaring contradictions bore little weight, and thus had no ability to undermine the magical basis of society. Predictably, the rise of science has been associated with legions of detractors, or overt opponents, and even today, there are many who argue against it (*The Flight from Science and Reason*, Ann NY Acad. Sci, vol. 774).

In the practice of medicine, the inability (or unwillingness) to perceive how knowledge based on clinical trials involving many participants can be applied in the service of the individual patient has constantly hindered the assimilation of the scientific method. This attitude, part of the backlash against science, has similar origins - discomfort with novelty, a perceived challenge to the supremacy of professional leadership, and, to a degree, an aversion to the need to acquire new knowledge. According to Murray Enkin's foreword in Alejandro Jadad's excellent book, *Randomized Clinical Trials*, practicing physicians confronted by the initial stirring of clinical science "were unwilling to hold their decisions in abeyance till their therapies received numerical approbation, nor were they prepared to discard therapies validated by both tradition and their own experience on account of somebody else's numbers."

Enkin describes how, in 1836, an article by the Frenchman PDA Louis in

the *American Journal of Medical Sciences*, hailed by the editor as "the first formal exposition of the results of the only true method of investigation in regard to the therapeutic value of remedial agents," caused a storm of criticism. Comments such as "The physician called to treat a sick man is not an actuary advising a company to accept or deny risks, but someone who must deal with a specific individual at a vulnerable moment" and "Averages could not help and might even confuse the practicing physician as he struggles to apply general rules to a specific case." Louis' study, by the way, was on the role of blood letting in the treatment of pneumonia, a method widely accepted at the time, but which he clearly demonstrated to be useless. To be fair, the lack of understanding of the nature of disease must have had a lot to do with the inability of doctors to comprehend the value of clinical trials. Today, we must be equally concerned with the difficulty patients have in understanding the need for clinical studies, particularly randomized trials. This problem is frequently aided and abetted by the culturally-instilled presumption of the physician's omniscience, although doctors too, must bear some responsibility in this regard, for their frequent unwillingness to admit their ignorance.

Clinical scientists, of course, know that evidence from clinical trials rarely provides a precise ability to predict the outcome of a treatment or preventive method in a particular individual, but rather provides a reasonably accurate assessment of the likelihood that benefit or harm will accrue. It does have the ability to predict, within statistically defined limits, the outcome in a reasonably sized *cohort* or *group* of patients, assuming that the cohort in question is similarly structured, in terms of the patient population, to the cohort that participated in the clinical trial.

James Lind and Scurvy

The first documented controlled clinical trial of modern times is believed to be that of James Lind, a ship's doctor in the Royal Navy. Lind performed a study whilst at sea, which involved 12 sailors with scurvy (a disease caused by deficiency of vitamin C) and the use of six different remedies applied for two weeks. The many arms related to the many traditional nostrums that needed to be refuted. He demonstrated the therapeutic effect of two oranges and a lemon given daily and reported his findings in *A Treatise on Scurvy* published six years after the trial (1747). Lind also provided considerable evidence that citrus fruits could both cure scurvy and prevent it. Yet it was not until 1795, approximately 50 years later, that the Royal Navy introduced citrus fruits or juices into the diet of British sailors, earning for them the nickname of "limeys" but greatly increasing their efficiency as a fighting force. This delay might be thought to have been unconscionable and even short-sighted - primarily in terms of the human suffering and death it caused, but also on account of its profoundly negative effect on the Royal Navy, the British economy and the ongoing colonization of the New World. Even today, however, the Institute of Medicine in Washington has estimated that the results of clinical trials take, on average, 17 years to become part of accepted medical practice! Controlling the treatment administered by health service providers in a non-research setting remains difficult, but the Royal Navy could have decreed that sailors should be protected against scurvy in the manner shown by Lind to be effective. Why did it take so long? While many factors may have played a role, the lack of understanding of the scientific method is likely to be an important one. But further insight may be gained by an experiment, also described in Lind's book, of another "clinical trial," carried out in the previous century, this time on the scurvy developing in the course of lengthy sojourns in inhospitable places with no access to fruits and vegetables.

As reported by Lind: "Whereas the first adventurers to that part of the world, who wintered in the same places, were almost all destroyed by the scurvy (1619 and 1631) … a set of sailors consisting of seven men, was left two winters successively, in the years 1633 and 1634, at Greenland and Spitzbergen, by way of experiment, but every man of them next spring was found to have died of the scurvy." Methods recommended to these luckless sailors "for preservation" included purging, anti-scorbutic potions and brandy, although these "infallibly increased the malady… and hastened their unhappy end." There could have

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

—Declaration of Helsinki, 2000

been little thought for the rights of the sailors, nor, indeed, is there much evidence of concern for their suffering. Perhaps even more disturbing is the lack of any hint that the experiments might have been considered highly unethical. It seems as though the lot of these unfortunate men had been cast by their lowly status, rather than by the decision to perform such an ill-conceived experiment. Even the well-intentioned may have blind spots where cultural mores and received attitudes obscure principles that may, in another culture, time or place appear glaringly obvious.

Dan Michel of Northgate

In 1340, an obscure Kentish monk, Dan Michel, wrote a book titled *Ayenbite of Inwyt*. Michel's work was a rather poor English translation of an earlier French treatise, commissioned by Philip the Bold, on all known vices and virtues. Presumably, the title, which refers to the repeated gnawing (remorse) of inner knowledge (wit), implies that conscience, and the psychological pain engendered by ignoring it, are the determinants of moral behavior. Science, of course, and knowledge obtained by the scientific method, can be used for good or evil. In this respect, scientific knowledge differs from received knowledge based on faith rather than evidence. For faith can be used only as inspiration or justification rather than a springboard for technical progress. Belief in a deity, it would appear, is insufficient to allow the creation of machines capable of flying across the Atlantic, reaching the moon, or raining high explosives on a perceived enemy - although it may be used to foster all of these activities. Thus it is that science, and only science, can advance the practice of medicine - by identifying the causal factors and mechanisms of disease, thus creating the opportunity to prevent them, by classifying diseases, thereby creating a basis for diagnosis and treatment, and by systematically identifying chemical, biological and physical methods of ameliorating or curing disease.

But science, born of individualism, is not enough. While the primary purpose of medicine is to relieve human suffering, there are many who make their livelihoods from its practice, with the consequent inevitability that their individual interests may on occasion be put before those of the patient. Multiple safeguards are necessary to ensure that the patients' interests (including their psychological well-being) are protected, particularly since patients are usually unable to assess the appropriateness and quality of care. Similar considerations apply in the sphere of public health. Ultimately, where risks are not perceived by the public, the only reassurance that the science of medicine is subservient to the general good, and that it is practiced with responsibility and compassion, is conscience - in part, the conscience of corporations and individuals involved in the production or administration of health care products and in part, the conscience of regulatory bodies. Regulations pertaining to clinical research are, in part, a codification of the consciences of thoughtful persons concerned about patients (and sometimes, lawsuits!), but their effectiveness is dependent upon the individual consciences of those involved at all levels of the delivery of health care. Regulations may be adequate or not, enforced or not, and obeyed or not. Moreover, the provision of medical care is minimally regulated (at least with respect to quality) at the point of service.

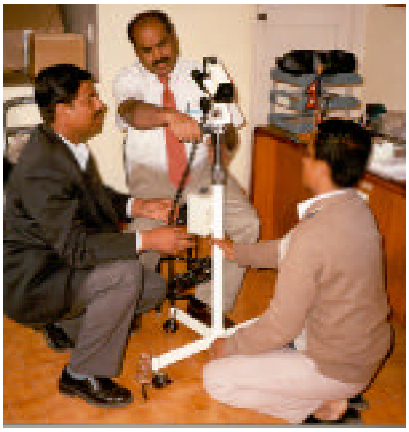
In 1758, Richard Price, a preacher and moral philosopher, published *A Review of the Principle Questions in Morals*, in which he argued that morality is an inherent characteristic of actions, and that good and evil could be distinguished entirely by reason, without the help of any "moral sense" or appeal to sentiment. Some 250 years later, we can safely conclude that either reason has not prevailed, or that Price was wrong. The atrocities that litter the history of mankind, instigated with the aid of scientific discoveries, seemed perfectly reasonable to their perpetrators, if not to others. One might conclude that a reversion to the tenets of magical thinking, and the preservation and promotion of "our community," however defined, had much to do with swamping the prick of the ayenbite of inwyt. Science does not beget conscience, but it surely needs it.

The year 1758 also saw the publication of the tenth edition of Linnaeus' work *System Naturae*, in which the Swedish naturalist classified humans, giving them the epithet *Homo sapiens (*wise man*)*. He was presumably referring to the ability to reason - which unfortunately is not at all the same thing as wisdom. Science and conscience *are* combined in the context of clinical research, such that here, we hope, wisdom generally prevails. An expression of the relevant aspect of conscience may be found in the Declaration of Helsinki, a document that has become something of a sacred text for clinical investigators. So it should be, although its contents must not become frozen and allowed to whither with age. Instead, it should be subject to periodic revitalization. *Le roi est mort. Vive le roi!* ■

NEPAL

In February, Dr Ian Magrath and Melissa Adde visited Nepal, where they met with Dr Sankaranayanan of the IARC and various collaborators to discuss joint studies (involving the IARC, INCTR and the Nepalese Cancer Relief Society) in population-based cancer registration and in the prevention and early detection of cervical cancer.

With respect to a population-based cancer registry, all agreed that this could be implemented at the BP Koirala Memorial Cancer Hospital (BPKMCH), a comprehensive cancer center supported by the government, located in Bharathpur in the Chitwan district in Eastern Nepal, 150 km from Kathmandu. The BPKMCH has steadily increased the number of new cancer patients cared for annually and is expected to see more than 2,000 new cases this year. Dr Sankaranayanan felt that a large proportion of the cancer cases in the Chitwan district (population 475,000)



At the INCTR Office at Scheer Hospital in Nepal, Dr Sankanarayanan (left) and his colleagues assemble a culposcope provided by IARC to help detect cervical cancer.

are presently being seen at the BPKMCH itself, while the remainder are probably treated at one of three existing radiotherapy facilities in Nepal – Bir Hospital, Kathmandu, Bhakthapur Cancer Care Centre (BCCC), Bhakthapur, and the radiotherapy facility at the Medical College, Pokhara – or through the medical and surgical oncology facilities at the Tribhuvan University Hospital, Kathmandu.

If we implemented active case finding at the above five facilities and other selected sources (e.g., major centers in India), a population-based cancer registration for the Chitwan district would be feasible. One staff member at the BPKMCH has already received training in population-based cancer registration at the IARC. An additional cancer registrar's position would greatly facilitate cancer registration and communication among the other institutions.

Further discussion of existing and planned cancer control activities in Nepal took place with representatives of BPKMCH, BCCC, Tribhuvan University Tech Hospital, Bir Hospital, and the voluntary agencies including the Nepal Cancer Relief Society and the Nepal Network for Cancer Treatment and Research (NNCTR) who were enthusiastic about such collaboration. The BCCC, BPKMCH, and the Scheer Memorial Hospital (where the NNCTR office has been established) will participate in an IARC-supported early detection program for cervical cancer. A training course will be organized to train nurses in the screening methods and to train doctors in colposcopy and LEEP. The IARC would provide the equipment required, including colposcopes, cryotherapy devices, LEEP apparatus, speculae, reagents, punch biopsy kits and other supplies. The screening method to be used is visual inspection of the cervix with acetic acid. This is considerably cheaper than the western standard of pap smears. Because no delay is involved in receiving the results, as is the case when pap smears are per-

Dhurba Bahadur Rawat, president of the Lalithpur branch of the Nepal Cancer Relief Society, illustrates the conditions under which doctors operate an Early Detection Cancer Clinic in Lilithpur, Nepal.

formed, this will also eliminate the need to recall screened women and will reduce the chance that early lesions will go untreated. Women with positive lesions can usually be treated at the same visit, e.g., with cryotherapy.

Radha P Nakarmi, Program Officer, and Amala Devi Manandhar, Assistance Officer, presently staff the INCTR office at the Scheer Memorial Hospital. During this visit, it was agreed that the NNCTR would become a Branch of the INCTR, since it will function at the regional and national levels.

Magrath and Adde also visited the Medical School of Kathmandu University, located at the Scheer Memorial Hospital. Dr Arjun Kaki, the Director of the Medical School and Dr Sharma, the Vice-Chancellor of Kathmandu University have expressed an interest in having the INCTR design and conduct an intensive course for medical students in cancer control. Plans were made to schedule a course for June 2003. ■

NEW DELHI, INDIA

During the same trip, Magrath and Adde visited New Delhi to discuss the establishment of an INCTR Office in India at the Sir Gangaram Hospital in Delhi. They also discussed the results of an analysis of data from more than 1,000 patients with acute lymphoblastic leukemia (ALL) treated at three centers with protocol MCP841 between 1990 – 1997. A successor protocol to MCP841 with these same three centers, and molecular studies in ALL in India in collaboration with the King Fahad Children's Medical Center Research Department in Riyadh, Saudi Arabia, were also part of the dialogues.

Doctors at the Nepal Network for Cancer Treatment and Research (NNCTR) are eager to join a collaborative effort to facilitate cancer control activities in Nepal.

Adde presented the analysis of the results obtained by the three participating centers in the project "Treatment of Acute Lymphoblastic Leukemia in Children and Young Adults with Protocol MCP841." Dr David Venzon and Dr David Lieuwheuer of the Biostatistics Branch of the NCI performed the statistical analysis, which revealed clear differences in the patient populations at presentation, particularly with respect to the distribution of white counts, age, presence of organomegaly and T cell disease. The analysis of patient characteristics in Mumbai revealed that the patient population at the Tata Memorial Hospital has changed over time. The group agreed that the data should be published, and that an abstract would be prepared by the INCTR for approval by the group and submitted to a suitable meeting. A complete manuscript will subsequently be submitted for publication.

Discussion with respect to a successor protocol to MCP841 took place. Given the excellent results now being obtained in Mumbai, it was felt that the most appropriate design would be to use a basic MCP841 protocol, but to include additional induction/consolidation elements. Two possible new treatment schemas will be prepared by the INCTR and circulated to the group for consideration.

Dr Kishor Bhatia led a discussion about a plan for a detailed molecular analysis of ALL in India, and comparison with results from Saudi Arabia and Egypt. Dr Sultan Al-Sedairy, Director of the Research Centre of the King Faisal Specialist Hospital in Riyadh also was present at this meeting. Dr Al-Sedairy agreed to support the study in various ways, including training Indian technicians and investigators in Riyadh, in methodology. ■

INCTR EDUCATIONAL WORKSHOP ON CLINICAL TRIALS IN CHINA

In conjunction with the Chinese Society of Clinical Oncology, and supported by Eli Lilly, INCTR held a three-day educational workshop on the *Value and Conduct of Clinical Trials in China*. There were 37 participants and 16 faculty members from INCTR, the National Cancer Institute, Bethesda, the International Agency for Research on Cancer, the World Health Organization, St Bartholomew's Hospital, London, the International Drug Development Institute, Brussels, the Chinese Academy of Medical Sciences, the Chinese Society of Clinical Oncology and the Chinese State Drug Administration.

Dr Lorenzo Tallarigo, President of Intercontinental Operations for Eli Lilly, participated in the opening ceremony. Six officials represented the Chinese Society of Clinical Oncology.

The workshop covered all aspects of clinical trials, including design, ethical considerations, regulations, documents, management, quality control, analysis and presentation of results and was set in the context of cancer control in China. The workshop appeared to be well-appreciated by the participants.

We anticipate developing several educational tools from the workshop, again with the support of Eli Lilly, who sent 11 people to this workshop. An edited video of the meeting will be available, and the presentations will be assembled on a compact disc that will be made available for educational and teaching purposes. INCTR is considering making the CD material available on its website, and would appreciate feedback as to whether this would be useful.

We hope to facilitate additional workshops of this kind, focused primarily on training of clinical investigators, in other world regions. Interested parties should contact the INCTR. ■

INCTR MEETINGS

The Annual General Assembly of INCTR was held on February 23 in conjunction, for part of the day, with a meeting of the Governing Council. It was decided that an Advisory Board to INCTR should be formally constituted, and that the main panel of the Advisory Board should be comprised of individuals from developing countries. The new Panel will advise INCTR on its programs and projects, and play a major role in the selection of recipients of INCTR's Awards. The first meeting of the Advisory Panel will take place during INCTR's Annual Meeting this year. ■

NEW STAFF

Two trainees, Capucine Deriez and Mounia Meftah, from the Institut Supérieur Economique de Secrétariat in Brussels, each have spent ten weeks in the INCTR Offices. Both have made valuable contributions to the INCTR and also benefited from the experience of INCTR administrative staff. Our two volunteers, Sandra Jackson and Hilary Wallace, continue to provide outstanding support, and have now been joined by a third person, Caroline Houard. Welcome on board, Caroline! ■

INCTR has enlisted the support of Eli Lilly to help train clinical investigators in developing countries like those here in China.

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children under 15 years of age and accounts for 25% of all childhood cancers in industrial nations. Incidence data from many developing countries indicates that ALL is also the most common childhood malignancy in most world regions, with some notable exceptions such as equatorial Africa where Burkitt's Lymphoma occurs in greater frequency. In the USA, there is an incidence of three to four new cases of ALL per 100,000 children per year. The incidence of ALL in developing countries tends to be lower than in the USA or Europe, although there is country-to-country variation and some cases may not ever be diagnosed. There is a peak age incidence in children, ages two to five years in most countries, but this age peak, due to a specific sub-type of ALL, varies and is sometimes missing. The incidence continues to decrease throughout adolescence. Males have a higher incidence than females and, in the USA, white children have a higher incidence than black children. Children with chromosomal abnormalities are more likely to develop ALL than are normal children.

Normal lymphocytes fight infection, in part, by making substances e.g., antibodies that attack viruses and bacteria. There are three types of lymphocytes, B, T and Natural Killer (NK) cells. Lymphocytes are made by the bone marrow and undergo further maturation and differentiation in the organs of the lymphatic system - the spleen, thymus, and lymph nodes. ALL is a malignant disease that results when developing lymphocytes become too numerous and fail to mature. The excess of immature lymphocytes (lymphoblasts) can involve different stages of maturation during the lymphoid differentiation process, giving rise to subtypes of ALL. The leukemic lymphoblasts are found predominantly in the bone marrow and bloodstream but can generally be found in the organs of the lymphatic system, particularly lymph nodes, liver and spleen. These malignant cells may also invade many other organs, including the spinal cord and the brain.

The signs and symptoms of leukemia reflect the degree of bone marrow infiltration and the extent of spread of the disease to other organs. The most common signs and symptoms include fever, pallor, fatigue, bleeding, bone pain, and swollen lymph nodes. The duration of symptoms may be days to months. The early signs and symptoms of ALL may be similar to other illnesses, such as infections or other causes of anemia. Therefore, when a child presents with signs and symptoms that could be caused by ALL, a blood count is usually performed. In a child with ALL, the blood counts typically reveal a high white blood count (WBC) with abnormal circulating lymphoblasts and often a reduced number of normal white cells (granulocytes), predisposing to infection, fewer red blood cells (anemia) and a low platelet count (potentiating bleeding). In the presence of suspicious findings in the peripheral blood an examination of the bone marrow is required to make the diagnosis and to determine the type of leukemia that is present.

Immunophenotyping is a valuable and relatively inexpensive tool that is part of the standard diagnostic work-up of patients with leukemia and is used to determine the sub-group of ALL as well as to differentiate ALL from other types of leukemia. It is more precise than cytochemical tests used in the past, although these are still sometimes used to distinguish ALL from acute myeloid leukemia (AML). The two major sub-groups of ALL are precursor B cell and precursor T cell. Cytogenetics has played an important role in the identification of

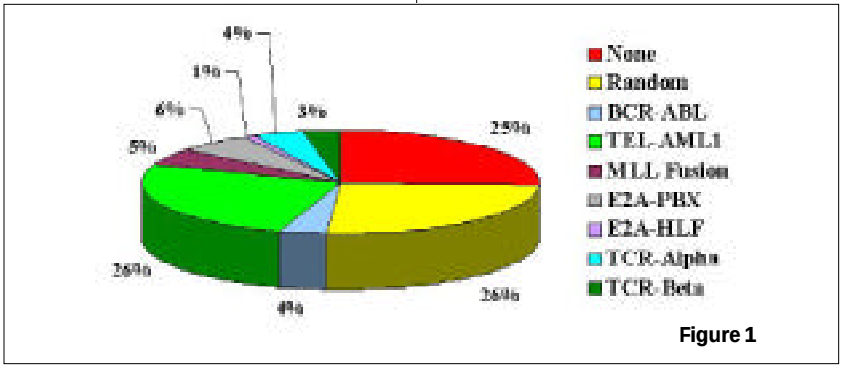


Figure 1

The diagram shows the relative frequencies of various molecular lesions in childhood ALL (both pre-B and pre-T) in the USA (After Rubnizt and Look, *Childhood Leukemias,* Ed. Ching-Hon Pui). Most lesions result in fusion proteins derived from genes involved in cell growth, differentiation and survival, the letters stand for the involved genes. Some of them are mentioned in the text.

smaller sub-groups of patients with specific chromosomal abnormalities which have considerable prognostic significance. However, cytogenetics has largely been replaced by molecular techniques (particularly PCR) and flow cytometry (DNA index).

POTENTIAL PROGNOSTIC FACTORS

Prognostic factors are those that reliably predict outcome. These are categorized as follows: clinical and laboratory features at diagnosis; molecular characteristics at diagnosis; and response to initial treatment. *It is important to point out that prognostic factors are largely treatment-dependent.*

Many clinical and laboratory features at diagnosis have been described as having prognostic significance, perhaps the most important being age at diagnosis, WBC at diagnosis, gender, and race. Infants under one year of age are at a very high risk of treatment failure. In western countries, older children and adolescents (10 years and older) have less favorable outcomes, while children ages 1 to 9 years tend to have more favorable outcomes. Patients with high WBCs tend to have a worse outcome. Girls with ALL have a better prognosis than boys in some series. White children have a better prognosis than black children.

Molecular and biological characteristics of leukemia cells at diagnosis that are associated with outcome include immunophenotype, chromosome number, and certain chromosomal translocations. Precursor B cell ALL, one of the two main sub-groups of ALL, can be further divided into early pre-B and pre-B cell ALL. Patients with an early pre-B phenotype (no expression of surface or cytoplasmic immunoglobulin) have the best prognosis. The T cell phenotype used to be associated with a worse outcome, however, when treated with modern treatment protocols, patients with T cell ALL generally have an outcome similar to those with precursor B cell ALL. Hyperdiploidy, which is the presence of additional copies of whole chromosomes, can be evaluated by measuring the DNA content of cells, a measure known as the DNA index. Hyperdiploidy or a DNA index of > 1.16 is associated with a better prognosis. Hypodiploidy (fewer than normal chromosomes) is associated with a higher risk of treatment failure. Recurring chromosomal translocations (see Figure 1) that have prognostic significance include the t(12;21) cryptic translocation (i.e., normally undetectable by cytogenetics), resulting in the fusion of two genes, TEL and AML1, to create a single protein (TEL-AML1). Such patients have a good outcome. The t(9;22), which involves the same genes as in chronic myeloid leukemia, and also results in a fusion protein, BCR-ABL, has an unfavorable prognosis. Several translocations involve the MLL gene, situated on chromosome band 11q23, each being associated with a different prognosis, depending upon other factors such as the age of the patient, the WBC, the immunophenotype, and the specific translocation. One of them, for example, the t(4;11) is associated with up to 80% of infant leukemias, which do poorly.

Early treatment response has proved to be a particularly good measure of outcome, being, in fact, a direct measure of the effect of chemotherapy. Early response has been evaluated by examination of the bone marrow during induction therapy (e.g., 7 or 14 days after the initiation of treatment), or by the clearance of circulating lymphoblasts from the peripheral blood at day 7 or 10 days of treatment with corticosteroid alone, or other drugs used in induction. Patients who have a rapid reduction in the percentage of leukemic cells in the bone marrow or those who have a rapid clearance of circulating leukemic blasts have a better prognosis than those who clear leukemic cells more slowly. The adverse impact on prognosis related to slow early response may be overcome by modifying therapy in such patients, e.g., by prolonging and intensifying induction therapy.

TREATMENT OF ALL

Approximately 70 to 80% of patients with ALL diagnosed in industrialized countries can be cured. The primary treatment is chemotherapy. Treatment consists of remission induction, the prevention of spread to the central nervous system (CNS), consolidation, late intensification and maintenance cycles. A typical remission induction consists of a glucocorticoid, vincristine, and l-asparaginase, with or without an anthracycline. Complete remission is achieved in 95-98% of patients in industrial nations. Many variations exist with respect to continuation therapy, but most include agents such as cyclophosphamide, cytarabine, methotrexate and mercaptopurine in addition to the periodic reintroduction of agents used for remission induction. This so-called late intensification, or re-induction therapy, appears to make an important difference to outcome in all risk groups. CNS preventive therapy may include intrathecal therapy with methotrexate and cytarabine and, in some circumstances, cranial radiation. The total duration of therapy is between two to three years.

ACUTE LYMPHOBLASTIC LEUKEMIA IN DEVELOPING COUNTRIES

Patients with ALL in developing countries often present with more advanced disease (see Case History) in which leukemic cells have not only infiltrated the bone marrow, but also invade other organs – in some cases this may be because the ALL was not suspected initially, but the disease may also be more aggressive in poorer socioeconomic groups (see below). Co-morbidities such as hepatitis, malaria and malnourishment are also much more common, which may affect the patients' ability to tolerate treatment. Access to care in cancer centers or pediatric oncology units is much more limited in developing countries, and patients and their families often have to travel long distances to reach hospitals capable of making the diagnosis and/or providing necessary treatment. Further, even when they reach these centers, a family's inability to pay for treatment due to socioeconomic factors or the lack of health insurance often impacts upon the type of therapy that is ultimately provided to the child. Continuation of treatment and follow-up is often difficult, again because of socioeconomic factors, the need to travel long distances, and the lack of trained physicians who can manage their care outside the major cancer center or pediatric oncology unit.

Treatment protocols typically administered to patients in more affluent countries may not necessarily be optimal for the treatment of children with ALL in developing countries, since prognostic factors may differ, and, as studies in India suggest, the proportion of the major sub-types of ALL differ in various world regions or in different ethnic or socioeconomic groups. Preliminary research on the molecular characteristics of ALL in India suggests that chromosomal translocations associated with a poorer prognosis in western series are more frequent, and those associated with a good prognosis, less frequent. Research into the optimal therapy for children with ALL in developing countries needs to take into consideration differences in clinical and laboratory features at diagnosis and molecular and biological characteristics of the leukemia as well as other relevant factors, such as co-morbidities.

INCTR ACTIVITIES IN ALL

INCTR is working to support research on the treatment and characterization of childhood/adolescent ALL in India, including assisting with the development of a cooperative group within India so that more patients with ALL have better access to care. We also plan to extend and further develop this model in other countries such as Brazil, China and Egypt. ■

—Melissa Adde

THE CASE OF MISTAKEN IDENTITY

by Shripad Banavali, MD, Tata Memorial Hospital, Mumbai, India

The patient, a 13-year-old male, presented on May 3, 2001 to a local hospital in a small city near Mumbai. He had a seven-month history of breathlessness on exertion which had significantly worsened in the days immediately prior to admission to the local hospital. At the time of admission, he had no palpable lymphadenopathy or organomegaly, and routine laboratory tests were normal. A 2-D echocardiogram performed at this time showed normal heart function, but revealed a mediastinal mass that was confirmed by a CT scan (Fig 1). The surgeon at the local hospital, who was not a specialist in oncology, made a presumptive diagnosis of thymoma. The patient underwent a median sternotomy and excision of the mass on May 5. The diagnosis made by the local pathologist was thymoma: lymphocytic type. Within one week from surgery and prior to discharge from the hospital the patient developed bilateral cervical lymphadenopathy. He was referred to the Tata Memorial Hospital (TMH) for evaluation and pathology review.

The patient was admitted to the Thoracic Surgical Unit of the TMH on May 29. Physical examination revealed bilateral gross cervical lymphadenopathy. His blood counts were within normal limits. He underwent a fine needle aspiration biopsy of one of the lymph node masses and samples obtained from the thymic mass were reviewed. The diagnoses reported by the pathologist at TMH were suggestive of lymphoblastic lymphoma (LL) in the lymph node, but this diagnosis was confirmed when the sample from the excised thymic mass was reviewed. The tumor cells in the thymic mass were shown to be of T cell type and expressed CD3. Unfortunately, the patient and his family returned to their hometown before receiving the pathology reports. The patient was then lost to follow-up.

A month later, on June 29, the patient presented to TMH and was promptly referred to the Pediatric Oncology Unit. The patient had clinically deteriorated and had increased breathlessness. On physical examination, multiple, moderately sized (2 x 3

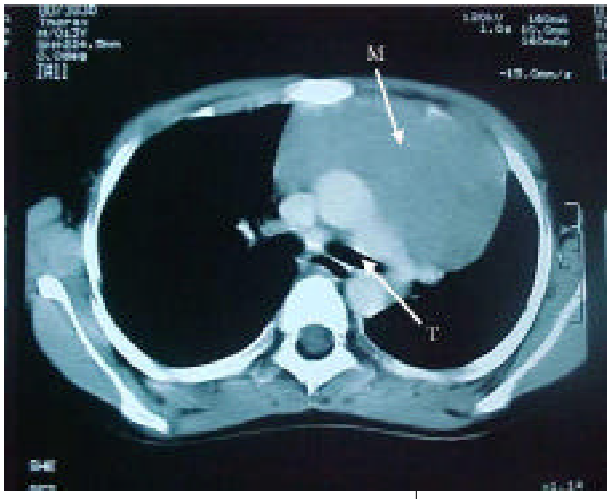


Figure 1: This computerized tomographic scan of the upper thorax shows a large anterior mediastinal mass (M) and compression and deviation of the trachea to the left (T). The CT scan was performed before surgery.

cm each) lymph nodes were palpable in the neck, one in the right axilla, and there was bilateral testicular enlargement. The liver and spleen were normal in size. Routine laboratory tests revealed an elevated white blood count of 153,000 per mm^3 with 43% circulating lymphoblasts and high serum lactic acid dehydrogenase and uric acid levels (7060 U/L and 8.2 mg%, respectively). A chest x-ray revealed mediastinal widening. Extensive retroperitoneal lymphadenopathy and bilateral enlarged testes were confirmed by ultrasound examination. A bone marrow aspirate showed 81% leukemic blasts of L1 morphology and T cell immunophenotype. An examination of the cerebrospinal fluid was also positive for leukemic blasts.

A diagnosis of acute lymphoblastic leukemia (ALL) of T cell immunophenotype was made and the patient was immediately admitted to the Pediatric Oncology Unit and prepared for chemotherapy. He was started on protocol MCP841, a standard protocol for the treatment of ALL in India with hydration and allopurinol. At the completion of induction therapy, the patient achieved complete remission. He went on to receive cranial and testicular radiation with 2340 cGy each, followed by reinduction and consolidation therapy. He is currently in his second maintenance cycle and will continue maintenance therapy until he has completed a total of six cycles.

This case is an example of the natural history of the evolution of lymphoblastic lymphoma into acute T-cell leukemia (the distinction between these "diseases" is arbitrary, being based on the degree of bone marrow involvement). This case also demonstrates some of the reasons for delays in the diagnosis and treatment of pediatric oncology cases in developing countries. The lack of knowledge of pediatric oncology by the surgeon at the local hospital who initially evaluated the patient was evident in the preliminary differential diagnosis. In patients of this age who present with mediastinal masses, the most common diagnoses include Hodgkin's disease, lymphoblastic lymphoma/leukemia and large B cell lymphoma. In a younger patient, germ cell tumor and neuroblastoma would need to be considered; thymoma is rare in children and adolescents and often associated with an underlying disease. A standard diagnostic procedure would be CT-guided or fine needle biopsy, thus avoiding surgery.

Because he had not considered other possible diagnoses, such as lymphoma, the surgeon did not order supplementary immunohistochemistry tests on the biopsy material. This resulted in an inaccurate diagnosis and also caused the patient to undergo an unnecessary major surgical procedure (albeit, the correct procedure for thymoma) which entailed significant risk given the size of the mass and the presence of tracheal compression (cardiac arrest, or the need for prolonged ventilation after surgery are potential complications). It is often worth incurring the small additional expense of potentially definitive diagnostic tests in order to ensure that an accurate diagnosis is made rather than using valuable resources in giving incorrect treatment – which can be extremely expensive and sometimes carries significant risk. Although the surgeon correctly referred the patient to TMH after the development of lymphadenopathy, there was poor communication with the patient and his family, which led to them being unaware of the diagnosis and resulted in the patient becoming lost to follow-up. The delay in obtaining an accurate diagnosis and in starting appropriate therapy resulted in disease progression, including the development of CNS and testicular disease, and a consequently worse prognosis, requiring more prolonged therapy. We strongly recommend that children with tumors are referred immediately to a specialized center where appropriate expertize in diagnosis and therapy exists. ■

TATA MEMORIAL CENTRE, MUMBAI; INDIA

by Suresh Advani; Chief, Dept of Medical Oncology

The credit for developing oncology in India is duly given to the House of Tata's, one of the leading industrial families of India. They established the Tata Memorial Hospital (TMH) in memory of Lady Meherbai Tata, the first lady of the House of Tata's, who died of leukemia in 1932 after treatment abroad. The hospital, the first cancer facility in the country, was opened on Feb 28,1941. As the activities of the hospital grew, it was handed over to the government, and since 1962 has been operated by the Department of Atomic Energy. In addition to the hospital, the government established in 1952 what is now the Cancer Research Institute (CRI). The hospital and the Institute were merged in 1966 under the flag of Tata Memorial Centre (TMC). For more than half a century, the TMC has been at the forefront in the fight against cancer in India.

THE PROBLEM

India faces 2.5 million cases of cancer at any given time. The most commonly encountered cases are those related to tobacco use in men, i.e., cancer in the head and neck region, lung and esophagus. In women, the most common cancers are cervical, breast, oral cavity, esophagus and stomach. Since most of these cancers are related to lifestyle, many are amenable to both primary and secondary prevention. The high cancer toll in developing countries like India is attributed to late detection (70% of all cases). Also, there are very few comprehensive cancer centres with good infrastructure.

TMC is the largest comprehensive cancer centre in the subcontinent. Nearly 650 new cases of children with cancer are seen every year. More than 75% of the patients are treated for free or at a nominal charge.

FACILTIES

The medical oncology department is the largest in the country; here thousands of patients are treated each year. We see and treat the largest number of leukemic (both myeloid and lymphoid) patients in the country. The department also has a six-bedded bone marrow transplant unit where approximately 30 transplants are performed every year. The medical oncology department has its own hematology lab (with automated cell counters, flow cytometers, etc.), cytogenetic lab, and molecular lab.

Most remarkable, however, may be that TMH is the first hospital in the country to introduce joint clinics. Here, the onco-surgeon, medical oncologist, and radiotherapist meet with the pathologist, radiologist and molecular biologist to discuss each patient, after which detailed management is planned. In addition to lymphoma and cervical cancer joint clinics, we have joint clinics for breast cancer, ovarian cancer, head and neck cancer, retinoblastoma and other pediatric solid tumors.

ACADEMIC PROGRAM

There are about 400 students undergoing training every year in medical and non-medical fields, and over 200 professionals obtain short-term training. TMC is a recognized center for post-graduate training in field of medical, surgical and radiation oncology as well as a center for obtaining Ph.D.'s in various specialties. About 70 faculty members are recognized as guides in the University for Ph.D work. TMC also imparts master's degrees in oncological nursing.

RESEARCH

The Cancer Research Institute activities cover a wide spectrum and include areas such as lifestyles in relation to cancer patterns, environmental carcinogens (both chemical and viral), cancer immunology, cell and molecular biology. There are groups working on development of new laboratory models for human cancers. Clinical research is conducted, using a multi- disciplinary approach, in collaboration with clinicians at the TMH, mainly in cancers prevalent in

India. The Institute has achieved national distinction as the first to develop transgenic mice, carry out research in human gene therapy and develop an indigenous diagnostic kit to detect HIV infection. Along with basic and lab research, pure clinical research is also carried out in the fields of radiation, surgical and medical oncology either through institutional trials or in collaboration with national and international groups.

COMMUNITY OUTREACH

Education and prevention are vital weapons against cancer. Thus TMH has paid particular attention to preventive oncology, with very satisfying gains. More than 7,000 patients were evaluated; thousands more were reached through talks in schools, public places, radio, etc. The Bill and Melinda Gates Foundation, through International Agency for Research on Cancer (IARC) of WHO, is helping to fund a collaborative project on cervical cancer prevention with the rural cancer project of TMH at Barshi, a village in the state of Maharashtra.

Whenever help is required to start a cancer hospital or a cancer wing in a general hospital, TMC plays its appropriate role in providing the know-how. TMH has always felt that it should act as a catalyst rather than as a magnet. The hospital has therefore always placed emphasis on training doctors from other regions, so that they can return to their own areas with new skill and knowledge.

INTERNATIONAL COLLBORATION

TMC has received international acclaim as a center of excellence in cancer research and treatment. There have been several important international collaborations. Studies are being conducted in collaboration with the National Cancer Institute (NCI), USA for treatment of childhood acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma. Collaboration was established with the International Agency for Research in Cancer (IARC), France regarding the epidemiological study for neoplasms of the lung, lymphatic and haematopoetic system. A large cohort study to detect early cancers in women is supported by the National Health institute (NIH), USA. TMC is an active member of the INCTR, through which it helps develop of protocols for the treatment of childhood cancers like retinoblastoma, osteogenic sarcoma and acute lymphoblastic leukemia.

LOOKING INTO THE FUTURE

To meet the challenges of the next century, various facilities of the hospital were recently upgraded and state-of-the-art equipment was commissioned. This includes MRI, new X-ray machines, mammography unit, color doppler, a Clinac 2100 C/D Liner Accelerator with stereotactic radiosurgery and radiography facilities. Through a Computerized Management Information System and complete networking, on-line transactions are being made for patient administration, materials management and other similar activities. With the installation of hydroclave waste management facility in 1999, TMC was well ahead of the rest of the country in fulfilling its obligation to protect the environment.

The Clinical Research Secretariat along with the state-of-the-art Digital Library has been established to provide the necessary infrastructure and crucial technical support to cultivate research environment. The hospital with its Scientific Review Committee, Ethics Committee and Data Monitoring and Safety Committee is committed to maintain highest scientific and ethical standards in medical research and treatment.

As we enter into the 21st century and our 60 year anniversary, the fight against cancer will go on. ■

ALL CLINIC

A good axiom in research is to make a difference in a field where it matters. One such case R TMH has been in Acute Lymphoblastic Leukemia (ALL). This constitutes 35% of all pediatric cancers seen at TMH. It is also here that the cure rate has increased significantly from less than 10% in the 1970s to 60% today. The protocol used was specially designed in collaboration with Dr Ian Magrath at the National Cancer Institute, USA, and is particularly relevant for conditions in the developing countries. The experience over the years has helped us to anticipate possible complications. The visible impact is that in the last decade, even after using the same protocol, the disease-free and event-free survivals have grown by 20 percent. This protocol has become the gold standard in India and in fact, in this part of the subcontinent. Nearly 500 patients have been cured and are followed up systematically to see if there are any residual long-term effects of the treatment, and effort is being made to prevent them from occurring.

PROFILES IN CANCER MEDICINE

DOING MORE WITH LESS

Dr. M. Krishnan Nair takes a very pragmatic view of cancer treatment in India: catch it early when you can, and reach out to as many people as possible, and for those patients who have terminal cancer, provide them a pain-free and dignified end.

"We do not need to spent a lot of money to die," he says. "Every Indian knows he will die one day. He looks forward to death, and to rebirth. Indians don't welcome the western philosophy of fighting death. What they do welcome is a painless death."

Nair, director of the Regional Cancer Center (RCC) in Trivandrum, India, also believes Indians don't need to spend a lot of money - money they don't have - to treat cancer. That's why early detection is so important. That, and a standardized approach to treatment that is cost-effective.

"Early detection strategies should focus on cost-effectiveness," he insists, pointing to the Swedish model where regular screening programs and treatment facilities are readily available in a community setting. The young doctor who used to go into the villages to pick up cancer patients for treatment; the activist who started training health workers, dentists and volunteers to detect tell-tale lesions in the mouth; the idealist who convinced the Chief Minister of State to fund a modern cancer center in India, still dreams of doing more with less. The RRC, under Nair's direction since the doors first opened in 1981, was the first to start a community cancer center. Through public education and training of volunteers and doctors, they were able to reach more cancer patients earlier. Nair also was responsible for launching the first pediatric cancer canter, and for developing the largest network of pain and palliative centers in the entire country.

Dr. M. Krishnan Nair is one of the most respected doctors in India. He was awarded the prestigious Padmasree Award in 2000.

Nair's philosophy about drug therapies reflects his constant endeavor to stretch precious resources. He believes that there is too broad an application of the latest (and more expensive) drugs, and wants to standardize diagnostic tests and cost-effective treatment. He also wants to channel resources to those areas, such as pediatric cancers, where there is the greatest opportunity for cure. "The main objective should be to identify treatment that can be universally employed. We could reach more people and serve them much better," he says. The streamlined administration of morphine he engineered is a perfect example. Where 14 years ago a terminal cancer patient might have received a 1-kilogram dose of morphine, today that same patient would receive 30 grams. This means that those patients who might not have had access to morphine are now receiving it. And still, no cancer patients die in pain.

Nair is equally committed to advancing cancer research in his country. As chairman of the board of studies in health sciences at Kerala University, he is responsible for training a new generation of doctors. He also has led more than two decades of research, formulating and conducting more than 75 research projects investigating, for instance, the effects of natural background radiation, the relationship between cervical cancer an HPV infection, and low-cost strategies for early detection of cervical and oral cancers. In collaboration with major pharmaceutical companies such as Pfizer and Johnson & Johnson, RCC doctors are currently running 12 clinical trials in breast cancer, lymphoma, and other types of cancer.

"It is now known that over one-third of cancers are preventable, one third are potentially curable provided they are diagnosed early in their course and for the majority of incurable patients the quality of life can be improved by palliative care. However, control of cancer will not come about without an established mechanism."

--Marcia C. Landskroener