N E T W O R K

THE NEWSLETTER OF THE INTERNATIONAL NETWORK FOR CANCER TREATMENT AND RESEARCH

INCTR

Volume 3, Number 1, Autumn 2002 — **Inside**: Review-Pediatric Liver Cancer - **6** Forum - Brain Tumor and Retinoblastoma - **10** Report on Palliative Care - **13** Letters - **14** News - **16** Partner Profile: - **18** Profile in Cancer Medicine - **20**

THE PRESIDENT'S MESSAGE

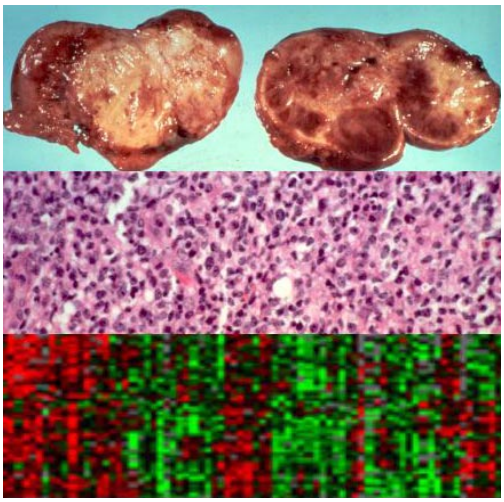
THE WORD ON CANCER

by Ian Magrath

In the beginning was the Word.
—The Gospel of St John

Wittgenstein's *Tractatus Logico-Philosophicus*, the only philosphical work he published during his lifetime, is written in a style reminiscent of a sacred Hindu text. Each of its short paragraphs—the equivalent of a sloka in, for example, the Bhagavad Gita—expresses a thought or concept that can be fully understood only by the "initiated" or, as Wittgenstein himself says, by those who have "thought the thought, or a similar thought, before." This statement can be applied to a great deal more than the *Tractatus*. It might well be taken to heart, for example, by all teachers and students, for it implies that education is an active, not a passive process. Real understanding does not come from an ability to regurgitate the words of one's teachers, or of essential texts — sacred or otherwise — for this entails the exclusive use of memory and does not necessarily imply understanding. Even deciding what is useful to commit to memory can be difficult in the absence of the advice of a "guru"; learning the Brussels telephone directory by heart, for example, would scarcely be of value in understanding the telephone system to which it relates. And much useful information learned by rote, such as the five principal causes of a malar flush I was made to memorize as a medical student, doesn't teach an ability to reason, only to associate one thing with another. This form of learning is better categorized as training rather than education, in which the ability to carry out a specific task is conferred on the trainee, but in which an understanding of the task or its purpose is not necessary to its successful completion. The word *education* implies, in its Latin origin, the act of leading or drawing *out*. Not, in other words, a process of filling empty space, but one of guiding the student in the use of his or her intellectual capacity.

The ability to make use of knowledge depends very much on access to those who have "thought the thoughts before." Good teachers do not merely impart knowledge,



Progress in pathology: Upper third (gross pathology) shows enlarged ovaries due to infiltration by tumor removed at a post-mortem examination. Middle third (histopathology) shows a histological section (slice) of a tumor stained with the standard dyes, hematoxylin (blue) and eosin (pink) and viewed under a microscope. Lower third (molecular pathology) shows a DNA microarray in which each spot represents the expression (at transcriptional level) of a different gene in the tumor cells. Tens of thousands of genes can be examined simultaneously. Red spots indicated genes expressed at a higher than average level, green spots at a lower than average level. The expression of specific sets of genes (signatures) provides information about the tissue of origin, the molecular abnormalities present, or the likelihood that the tumor will respond to a particular therapy.

Giovanni Battista Morgagni is considered the father of pathological anatomy. His magnum opus, *De sedibus et causis morborum per anatomen indagatis (On the Seats and Causes of Diseases, Investigated by Anatomy)*, includes 70 letters describing some 700 cases. (*Photo courtesy of the Claude Moore Health Sciences Library, University of Virginia.)*

but also, through their demonstration of analysis and reasoning, show the way to understanding, a foundation upon which imagination can find solutions or create new knowledge. Isaac Newton, famously, pointed out that: "If I have seen further than most men, it is by standing on the shoulders of giants." In other words, by first thinking their thoughts, he was able to think his own.

The acquisition of understanding then, is essential to the scientific method, enabling hypotheses to be generated which can be tested for legitimacy through observation and experiment. Through our understanding of natural laws we create a limited ability to predict the future, or at least to know in advance what will happen in certain circumstances (e.g., that an apple, detached from its branch, will fall to the ground). In the context of cancer, knowing which disease one is dealing with (the *diagnosis*) allows prediction of the natural history, or response to treatments applied in the past (the *prognosis*). The foundation of understanding which allows diagnoses and prognoses to be made is known as *pathology*.

Logos

The Greek word *logos* was rendered by the translators of the King James Bible as "word," which, in the context of the first sentence in St John's Gospel (see epigraph), probably conveys very little meaning to the modern reader. In ancient Greek, its meaning extended to include truth and reason (the English word logic, of course, is also a cognate form) — and, as such, it was subsequently used metaphorically to refer to God incarnate (the equivalent of the Hindu Avatar). Thus, combined with the Greek word "pathos," meaning "suffering," we can see that *pathology* refers not only to the understanding of the nature of diseases, but to the discipline whereby these truths are rendered accessible to the human mind — the Avatar, if you will, of disease!

Modern pathology is an amalgam of many disciplines (e.g., microbiology, biochemistry, immunology) which historically have been intermingled more or less with the practice of clinical medicine. For centuries, the pre-eminent pathological tool, at least in the context of patients, was the conduct of a post-mortem examination — usually by the clinician who cared for the patient in life. One down side of the clinician-pathologist was pointed out by Semmelweis, who recognized that examining a patient after conducting a post-mortem was a principal cause of puerperal fever in his hospital. Unfortunately, his demonstration that this problem could be effectively dealt with by the simple expedient of hand-washing prior to examining a patient led to him being drummed out of Vienna! The techniques of pathology have changed dramatically only in recent years, as new tools for the study of disease have emerged. The theory of imbalance in the four humors (yellow bile, phlegm, blood and black bile), held sway as the principle theory of the causation of human disease for some 2000 years, and is generally ascribed to the Graeco-Roman physician Galen (130-201 AD), who built upon the ideas of Hippocrates (460-370 BC). The emergence of pathology as a scientific discipline was finally made possible by the publication, in 1543, of the first complete textbook of human anatomy, *De Humanis Corporis Fabrica* (*On the Fabric of the Human Body*), by Andreas Vesalius (1514-1564). Subsequently, morbid (pathological) anatomy evolved through a succession of concepts pertaining to the "seat" or origin of human disease, each championed by a leading medical scientist of the era. Giovanni Morgagni (1672-1771) claimed it was the organs, (Marie Bichat, (1771-1802) the tissues, and (Rudolf Virchow, 1821-1902) incriminated the recently discovered microscopic building blocks of the body—cells. But the study of structure can never be enough, and knowing *what* automatically leads to asking *why* (a critical question for ontologists, and one to which oncologists could, with benefit, give greater weight!). It is Claude Bernard

(1813-1878) who is usually claimed to be the father of the discipline known as patho-physiology, the study of disordered function in the human body. He stressed the importance of laboratory experiments in understanding disease, and pointed out in the mid-nineteenth century that: *"We cannot imagine a physicist or a chemist without his laboratory. But as for the physician, we are not yet in the habit of believing that he needs a laboratory; we think that hospitals and books should suffice. This is a mistake; clinical information no more suffices for physicians than knowledge of minerals suffices for chemists and physicists*." Few would doubt the truth of this statement today, at least in the sense of the importance of laboratory studies to understanding disease. Yet physicians still tend to have little more than a smattering of laboratory training and a limited understanding of the basic principles of research. To remedy this situation would surely lead to more rapid progress in preventing or curing disease.

In the late 20th century, a further paradigm shift occurred in the attempt to understand the nature and origin of disease — the recognition that ultimately, it is derangements in the structure and function of genes and proteins that cause human disease. Some molecules, of course, invade the body in the shape of microorganisms, but these must still act via their effects on the molecular pathways of the cells. The historical march of ideas from organs, through tissues, cells, and finally to macromolecule as the "seat" of human disease did not, of course, lead to the replacement of one idea with another. On the contrary, all are necessary to understand disease. Cancers arise in particular tissues in particular organs, and are comprised of cells which, by virtue of disturbances in their normal molecular pathways, are able to replicate in circumstances when they ought to die (via the process of programmed cell death, or apoptosis). Cancer cells frequently develop the ability to spread and survive in cellular and tissue environments that are normally hostile. In effect, we might say that cancer is the consequence of a longer life, or even potential immortality being conferred upon specific cells (Jorge Luis Borges has speculated on the consequences of immortality being conferred upon specific people in his well-known story, *El Inmortal*). But once again, *what is*, promotes the question *why*. Looking at pathological tissue alone cannot give a complete picture of human disease, since it omits the influence of the world in which the patient lives. Most diseases (inborn errors of metabolism and inherited malformations are possible exceptions), including cancer, arise from interactions with the environment and it is the discipline of epidemiology, the study of the way in which diseases emerge in populations, that deals with this area.

In the space of little more than 150 years, basic tissue stains, which enable the pathologist to distinguish the various elements of the tissue that he or she places under the microscope, have been supplemented by a large panel of monoclonal antibodies, which, when coupled to appropriate markers, make visible the expression of an equally large number of individual proteins within, or on the surface of tumor cells. With the advent of the "microarray" or microchip, we are now on the threshold of an era in which the entire "transcriptosome" or "proteosome" — i.e., the totality of the transcription products of the genome, and all the proteins expressed in any given cell type (even in individual cells) will be measured in a single test. Ultimately, it is the pattern of protein expression (and, of course, changes in the pattern that are governed by internal programs and external events) that are responsible for all aspects of the life and death of a cell — whether a cancer cell or a normal cell. It would seem to be a self-evident truth that the further development of methods to study these patterns — either in cross section (a slice in time), or, ultimately, in real time, in response to changes in the cellular environment — will reveal the ulti-

Marie Francis Xavier Bichat has been called the father of "tissue pathology," or histopathology. He studied over 600 cadavers and identified 21 tissues, but he did not use a microscope, which he thought unnecessary. *(Photo courtesy of the Claude Moore Health Sciences Library, University of Virginia.)*

Rudolf Virchow claimed that every cell can come only from another cell (Omnis cellula e cellula). He is often considered the father of cellular pathology. ***(Photo courtesy of Axel Bauer's Virtual Office for History, Theory and Ethics in Medicine.)***

mate secrets of cancer, and thus permit rational and highly specific approaches to treatment. Pathology, and its primary incarnation, the diagnosis, will necessarily undergo revolutionary changes as the techniques for understanding what makes a cancer cell malignant become more widely available. This is, doubtless, simply a question of time.

Gnosis

Long before the comprehension of human disease in terms of the broad range of pathophysiological processes that we discern today, the observation of the symptoms and signs was established as a critical element — for long, the only objective element — of reaching a diagnosis. The logic of the Egyptian medical papyruses, written some 3,500 years ago, in this regard, is impeccable. Specific symptoms and signs were provided for each diagnosis, and the diagnosis led, in turn, to a prognosis and recommendation for treatment. In ancient Egypt, medical knowledge was considered sacred, and therefore, by definition, already perfect. We might conclude that Egyptian medical *gnosis* (knowing, from the Greek, gnostikos), without continued nourishment from Logos, petrified and eventually wasted away. Knowledge based largely on intuition, as diagnosis and prognosis were until the emergence of the science of pathology, provides a precarious basis for treatment decisions, although this mattered little prior to the development of effective therapy in the 20th century. Intuitive knowledge is not, of course, verifiable and in the absence of rational appraisal the ideas that prevail are those of the most powerful advocate. Thus, the Cathars, a gnostic sect which emerged in Occitania (later to become part of France) in the eighth century, and which espoused religious ideas that differed from those of the church, came to be viewed as heretics. Aiming to achieve direct knowledge of God through intuitive, personal means (i.e., to become "Perfecti"), their spiritual form of religion left no room for Papal authority. In 1209, Pope Innocent III launched a genocidal campaign against them — the Albigensian crusade. Lasting until 1255, it was characterized by indiscriminate slaughter of the citizens of towns known to harbor Cathars. Its climax was the siege of the Cathar fortress, Montségur, in 1244, which ended in a fiery holocaust in which over 200 Cathars were immolated. In a later era, the observations of scientists, such as Galileo, were also considered to be in conflict with the dogma of the church, but scientific reason has, for the most part, prevailed over intuitive explanation, at least with respect to the question *what*, if not the question *why*.

But scientific understanding, even today, has significant limitations. Our ability to predict the outcome of treatment in individual patients, for example, is limited to statistical probability gauged from observation of previous patients, or from the results of clinical trials conducted in sample populations. Nonetheless, this provides a rational basis for the selection of treatment, assuming an accurate diagnosis and evaluation of prognostic factors in the disease in question. As time goes by, the much greater "depth" of the diagnosis, i.e., the increasing amount of information that is encapsulated in it, will lead not only to more accurate predictions of prognosis in the context of various potential therapies, but also to a movement away from the present practice of defining therapy for specific patient populations and towards *individualized* treatment. This will be made possible by the design of drugs targeted at the molecular abnormalities that are the immediate cause of cancer — molecular abnormalities that are largely specific to the tumor cells. Each type of cancer has multiple molecular abnormalities, some present in all cells, and some not, such that each individual cancer has its own "fingerprint" which might be used to specify a particular combination of drugs, each targeted at a different molecular lesion.

Pathology Today

The value of the pathological examination of cells or tissue obtained from a presumed malignant tumor cannot

be overemphasized. At the extremes, the patient may be shown to have a benign tumor, for whom simple therapy may suffice, or a cancer for which there is no curable option. In between, a diagnosis based on tests that go beyond the basic, subjective histological examination (which largely involves pattern recognition), by including the detection of a set of signature proteins, will not only improve the accuracy of the diagnosis, but increase its depth. Since treatment costs (including the use of hospital facilities, staff time, the cost of drugs, surgery or radiotherapy, and the cost of managing toxicity) are generally much greater than the costs of improving the quality of the diagnosis, reluctance to use the tools of modern pathology may well lead both to an inadequate diagnosis and to sub-optimal therapy, with consequent wastage of resources. Better diagnosis requires, first and foremost, a well-trained and well-informed pathologist, but even the best pathologist is limited by the quality of the diagnostic materials, particularly if relying upon histopathology. Important in this respect are the representativeness of the biopsy, and the handling, fixation, sectioning and staining of the tissue.

As more objective tests, such as immunohistochemistry and other kinds of gene expression assays, including polymerase chain reactions (PCR) or *in situ* hybridization techniques (to say nothing of microarray examination of large numbers of genes), become increasingly available, the pathologist's skills will continue to move away from pure pattern recognition to a knowledge of the range of tests best able to supplement (and perhaps eventually replace) basic histological examination. Such objective tests also provide the pathologist with a means of improving his or her ability to more accurately interpret histomorphology (the pattern) since they provide confirmation of the diagnosis. Additional means of improving the skills of the isolated pathologist (all too often the case in developing countries) include reference materials (images and descriptions) made available through the Internet. With appropriate telepathology equipment, "virtual" consultations or teaching sessions with specialist pathologists can be held.

Interactions between the pathologist and clinician will need to improve as more information of prognostic importance emerges from the examination of the tumor tissue. Clinicians will also need to be aware of the increasing amount of information that may be obtainable from serum — sensitive and quantitative tests for tumor DNA and marker proteins in serum will become increasingly available, and will help not only in establishing the diagnosis, but in following the response to treatment. Already, the detection of particular molecular abnormalities, such as tumor-associated chromosomal translocations, provides a more sensitive assessment of response to therapy, and is becoming increasingly important in the management of some diseases (e.g., chronic myeloid leukemia). In the context of chemotherapy, the molecular profiles of both tumor and patient are important. Factors governing the metabolism and distribution of drugs (including entry and exit from cells), free radical scavengers, DNA repair and programmed cell death are critically important to the efficacy and toxicity of therapy and may be modified by a host of genetic factors, either inherited, or emerging in the context of ongoing mutations in the tumor cells. As more drugs targeted at the causative molecular lesions of cancer are developed, it will become essential to know whether their molecular targets are indeed present in the tumor cells, just as it is necessary to know whether the target of monoclonal antibody-directed therapy is expressed. In other words, we shall see an increasing overlap between diagnosis and prognosis.

While many of the more recent diagnostic techniques are simply not available in most institutions in developing countries, the investment in at least some new technologies, such as PCR, may be appropriate. It would seem premature at this time, except for major research institutions, to invest in microarray or similar technology for major transcriptosome or proteosome analysis. Still a research tool, it is probable that the relevant findings from detailed expression profiling, e.g, a signature set of genes that reflect prognosis, will direct the use of simpler techniques (PCR, immunohistochemistry, small arrays) for the detection of only those gene products identified as important by large microarrays. In any event, a great deal of clinico-pathological correlation will be necessary in prospective studies before the value of these newer and expensive technologies can be fully assessed.

One of Galen's great works dealt with the value of dreams in making a diagnosis *(On Diagnosis from Dreams)*. Today we may dream of the day when diagnosis not only fully encompasses prognosis, but also provides a precise guide to therapy, not in a particular disease, but in a particular patient. ■

LIVER CANCER IN CHILDREN - NOW USUALLY CURABLE

In Volume 2, Issue 2 of "NETWORK", an article compared the outcome of two infants with hepatoblastoma recently diagnosed in the same city. These two children reflect the improvement in prognosis for infants with this rare tumor (median age 18-24 months) over the past 20 years.[1] Until the early 1980s, most patients with hepatoblastoma were considered incurable because in only 20-30% were the tumors considered to be "resectable" at diagnosis, and only half of these children (10-20% of the total) survived. The remainder died of progressive disease. Chemotherapy was not considered particularly useful and Transplant Centres were unwilling to accept children with hepatoblastoma for orthotopic liver transplantation (OLT) because the risk of recurrence was so high. Treatment of the "Hospital A" patient, who died of progressive tumor, represents this "old-fashioned" approach, whilst the patient managed by "Hospital B" benefited from two major recent advances and survived. First, in the early 1980s, Cisplatin and Doxorubicin (PLADO), were recognised to be the most active available agents for hepatoblastoma. Second, it seemed more logical to give chemotherapy prior to as well as after surgery—as in the case of most solid paediatric tumors—rather than only afterwards. Pre-operative PLADO was recognised to make tumors (a) smaller, (b) less vascular and (c) more "discrete," thereby making surgical removal considerably safer (Figure 1).

The rarity of primary liver cancer in children—only 1 in 30,000 are affected—means that national and international collaboration is essential if treatment is to be improved via the conduct of clinical trials. Only three national groups - the USA/Canada (Intergroup), Japan and Germany/Austria (GPOG)—were sufficiently large to set up independent studies. Many of the remainder have joined trials coordinated by the International Society of Pediatric Oncology Liver Cancer (SIOPEL) Group. For example, in SIOPEL 1, a single-arm study of children with hepatoblastoma in which the PLADO combination and delayed surgery were used, a total of 91 Centres in 30 countries—representing all five inhabited continents—recruited 154 patients with hepatoblastoma in just over four years (35-40 patients/year).[2] Differences between SIOPEL 1 and the Intergroup studies were, first, that in the Intergroup trials, surgical resection was recommended at diagnosis, with "second look" surgery being carried out in initially "unresectable" cases—patients who had responded to chemotherapy. Second, the Intergroup study included a randomised trial comparing the Cisplatin/5-FU/Vincristine and

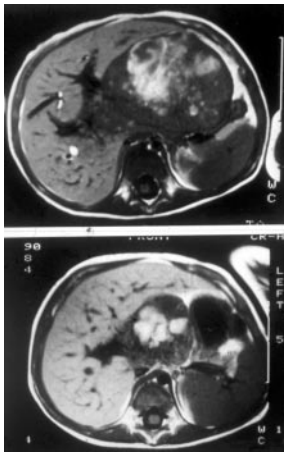


Figure 1: MRI scan of hepatoblastoma in a 2-year-old boy pre- and post- four courses (12 weeks) of "PLADO" chemotherapy. The tumor has shrunk dramatically and the abdomen and liver have a much more normal contour.

TABLE 1:
MULTI-CENTRE STUDIES IN HEPATOBLASTOMA — COMPARISON OF RESULTS

Study	Number of Patients	Complete Resection Rate (%)	5-Yr Event Free Survival (% + CI)	5-Yr Overall Survival (%+CI)
SIOPEL 1 (Pritchard et al, Ref 2)	154	106 (77%)	66% (59-74%)	75% (68-82%)
GPOG (H-89) (von Schweinitz et al, Ref 4)	72	66 92%	72% (*)	76% (*)
US Intergroup (INT-0098)	182	n/a	57/69%** (*)	69/72%** (*)
Japanese (JPLT-1 (Sasaki et al, Ref 5)	134	72% (*)	66% (*)	73.4% (*)

GPOG = German Paediatric Oncology Group; CI = Confidence interval; * = Overall CI not provided; n/a = not available
** = Results from Regimen A (Cisplatin, Vincristine and 5-FU) (first figure) and Regimen B (PLADO) (second figure) provided separately

Cisplatin/Doxorubicin combinations. These two regimes showed equivalence, with respect to response and 5-year survival although greater toxicity was observed with the two-drug regime.[3] The results of the German and Japanese studies, both of which also included "up front" (i.e., initial) surgery, show that there is no therapeutic advantage to (a) the addition of Ifosfamide (GPOG)[4] or (b) the infusion of anthracycline directly into the hepatic artery (Japanese study)[5] [Table 1]. Despite the fact that the SIOPEL study was conducted in so many centres with diverse facilities and varying experience, the results are at least as good as those of the other study groups, with an overall 5-year event-free survival of 66% (confidence interval 59 - 74%) and a 5-year overall survival of 75% (CI 68 - 82%) [Figure 2]. Notably, 7 of the 10 cured patients had received liver transplant because many OLT Centres had by now become convinced that PLADO really did eradicate "micro-metastatic" disease and even, in some cases, visible metastases (ie Stage 4 patients).[6]

There were both surgical and chemotherapy considerations for the SIOPEL Group as they planned their next studies. The "delayed surgery" strategy was successful in that, unlike the situation in the other three collaborative groups, no patient needed a second surgical resection with its attendant complications; SIOPEL surgeons unanimously agreed that delayed surgery was also much less risky than surgery "up front" because of tumor shrinkage. This was consistent with the finding of a high percentage of necrosis (100% in some specimens) in the resected tumors. With respect to the chemotherapy regimen, the fact that 5-FU and Vincristine had not been notably "active" against hepatoblastoma in studies performed in the 1960's and 1970's, and the equivalence of two Intergroup regimens suggested that Cisplatin was the crucial element of PLADO. Moreover, whereas the Doxorubicin dose and dose intensity could not be readily increased, for fear of the higher incidence of cardiotoxicity noted in the Intergroup PLADO regime (in which the dose of Cisplatin was 80 mg/m^2 over 4 days, compared with 60 mg/m^2 over 2 days in the equivalent SIOPEL regime), Cisplatin could be intensified because there had been little nephrotoxicity or ototoxity in SIOPEL 1.

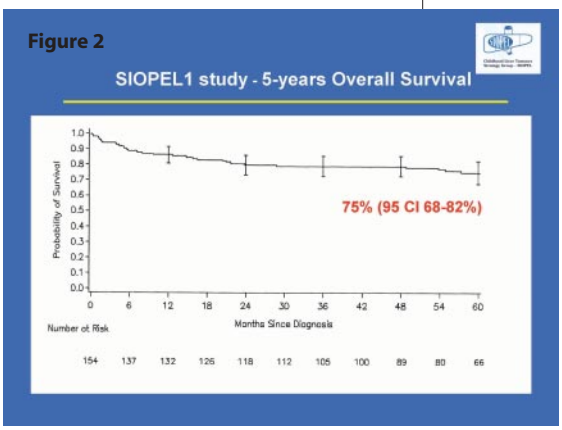
Analysis of the SIOPEL 1 results indicated that two "risk groups" could be delineated[7] [Table 2]. On the one hand, there were patients with no evident metastases and tumors limited to 1, 2 or 3 sectors of the liver (designated "standard risk" patients) and on the other, those with either all four sectors involved or extra-hepatic tumor, usually lung metastases. Patients in these two latter categories were combined as a "high risk" group [see Table 2]). In the SIOPEL 2 study, using these criteria, patients were stratified into two risk groups. All patients again had delayed surgery, including OLT if tumours responded to chemotherapy but all 4 hepatic sectors remained involved. "Standard risk" children (70% of the total) received single agent but more intensive Cisplatin at 2-weekly, rather than 3-weekly intervals, with careful auditory and renal monitoring. "High risk" patients (30%

TABLE 2: SIOPEL RISK STRATIFICATION FOR HEPATOBLASTOMA

Risk Group (% of Total)	Features of Tumors
Standard risk tumors (70%)	PRETEXT group 1, 2 or 3 No metastases and no vascular extrahepatic spread
High risk tumors PRETEXT group 4 (30%)	or Spread outside the liver (usually lung metastases)

PRETEXT = Pre-Treatment Extent of Primary Tumor
Tumor involving one hepatic sector only = PRETEXT 1, two sectors = PRETEXT 2 etc
The 4 sectors are: right anterior, right posterior, left medial, left lateral (see Ref 2 for details)

Figure 2

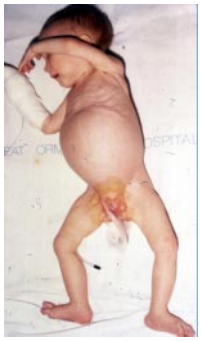


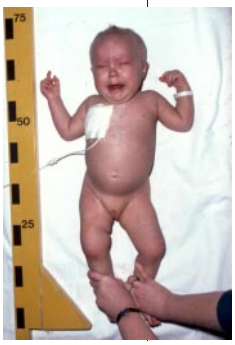
of the patients) received Doxorubicin, Carboplatin and Cisplatin in an alternating myelotoxic/non-myelotoxic sequence, a regime sometimes referred to as "Super PLADO". A total of 140 patients were recruited to this "pilot" trial over 3 years - a higher recruitment rate than for SIOPEL 1. The results are reassuring since "good risk" patients in SIOPEL 2 appeared to have a similar prognosis to those in SIOPEL 1 [Table 3]. This finding greatly influenced the design of the third SIOPEL trial (SIOPEL 3), now in progress. In SIOPEL 3, "good risk" patients are randomised to receive either PLADO, according to the SIOPEL 1 schedule, or single-agent Cisplatin, according to the "good risk" SIOPEL 2 regime. The number of "high risk" patients in SIOPEL 2 was insufficient to draw conclusions about any advantage of the Super PLADO regime over standard PLADO, so SIOPEL 3 continues to use this treatment in the "high risk" group. SIOPEL 3 is recruiting well and new Centres are joining in. Secure funding has been acquired from the major UK cancer charity, "Cancer Research UK", with important contributions from the Swiss Cancer League and a group of families of UK children who had developed hepatoblastoma. SIOPEL 3 is coordinated and administered by Data Managers in the Leicester Office of the United Kingdom Children's Cancer Study Group (UKCCSG) and statistical input is from Dr Rudolph Maibach in Bayern, Switzerland.

Resection of hepatic lesions in children is a major undertaking and requires optimising the patient pre-operatively to achieve the best possible results. Malnutrition or infection must be treated. This is especially important in geographical areas where specific types of malnutrition or endemic infection, e.g., malaria, occur. Both can affect the patient's tolerance of a major hepatic resection. The functional status of the liver must be assessed, to determine the capacity of the remaining liver mass to sustain the child post-operatively. Liver enzymes, complete blood count, coagulation factors and serum proteins are measured pre-operatively. Adequate amounts of blood products must be available. The coagulation profile should be as close to normal as possible. Some children may benefit from a pre-operative dose of vitamin K. Occasionally an enema is administered the day before the procedure, though formal "bowel prep" is usually unnecessary. Intravenous antibiotics are given pre-operatively to cover for organisms that might cause cholangitis.

The PRETEXT scheme is helpful for "risk group" classification, but thorough knowledge of the functional anatomy of the liver, as described by Couinaud and others, is essential for safe and successful resection of liver tumors because it allows the surgeon to perform a relatively bloodless dissection by dividing the tissue along the natural lines of demarcation between segments. Using this classification, which is based upon the location of the portal pedicles and the hepatic veins, the liver has 8 segments (I-VIII).

The procedure is performed under general endotracheal anaesthesia with positive pressure to prevent air embolisation from the hepatic veins or inferior vena cava during the dissection. Monitoring lines and catheters usually include two large bore peripheral lines for volume infusion, a central venous catheter and arterial line to monitor central venous pressure and systemic arterial pressure respectively, an indwelling urinary catheter to measure urinary output, a nasogastric tube for gastric decompression, and a probe for core temperature measurement (oesophageal or rectal). In the event that the vena cava is occluded during the procedure, it is vital to have enough intravenous access in the upper trunk in case rapid fluid infusion is required, and to administer any necessary products to stop bleeding. Sometimes, an intra-operative cholangiogram or ultrasound can be very helpful. Details of surgical technique are beyond the scope of this article.





At left: Patient with hepatoblastoma: (a) at 18 months, at diagnosis. She had a huge "PRETEXT 3" primary tumor and multiple lung metastases; (b) after four courses of PLADO via the Hickman catheter, but before surgical resection of primary; and (c) at 12 years, 10 years off treatment, with hearing aids as a result of cisplatin ototoxicity.

TABLE 3: COMPARISON OF RESULTS OF FIRST TWO SIOPEL TRIALS

Study	Actual Resection Rate	3 year EFS % (CI %)	3 year OS % (CI %)
SIOPEL 1	77%	68% (61-77%)	78% (70-85%)
SIOPEL 2			
Standard risk Patients	96%	91% (84-98%)	89% (82-96%)
High risk Patients	54%	52% (39-65%)	47% (34-60%)

EFS = Event-free survival OS = Overall survival CI = Confidence interval

Excessive bleeding is by far the most common surgical complication encountered, but can usually be avoided by strict adherence to safe surgical technique. Other intra-operative complications include bile duct injury, air embolisation, injury to adjacent intra-abdominal organs, or tumor rupture with spill. Subhepatic closed suction drains are usually placed and retained for 24-48 hours. The child can usually be extubated post-operatively and would normally spend about 24 hours in the intensive care unit. Metabolic abnormalities known to occur after major hepatic resections including hypoglycaemia, hypophosphataemia, hypoalbuminaemia, and prolonged prothrombin time should be anticipated (and monitored for) and promptly corrected. Later complications of hepatic resection include atelectasis, fever, intra-abdominal or wound infection, pneumonia, bile leak, "biloma" or biliary fistula, post-operative bleeding and liver failure. This is not "easy surgery" and referral to a tertiary or quaternary centre may be advisable.

In summary, hepatoblastoma—a rare tumor recently considered "incurable" in most cases—is now regarded as one of the success stories in paediatric oncology, with cure rates now approaching those for Wilms' tumor. Pleasingly, treatment is usually not complex, lengthy or especially expensive. For instance, the estimated chemotherapy and antibiotic costs for the 2 arms of the SIOPEL 3 trial are approximately 550 pounds sterling (Cisplatin only arm) and 1080 pounds sterling (PLADO arm), respectively (although these costs will vary from one country to another). Toxicity is mild or moderate with easily manageable complications, so that most patients are "cured at little cost." Requirements for centres treating these children include: (a) resources for the placement of secure central venous lines, the measurement of serum alphafetoprotein (AFP) levels and monitoring for the toxicities of Cisplatin, Carboplatin and Doxorubicin, (b) availability of expert liver surgery, including access to a paediatric OLT Centre and (c) the conviction that most children with hepatoblastoma can be cured, so that protocols are followed closely. These resources are now available in many "developing countries"—one reason for the popularity of the SIOPEL studies internationally. Some centres, however, are either unaware of, or unconvinced by the results of the SIOPEL trials. It is therefore our responsibility—nurses, doctors, pharmacists and other health "professionals"—wherever we work, to bring these results to the attention of our immediate paediatric and paediatric surgical communities, either by "word of mouth" or via our national Paediatric Cancer Study Group.

There are approximately 187 separate nations in the world. It appears that 150 of these countries are not taking part in clinical trials. Through various agencies, including the INCTR, we hope to increase the number of participating centres considerably over the next decade. Otherwise, children with hepatoblastoma may receive ineffective or unnecessarily toxic treatments and some of them will die needlessly. Promising collaborations are now being developing between the SIOPEL, US/Canadian, Japanese and GPOG Study Groups. In particular, new strategies for the improved management of "difficult" liver tumours—high-risk hepatoblastoma and also hepatocellular carcinoma[8]—are under discussion and pilot trials, including Phase I and II studies of newly available agents, have already started. Information on the SIOPEL trials can be obtained from Margaret Childs, SIOPEL Trials Coordinator, at the United Kingdom Childrens Cancer Study Group (UKCCSG) in Leicester, at e-mail: msc8@leicester.ac.uk or from one of the authors of this article, drjpritchard@hotmail.com

Submitted by: J Pritchard, Royal Hospital for Sick Children, EDINBURGH ; and K H Mutabagani, New Jeddah Clinic, SAUDI ARABIA

(see References next page)

REFERENCES

1 Hepatoblastoma – a bit of a success story. Eur J Cancer 1994:30: 1050-1051. EA Shafford and J Pritchard.

2 Preoperative chemotherapy with Cisplatin and Doxorubicin for childhood Hepatoblastoma – Results of the First Study of the International Society of Paediatric Oncology. J Clin Oncol 2000: 18: 3819-3828. J Pritchard, J Brown, EA Shafford, *et al.*

3 Randomized Comparison of Cisplatin / Vincristine / Fluorouracil and Cisplatin / Continuous Infusion Doxorubicin for Treatment of Pediatric Hepatoblastoma: A Report From the Childrens Cancer Group and the Pediatric Oncology Group. J Clin Oncol 2000: 18: 2665-2675. JA Ortega, EC Douglass, JH Feusner, *et al.*

4 Efficiency and Toxicity of Ifosfamide, Cisplatin and Doxorubicin in the Treatment of Childhood Hepatoblastoma. Eur J Cancer 1997 : 33 : 1243-1249. D von Schweinitz, DJ Byrd, H Hecker, *et al.*

5 Outcome of Hepatoblastoma Treated With the JPLT-1 (Japanese Study Group for Pediatric Liver Tumour, Protocol-1): A Report From the Japanese Study Group for Pediatric Liver Tumour. J Ped Surg 2002 : 37 : 851-856. F Sasaki, T Matsunaga, M Iwafuchi, *et al.*

6 Prognostic factors for hepatoblastoma in SIOPEL-1. Eur J Cancer 2000: 36: 1418-1425. J. Brown, G. Perilongo, E A Shafford, *et al.*

7 Hepatocellular carcinoma in children - Results of the first prospective study of the International Society of Paediatric Oncology. J Clin Oncol 2002: 20 : 2798-2804. P. Czauderna, G. MacKinlay, G. Perilongo, *et al.*

OPTIMIZING CARE FOR PATIENTS WITH BRAIN TUMORS

Cancer of the brain is a devastating illness. Because of the damage caused by the tumor itself (and by subsequent treatment, be it surgery, radiation or chemotherapy), most patients with brain tumors develop neurological, emotional and intellectual difficulties that compromise their ability to live independently, to study and to work.

In Brazil, 1400 new patients with brain tumors are diagnosed every year, the majority between the ages of 4 and 9 years. Today, if treated adequately, more than 60% of such patients may be cured. However, in addition to disabilities resulting from brain damage caused by the tumor itself, after treatment, patients may suffer from intellectual impairment, usually manifested as low IQ and memory loss, visual impairment or speech alterations. These late effects are seen especially in patients under the age of 3 who have been treated with radiotherapy. These side effects can also be associated with chemotherapy. Such sequelae can lead to social, learning and psychological disabilities. The protocols used are designed to avoid or delay the use of radiotherapy but this cannot always be achieved; an alternative, if available, is to use conformal radiotherapy in which the radiation beam is closely adapted to the shape of the tumor from whatever angle the radiation is directed, thus reducing the irradiation of normal brain tissue.

In order to cure more children while also reducing the likelihood of long-term ill-effects, the Brain Tumor Association for Children and Adolescents (TUCCA), a charitable organization, was founded in 1998. The association is dedicated to improving treatment, quality of life, and the long-term outlook for young patients with brain and spinal cord tumors through research, multidisciplinary support, education and advocacy for families and survivors.

Dr Sidney Epelman (far left) visits with Brazilian children being treated for brain and spinal cord tumors. He and his wife, Claudia, are founding members of the Brain Tumor Association for Children and Adolescents (TUCCA) in *São* Paulo.

Since last year, the association has also begun to develop strategies directed towards reducing late diagnosis and improving treatment results in patients with retinoblastoma, a tumor of the eye. A national campaign to draw attention to the significance of leucokoria (a white gleam in the pupil that is a frequent early sign of the disease), amongst pediatricians, ophthalmologists and the population in general was developed in association with INCTR.

TUCCA has joined in a collaborative effort with a number of institutions in Brazil to fund support programs and improvements in the quality of life for children and their families that would otherwise exceed the budgets of the institutions; TUCCA raises funds through donations and events, including gala dinners and recitals. The association also distributes a free guide for the parents of children with brain tumors throughout Brazil, co-sponsors educational seminars and conferences, and provides online information through www.tucca.org.br. ■

submitted by Claudia Epelman and Sidnei Epelman, TUCCA – Associação para crianças e adolescentes com tumor cerebral. São Paulo - Brasil

RETINOBLASTOMA MEXICO-BOLOVIA

El Instituto Oncológico del oriente Boliviano, fundado en 1974, es el único instituto de su clase en Bolivia, convirtiéndose en el único hospital donde se atiende exclusivamente pacientes oncológicos. Cuenta con un servicio de pediatría fundado en 1980 y reorganizado y actualmente dirigido por la Dra. Yolanda Ernst con 13 camas que funciona desde 1998. Nuestra área de cobertura abarca toda la región oriente, incluyendo parte del sur este del país; los departamentos de influencia son Santa Cruz, Beni, Pando, Tarija, y Cochabamba. Anualmente recibimos aproximadamente 90 nuevos pacientes de los cuales 6 a 10 por año son pacientes con Retinoblastoma, la mayoría en estadios muy avanzados. Luego de varios casos encontramos que una de las principales causas para el diagnóstico tardío de estos pacientes es la falta de información tanto de la población como de los médicos ya sean estos médicos generales, pediatras e inclusive algunos oftalmólogos por no tener la sospecha del tumor en estadios más tempranos. A través de nuestro contacto con el INCTR pudimos poner en marcha un proyecto para poder mejorar el diagnóstico temprano, y el manejo de los niños con retinoblastoma.

En contacto con el Dr. Carlos Leal del Instituto Nacional de Pediatría (INP) y con el apoyo del INCTR, realicé un viaje a la ciudad de México en agosto de 2002 para ampliar mis conocimientos en cuanto al manejo de pacientes con retinoblastomas. En el Instituto Nacional de Pediatría, el Servicio de Oncología cuenta con un grupo de atención especializada para pacientes con retinoblastoma. Este grupo esta conformado por el pediatra oncólogo clínico, Dr. Carlos Leal; el oftalmólogo pediatra, Dr. Juárez; una psicóloga, Lic. Martha Flores y un radioterapeuta, Dr. Amador. Estos doctores mantienen una estrecha comunicación consiguiendo de esta manera que los pacientes diagnosticados con retinoblastoma sean vistos en su integridad. El manejo se facilita de manera importante con la ayuda de la psicóloga la Lic. Marta Flores, quien tiene a su cargo entrevistas periódicas con los padres de familia para poder mantener una relación médico-paciente óptima, y así ayudar a que el paciente pueda completar de manera satisfactoria todo el tratamiento. Ayuda también en la adaptación del niño en su familia y su núcleo social luego de la enucleación cuando es necesario.

El compartir esta experiencia con los colegas mexicanos ha sido inolvidable por varias razones. Es siempre refrescante poder visitar un centro grande como es el INP, con la gran cantidad de pacientes que maneja, y la forma colaborativa de trabajar de pediatras de varias especialidades. El ver y aprender como se conforma un grupo y se trabaja para mejorar el manejo integral del niño con retinoblastoma me abre las posibilidades de poder realizar un trabajo similar en mi ciudad con el fin de poder convertir mi centro en uno de referencia para el resto del país donde los colegas que trabajan con oncología pediátrica en las otras ciudades puedan referir sus pacientes con esta patología para que reciban un manejo integral multidisciplinario.

Un aspecto muy importante en el cual se esta trabajando es el de disminuir la incidencia de diagnóstico tardío a través de información a la población y personal médico para que exista la sospecha temprana y la derivación de estos niños a nuestro centro donde se podrá confirmar el diagnóstico y en estos casos iniciar una terapia oportuna mejorando el pronóstico y calidad de vida de nuestros niños afectados por esta patología. ■

RETINOBLASTOMA IS A MOTHER'S ANGUISH, AN ACTIVIST'S CAUSE

Hunter Tylo, a celebrated daytime television actress in the United States and mother of four, was sitting in church when she saw the white glint in her infant daughter's eye. Despite her access to the best health care available in the world, Tylo suspected that her child's pediatrician had missed something, that something was terribly wrong.

She was right. Katya had retinoblastoma, a childhood cancer that is nearly always fatal if not treated before it escapes the eye. With early diagnosis, the disease is highly treatable and, in most cases, saves eyesight and lives.

Katya, now 5, lost an eye to retinoblastoma. Hunter Tylo and her husband, Michael, responded to this personal tragedy by establishing an international organization that educates parents about the disease and the best treatments available worldwide. They joined forces with another Hollywood couple, Matt and Christina Ashford, whose daughter also had been diagnosed with retinoblastoma. As founding board members of Retinoblastoma International (RBI), the Tylos and the Ashfords are endeavoring to raise public awareness of the disease, while raising funds to help treat children from developing countries.

"Retinoblastoma is a double-edged sword of pain," says Hunter Tylo. "When something as devastating as this disease happens to your child, it is worth every effort to save even just ONE child's life and hopefully, their eyesight."

Retinoblastoma International is based at Children's Hospital of Los Angeles, California, where Dr. A. Linn Murphree is professor of ophthalmology and pediatrics; he serves as chairman of the board of RBI. Dr Murphree recently served as a Visiting Expert for INCTR, spending time at the Instituto Nacional de Pediatria in Mexico City.

Actress Hunter Tylo is an advocate for early detection of retinoblastoma, starting in a series of public service announcements about the disease.

Retinoblastoma International recently launched retinoblastoma.net to reach parents, families, medical professionals and key decision-makers worldwide. Over the next few months, the site will offer materials and plans to build a significant international network in the fight against retinoblastoma.

The Tylos also are using their celebrity status in the United States to get the word out to the 350 million viewers worldwide who watch the CBS soap opera, *The Bold and the Beautiful*. They are producing a series of public service announcements about retinoblastoma featuring Hunter Tylo and Matthew Ashford (Ashford stars on *Days of our Lives*). The PSAs, in English and Spanish, will air worldwide.

There are no precise figures for the number of cases of retinoblastoma occuring each year worldwide, but given that the incidence is likely to be higher in many developing countries, it is probably in the region of 12,000 to 16,000, and perhaps more. At least 90% of these cases occur in developing countries, where many children die from the disease due to delay in diagnosis or to a lack of expert medical care. In contrast, 97% of infants survive their retinoblastoma in more developed countries, although most have a moderate to severe visual impairment. Katya Tylo was just six weeks old when her illness was diagnosed, and it was already too late to save the eye. Parents are urged to seek immediate medical attention if they notice a white glow or glint in one or both eyes, or if their child has crossed or misaligned eyes. Both may be early signs of retinoblastoma.

In addition, the feasibility, cost effectiveness and utility of examining the retina (back of the eye) after dilatation of the pupil to screen young infants in developing countries for retinoblastoma should be examined. INCTR's Retinoblastoma Strategy group is presently exploring the reasons for late diagnosis, and is working to develop public education programs to improve early detection. ■

NNCTR/INCTR (NEPAL) PALLIATIVE CARE INITIATIVE

At the last INCTR Annual Meeting in Brussels there were a number of meetings regarding palliative care. The general feeling was that INCTR was in a unique position to encourage and promote the development of palliative care.

A Palliative Care Subcommittee was formed and several members were able to meet in London in August with Dr Robert Twycross, Emeritus Clinical Reader in Palliative Medicine at Oxford University. At that meeting we felt that because INCTR already has a presence in Nepal, via the Nepalese Network for Cancer Treatment and Research, NNCTR/INCTR (Nepal), and in particular has recently successfully initiated a cervical cancer-screening program, we should explore the possibility of a palliative care initiative in Nepal.

By way of background, Nepal is an emerging country with a population of 23 million. The terrain varies from plains in the south to rugged mountains in the north. There are many ethnic groups in the country; 82% of the population are Hindu and 8% Buddhist. IARC estimates the mortality rate from cancer in Nepal to be 11,500 persons per year. We know that persons with advanced malignancy have many severe symptoms including pain and that 70% of these patients require opioids. Nepal, then, has many thousands of patients and their families who would benefit immensely from the development of palliative care.

As chairman of the Palliative Care Subcommittee, I was fortunate to be able to visit Nepal in November and met with a number of people who were passionately interested in the care of patients dying with advanced cancer. These, amongst others, included Dr Surendra B. Bade Shrestha, Dr Monahar Lad Shrestha, Dr Arati Shah, Dr Sudip Shrestha, Dr Y.P. Singh, Dr Pradeep Vaidya and Mr Roy Kline. I was able to visit the Trubuhvan Teaching Hospital, (TU) Hospice Nepal, the Bhaktapur Cancer Care Centre and the Scheer Memorial Hospital in Banepa all of which are in or near to Kathmandu.

At the Hospice Nepal and the Bhaktapur Cancer Care Centre, a strong start has been made in palliative care. At Hospice Nepal, which has been open for only about three months, there are 8 to 10 beds, with plans to increase this number. Full-time palliative care nurses work at the hospice and the two oncologists, who do daily ward rounds, are based at TU Teaching Hospital. The hospice was built through local donations.

Doctors strive to make cancer patients comfortable in the final stages of disease.

Bhaktapur Cancer Care Centre is a 25-bed oncology hospital run by two oncologists who carry out chemotherapy and radiotherapy. They estimate that at any particular time, five patients are receiving 'purely palliative care.' Even those receiving treatment in the hope of achieving tumor regression, or even cure, generally have very advanced cancer and are highly symptomatic. Plans are in place to rebuild the in-patient wards and to develop a dedicated unit of about 10 beds for palliative care.

The Scheer Memorial Hospital in Banepa houses the Kathmandu University Medical School, which has a strong emphasis on community medicine and outreach to small rural communities. It is also the location of the NNCTR/INCTR (Nepal) office. The administrative and medical staff feel that there is strong need for a palliative care unit at their hospital.

At the TU teaching hospital, plans have been made for a Home Hospice Program.

Like all visitors to the Kingdom of Nepal, I was impressed by the kindness and hospitality of all whom I met. I was just as impressed however, by the strong commitment to palliative care that I encountered in all the people I spoke to, especially those mentioned earlier. INCTR and NNCTR/INCTR (Nepal) plan to push forward with the development of a program for the care of dying cancer patients. With time and effort we feel that this will help many thousands of patients. It is also hoped that such a program might serve as a model for other INCTR collaborating sites. ■

submitted by Dr Stuart Brown, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

PEDIATRIC ONCOLOGY IN EL SALVADOR

El Salvador, the smallest country in Central America, has 6 million inhabitants, almost 34% of whom are under 15 years of age. There is one national pediatric hospital, where approximately 175 new cases of cancer were diagnosed each year between 1996 and 2001.

Before 1993, the overall survival was only 10%; since 1994, local and international efforts have brought together a pediatric cancer program which has resulted in the survival increasing to 65% for patients with acute lymphoblastic leukemia.

This program is the result of a collaboration between the Benjamin Bloom National Pediatric Hospital, the Fundacion Ayudame a Vivir and the International Outreach program of the St. Jude Children's Research Hospital (SJCRH) in the USA. Its three main aims are: to secure access to knowledge and basic technology related to the field of pediatric cancer, to consolidate a multidisciplinary team, and to promote the education of children with cancer and their parents.

In this context the priority becomes integrated medical care. The program promotes the best medical practices of all the health care providers, it also raises the quality of support needed for modern treatment and develops the parents' skills in improving the nutritional status and general hygiene of the child with cancer.

The greatest achievements of the El Salvador program includes the improvement in survival, establishing a multidisciplinary medical team and the coordination of local resources and international support.

Pediatric cancer is not a health priority for most countries with limited resources. Due to the transfer of knowledge and technology, international endeavors, like the INCTR, MISPHO and SJCRH initiatives, have significantly improved medical practice and have in a short time increased the survival of children with cancer.■

Miguel Bonilla
Head of Oncology Service
Benjamin Bloom Hospital
El Salvador

PEDIATRIC ONCOLOGY IN PERU

The Instituto de Enfermedades Neoplásicas (INEN) in Lima, Peru—the only cancer hospital in the country—began its reorganization 50 years ago with the development of specialties in the different fields of oncology. The medical oncologists treated pediatric patients until 1980 when two new pediatric oncologists joined the medical staff, upon completing training in the U.S. The pediatric ward started with a five-bed unit in 1960 and progressively increased its capacity to 41 beds by 2001.

As everywhere in the world, acute leukemia is the most frequent neoplasm affecting children, followed by lymphomas (Hodgkin's disease and non-Hodgkin's lymphoma) and retinoblastoma, which is the most common solid tumor seen at our Institution. Unfortunately, the majority of cases come to our hospital with advanced disease due to delayed or wrong diagnosis, or inadequate medical care. There are very few cases of neuroblastoma and Ewing's sarcoma compared to the incidence in other countries.

We are currently seeing around 400 new cancer patients per year from all over the country, which has a population of approximately 25 million inhabitants, of whom half are under 15 years of age. Only three pediatric oncologists manage this patient load and not many young physicians are interested in pursuing pediatric oncology as a specialty. This is the major reason for not having a bone marrow or stem cell transplant unit.

With the treatments used, we have an overall disease-free survival of 70% at five years, but more intensive treatments are being implemented to improve upon this.■

Antonio Wachtel M.D.
Head, Pediatric Oncology
Instituto de Enfermedades
Neoplásicas

PEDIATRIC ONCOLOGY IN COLOMBIA

Facing the challenge of developing pediatric oncology in developing countries is not easy. Limited resources and socio-economic constraints are the main obstacles.

Colombia's new National Health System has increased accessibility to care but does not provide all the facilities required for high-quality care of cancer patients. Although specialists are fully committed to pediatric oncology, lack of drugs and general medical supplies, together with the lack of high technology laboratory facilities such as molecular biology labs, all contribute to the high mortality rates in our patients. It might help if international organizations such as the INCTR and WHO could influence government policies.

The National Association of Pediatric Oncologists/Hematologists has recently been established. Our aim is

to conduct cooperative multicenter epidemiological studies in order to increase survival rates in children with cancer, despite our economic constraints.

The Hospital Universitario del Valle in Cali has become an associate member of the INCTR. We hope to strengthen this association and work closely in clinical research, also benefiting from INCTR's strategic approach to building capacity.

We look forward to continuing to develop cancer control under the guidance of the INCTR. ■

Dr. Margarita Quintero de Charry
Department of Pediatrics
Hospital Universitario del Valle
Cali, Colombia

LE TRAITEMENT DES CANCERS CHEZ LES ENFANTS AFRICAINS

Le Groupe Franco-Africain d'Oncologie Pédiatrique a 2 ans.
J. LEMERLE*, F. MSEFER ALAOUI**, P. DOUMBE***

Depuis le mois d'octobre 2000 et après une dizaine d'années de contacts et d'échanges variés, le GFAOP connaît enfin une existence officielle.

Son objectif est de développer des stratégies de diagnostic et de traitement des cancers de l'enfant adaptés à l'Afrique ainsi que de former des médecins, des infirmières et, des techniciens pour et sur ce même continent.

Sa motivation est de contribuer à mettre fin à une situation scandaleuse. En effet, en 2003, sur les dizaines de milliers d'enfants africains qui seront atteints d'un cancer et plus particulièrement d'une leucémie, bien peu guériront. Probablement guère plus de 5 à 10% d'entre eux.

Une injustice d'autant plus criante que 75% des petits malades des pays industrialisés peuvent eux être sauvés…

Afin de trouver des solutions, le GFAOP peut heureusement s'appuyer sur le travail de ses partenaires.

Huit "Unités Pilotes" ont été implantées à Alger et Oran, à Tunis, à Rabat et à Casablanca, à Dakar, à Yaoundé et enfin à Antananarivo à Madagascar.

Ces UP ont, dors et déjà, développé des traitements adaptés aux possibilités locales pour les néphroblastomes et les lymphomes de Burkitt. Trois cent cinq cas ont été rassemblés en 21 mois dont 175 cas de lymphome de Burkitt. Le recrutement des cas augmente de mois en mois, des milliers de questionnaires sont en cours de traitement et un nouveau projet de recherche clinique et biologique est déjà en préparation.

Le lymphome de Burkitt, lymphosarcome aux visages divers, semble être la tumeur la plus fréquente chez l'enfant dans certaines régions d'Afrique subsaharienne. Le GFAOP essaye donc d'en préciser la distribution, les particularités cliniques, mais aussi biologiques et thérapeutiques. Atteintes maxillo-faciales ou non, anticorps EBV, sensibilité variable aux chimiothérapies.

Le GFAOP est également à la recherche de facteurs pronostiques pour mieux adapter les traitements aux différents cas rencontrés. Quels sont les cas qui pourront bénéficier un jour de traitements plus légers, comme ceux basés sur la prise d'un seul médicament le Cyclophosphamide (Endoxan)? Cette hypothèse de travail est d'ailleurs déjà à l'étude de façon très active en Afrique australe et orientale.

En tout état de cause, l'état général des enfants lors de leur prise en charge médicale est encore trop souvent catastrophique, ce qui traduit un énorme problème de retard au diagnostic. En Afrique, il faudrait impérativement arriver à utiliser les moyens de communication modernes pour diffuser les images de ces enfants au ventre déformé et au visage défiguré par des tumeurs toujours rapidement évolutives et faciles à reconnaître.

La formation des infirmières africaines à la précision et aux précautions requises pour l'utilisation prudente des chimiothérapies est un des principaux chantiers du GFAOP. L'organisation de stages intensifs de 6 à 8 semaines dans des unités d'oncologie pédiatrique françaises, et des visites d'étude en Afrique faites par des équipes d'infirmières pour évaluer les besoins locaux, notamment en formation, sont déjà en cours.

Les problèmes d'éthique en rapport avec la recherche clinique sont abordés dans deux domaines principaux. L'un est celui des bonnes pratiques cliniques : l'éthique de la recherche clinique commence par le lavage des mains et la précision des prescriptions écrites et des mesures. L'autre est celui de la communication avec les malades et leurs familles, préalable indispensable à la signature d'un « consentement éclairé ».

Le secrétariat et la banque de données du GFAOP sont situés à l'Institut Gustave-Roussy (Villejuif – France). ■

* Président du GFAOP
** Vice-Présidente du GFAOP
*** Trésorier du GFAOP

NETWORK

Health Matters - BBC World Service

Dr Magrath participated in a BBC World Service broadcast of the program "Health Matters" on October 25 which covered cancer prevention, and particularly cervical cancer screening, acute lymphoblastic leukemia and palliative care. In the same program, Dr Suresh Advani, of the Leukemia Study Group of India (see below), pointed out that treatment results have improved from 25% to some 60% long-term survival in the last 30 years. These results have been achieved with a treatment protocol, MCP841, designed for a collaborative program among three major Indian centers and NCI/INCTR. ■

Meeting of the Brazilian Society of Pediatric Oncology and INCTR's Brazilian Branch

Dr Magrath participated in a meeting of the Brazilian Society of Pediatric Oncology between 30 October to 1 November, in particular in a session on the early detection of retinoblastoma. He also met with Dr Sidnei Epelman concerning the opening of the new INCTR Branch in Brazil and with representatives of the Bank of Brazil, which has supported the development of pediatric oncology centers in Brazil. This program has been very successful and INCTR will undertake discussions with the Bank to explore possibilities of working together in Brazil. ■

Progress in Leukemia Study Group of India (LSGI)

In late November, at the time of the SIOP Asia Meeting in Delhi, the LSGI, a subcommittee of INCTR's Leukemia Strategy Group, also met. In the course of this meeting a new treatment protocol for acute lymphoblastic leukemia (ALL) was finalized, and plans were made for implementation in mid-2003. A meeting was also held with the Sir Ratan Tata Trust in Mumbai regarding possible funding of this project along with plans to extend treatment with the existing protocol (MCP841) to other centers in India, which will work closely with the three major centers presently using this protocol (Cancer Institute, Chennai, All India Institute of Medical Sciences, and Tata Memorial Hospital). The achievements of our Indian colleagues was mentioned in a recent news article in *Lancet Oncology*. ■

Meeting with UICC and ESO Representatives in Antwerp

A meeting took place in Antwerp, on the occasion of a meeting on Women's Cancer in Europe, with several members of the UICC—including Dr Louis Denis, Treasurer, Dr Robert Hudson, Chairman of the UICC Copes program, Dr Arun Kurkure of the Lady Ratan Tata Medical and Research Center in India—and Dr Alberto Costa, Director of the European School of Oncology, to discuss possible areas of collaboration between these organizations. It was agreed that there would be much to be gained by working together, and cervical cancer was singled out as a worthy initial focus of concerted efforts. ■

Meeting on Development of an INCTR E-Learning Program

A meeting took place with Dr Jean-Claude Kurdziel and Dr Ali Khan on October 25 to discuss the development of an e-learning program for INCTR. Dr Kurdziel has extensive experience in the development of e-learning modules, and is willing to provide his services gratis to INCTR. It was recognized that INCTR must utilize modern educational tools in its programs, and further discussions on how this project can be moved forward and funded are planned. ■

Collaboration with the International Agency for Research on Cancer (IARC)

INCTR is undertaking collaboration with IARC in the context of cervical cancer, and in the establishment of a population-based cancer registry in Lahore. A meeting was held with Dr Max Parkin and Dr Sankaranarayanan of IARC on December 4 to discuss these projects. Training in both areas will be carried out by IARC, and INCTR will assist in coordination and data management relating to these projects. Additional projects, including collection of information on resources for cancer treatment and research and pediatric cancer registration were discussed. All expressed interest in expanding IARC/INCTR collaboration in these areas. ■

Meeting of MECCA in Riyadh

The Middle East Children's Cancer Association (MECCA) met in Riyadh on the occasion of the Cancer 2002 meeting which took place between October 14 and 16, and which was organized by the King Faisal Specialist Hospital and Research Center. In the course of the MECCA meeting, which was coordinated by Dr Abdallah Al-Nasser, several important areas of pediatric oncology were discussed. Six of the participating countries have agreed to explore the development of a joint protocol for the treatment of acute lymphoblastic leukemia. It

was decided that the treatment protocols used by the India Leukemia Study Group would provide a model for this project, and that a meeting would be held in Spring 2003, with a follow-up joint meeting with the ILSG at the Annual Meeting to discuss the specific treatment protocol design. ■

Ian Peter Rennert Lecture in Pediatric Oncology

Dr Magrath was invited to give the first Ian Peter Rennert Lecture at Georgetown University, Washington DC, on November 6. His lecture was entitled *Lessons from Burkitt's Lymphoma*. This provided an opportunity to discuss INCTR's work with several members of the Vincent Lombardi Cancer Center, including the Director, Dr Richard Pestell, and Dr Aziza Shad, a member of INCTR's Governing Council. Possibilities of working more closely with the Lombardi Cancer Center, and in particular, in the context of e-learning in pathology, were discussed. Dr Magrath also took the opportunity to visit NCI and to meet with Drs Harford and Welsch of the Office of International Affairs. ■

Lymphoma Strategy Group Meeting

A sub-committee of the Lymphoma Strategy Group met on December 6 and 7 to discuss a collaborative treatment program for patients with Burkitt's Lymphoma (BL) in Africa. Investigators representing five institutions in Africa (Kenya, Nigeria, Tanzania and Uganda) participated. The problems encountered by each of the investigators were discussed in detail. A uniform treatment regimen for newly diagnosed BL patients was agreed upon. It was anticipated that a year will be required in order to put into place the necessary infrastructure to conduct a formal clinical study. In this time, data managers will be appointed and common data collection forms will be created. A formal protocol will be developed during this time. A follow-up meeting is planned for May 2003. ■

Data Manager Training

Ms Bhasha Kolhatkar of the Tata Memorial Hospital in Mumbai received training relating to ethics, good clinical practice and data management practices in INCTR's Clinical Trials Office (CTO) in December. The experience proved extremely useful for both Ms Kolhatkar and the staff of the CTO. The exchange of information that took place during the two-week training period will be invaluable in preparing a formal training course for data managers in India. ■

Meetings of the Corporate Liaison Committee

INCTR's corporate Liaison Committee met on December 20 to discuss approaches to the development of sponsorships of INCTR's programs and meetings by the corporate world. Recent interest expressed by the presidents of two pharmaceutical companies in projects in Africa and in palliative care were mentioned. Several specific approaches were discussed and have been acted upon.

Autumn Visitors

Dr Norman Coleman, Associate Director of National Cancer Institute's Radiation Research Program and Chief of Radiation Oncology at NCI, visited INCTR to discuss potential collaboration, particularly in the area of telemedicine. Dr Coleman said that he thought the "progress (made) in two years by INCTR is remarkable."

Dr Pierre Scalliet, Professor of Radiation Therapy at the Catholic University of Louvain at St Luc University Hospital in Brussels, visited INCTR to discuss his interests in radiation therapy training in developing countries and the possibility of working with INCTR in this area of endeavor.

Dr Birendra Amatya, a pathologist from Nepal who has been undertaking advanced training in Leuven, will be the only hematopathologist in Nepal, and asked for assistance in establishing a program in Kathmandu. The possibility of INCTR assisting in the establishment of a collaborative program to be established in Nepal, with Dr Naresh, a hematopathologists in Mumbai, was discussed. ■

Award Winners

The Special Panel of the INCTR Advisory Board has selected the winners of the 2003 INCTR Awards. We are very pleased to announce that Dr Max Parkin of the International Agency for Cancer Research is the winner of the Paul P. Carbone Award in International Oncology. Dr Federico Sackman-Muriel, formerly of the Garrahan Hospital, Buenos Aires, is the winner of the Nazli Gad-el-Mawla Award. The Award Lectures will be presented on 29 May, after the opening session of the Annual Meeting in Brussels. ■

INCTR at the Institut Pasteur
Rue Engeland 642
1180 Brussels - Belgium
+32 2 373 93 23
bene@inctr.be
www.inctr.org

HEMATOLOGY AND PEDIATRIC HEMATO-ONCOLOGY SERVICES IN CASABLANCA

The Country, the City and the People

The Kingdom of Morocco, situated at the northwest tip of Africa and bordered by the Atlantic ocean and the Mediterranean sea, covers an area of 710,850 km^2. The population exceeds 31 million, with children under the age of 14 representing almost 40% of the population. Morocco faces the problems typical of developing countries: 19% of the population living below the poverty line and up to 50% being illiterate.

Casablanca is the capital; with more than 4 million inhabitants, it is the most densely populated city in North Africa. More than 60% of Morocco's economic activity is concentrated there.

Hematology and Pediatric Oncology

The Department of Hematology and Pediatric Hemato-Oncology was created in 1980 by Professor N Benchemsi and Professor S Benchekroun, at a time when there was no specialized unit in Morocco dealing with hematological malignancy. Given the inadequate quality of supportive care facilities, specifically the lack of blood products and antibiotics, intensive chemotherapy was not used. Most patients had no health insurance and could not afford to pay for their treatment. Likewise, the hospital had very limited resources and could not provide such expensive treatment. It thus became clear that quality of care would not improve without additional help. An association of volunteers and donors was therefore established in 1983.

The Children's Hospital in Casablanca.

Named 'Agir,' it has proven to be very efficient and has helped the hospital team in its endeavors to provide optimal care.

Unfortunately, the Department in Casablanca is still the only public facility in Morocco treating adult patients with hematological malignancies. Two pediatric units have been established, one at the Children's Hospital in Casablanca, the other in Rabat. The Department comprises an outpatient clinic and a day-care unit, where more than 100 patients are seen each day, together with two wards—one with 24 beds for adults the other with 13 beds for children. Mothers are encouraged to stay with their children.

Each year, the Department admits more than 1,000 new patients, of whom approximately 250 are children suffering from various kinds of cancer. Lymphomas, leukemias, myeloma and aplastic anemia, together with 'benign' conditions such as iron deficiency anemia, thalassemia, sickle cell anemia, and hemophilia, are the most prevalent conditions seen in adults, whereas in children, lymphomas, acute lymphoblastic leukemia (ALL), nephroblastoma, neuroblastoma and bone tumors are the most frequently seen malignancies.

Improvements in Supportive Care

Improvements in supportive care have resulted in a significant decrease in mortality from neutropenic sepsis. Initially this was 30%, but a retrospective analysis of 40 febrile episodes in children with AML treated between 1996 and 2001 showed the mortality rate to have fallen to 5% in an era when more intensive treatment was being used. In the initial series of 66 patients treated between May 1980 and January 1983, when hydroxyurea was the only drug being used, complete remission (CR) was achieved in only 5 patients. In contrast, CR was achieved in 15 of 20 patients admitted during 2002. Current treatment comprises remission induction therapy with daunorubicin and cytarabine (ara-C), followed by 2 cycles of high-dose ara-C, given with doxorubicin or idarubicin.

This progress has been made possible by improvements in supportive care, increased awareness of the importance of hygiene, education of patients and improvements in nursing education. Another factor has been the quality of blood products: a Quality Control Committee for Blood Transfusion Services sees to this. Screening for hepatitis B and C and for

HIV is now routinely carried out. As a result, the incidence of hepatitis C has fallen from 26% to 6% in patients receiving multiple transfusions. Morocco has a very low incidence of HIV, but an Infection Control Committee, which works closely with the medical staff, has been established.

Lymphoma

In view of the potentially good prognosis of patients with lymphoma, this group of diseases was considered to be a priority and resources were allocated to improve survival in these patients. Ninety-five patients with Burkitt's lymphoma (mean age 6.7 years, male: female ratio 1:2.5) have been treated according to the French LMB89 protocol. Most patients (73.5%) had an abdominal presentation; the diagnosis was made on the basis of fine needle aspiration in 60% of cases. The majority of cases (63%) had Stage III disease. Complete remission was achieved in 68.5% of cases and the five-year survival was 59%. Ten of the 15 patients who died did so before or shortly after initiation of treatment due to metabolic and nutritional complications.

The greatest problem is that patients present with very advanced disease because of delays in diagnosis and the long distances involved in reaching the hospital. For example, 441 adults were treated for non-Hodgkin's lymphoma between January 1998 and December 2000. Only 39 of them live in Casablanca. Only 10% had health insurance. The mean duration of symptoms before diagnosis was eight months; 70% had Stage III or IV disease at the time of presentation.

With regard to Hodgkin's disease, 181 children have been treated up to 2001. Chemotherapy regimens comprised 'MOPP', 'COPP' or 'ABV.' In 1986, a phase II study was conducted to evaluate the use of vinorelbine. Again, most patients presented with advanced stage disease. An unexpected finding was the incidence of Hodgkin's disease in very young children; 15 being 4 years or younger at the time of presentation.

Accomplishments and Collaborative Programs

The Department is a major referral center for the treatment of children with cancer and for adult patients with hematological disorders. We have participated in the creation of the Moroccan Society of Pediatric Oncology (SMOP) and have worked in collaboration with the Center for Pediatric Oncology in Rabat (Professor Msefer-Alaoui) in the organization of the third SIOP meeting of Africa. We have organized 13 workshops in hematology and pediatric oncology.

Currently there is no stem cell transplantation program in Morocco. With the help of our fundraising group we are working to set up a small unit for this purpose. We are also lucky to have been involved with Professor Jean Lemerle (Villejuif, France) in the Groupe Franco-Africain d'Oncologie Pédiatrique. The group is focusing on Burkitt's lymphoma and Wilms tumor.

We also have developed an ambitious program with the International Outreach Program of St Jude Children's Research Hospital (USA), directed by Dr Judith Wilimas and Dr Raul Ribeiro. This program has focused on nursing, together with improvement in pathology services and infection control, as well as data management, ethical issues, immunophenotyping for leukemia and the development of therapeutic protocols adapted to local circumstances.

The medical care provided at Children's Hospital in Casablanca, which focuses on both the physical and emotional needs of young patients, gets a "thumbs up."

What next?

There are several aspects of treatment which need improvement, including cytogenetics and services for the treatment of thalassemia, sickle cell anemia and hemophilia. Since there is no reliable data on the epidemiology of cancer in Morocco, a cancer registry is urgently needed. There is also a need for the creation of other units throughout the country to take care of children suffering from cancer; we will be helping with the establishment of this program. Finally, since there is no accommodation for the parents of children in the hospital, the fundraising group is working to remedy this.

The medical team is very dedicated and enthusiastic and is extremely interested in developing collaborative projects with experienced teams in hematology and pediatric oncology. ■

Submitted by: Mhamed Harif (MD), Asmaa Quessar (MD), Said Benchekroun (MD) Service d'Hématologie et Oncologie Pédiatrique Hôpital 20 août 1953, Casablanca, Morocco
e-mail : agir@wanadoopro.ma

PROFILES IN CANCER MEDICINE

DINSHAW LEADS CANCER REVOLUTION AT TATA

Radiation therapy is used in the treatment of two-thirds of all cancer patients in India today. It is often the treatment of choice as primary therapy, and is frequently used in combination with surgery or chemotherapy and for palliation in advanced cases. At the Tata Memorial Centre, Mumbai, India, where Dr. Ketayun Dinshaw is director, 400 patients receive radiation treatment every day.

As a radiation oncologist-turned-hospital administrator at one of India's foremost cancer hospitals, Dr. Dinshaw has played a significant role in the evolution of modern health care in that country, and radiation therapy has led the way. Her hospital's department of radiation oncology can deliver both external beam therapy and brachytherapy (temporary implantation of radioactive pellets or wires into the tumor). New, high precision treatment design and delivery methods such as three-dimensional conformal radiotherapy, in which the radiation beam is automatically adjusted to the shape of the tumor during treatment from several angles, and intensity modulated radiotherapy, in which the strength of the beam is similarly adjusted, are available. Both of these treatments minimize the amount of normal tissue in the irradiated field. The cancer treatment methods available at Tata Memorial Hospital rival any in the world.

Over the past 25 years, Dinshaw has revolutionized cancer medicine in India, refining multi-modal treatments as the exception rather than the rule. Most recently, she has turned her attention to expanding the hospital's capabilities for clinical research. Clinical trials—a relatively new

concept in India—are underway in treating various cancers including breast, cervical, head and neck, lymphomas and leukemias.

"We are very keen to be involved in new collaborations with INCTR," Dinshaw says. "Cervix is the most common cancer in my country, and in certain metropolitan areas breast cancer is overtaking it. It will be extremely useful to be part of organized trials that might evolve from INCTR's strategy groups in these areas."

Dinshaw joined the staff of the Tata Memorial Hospital, Mumbai, in 1974, and seven years later was named head of the department of radiation oncology. In 1995, she was appointed director of the Tata Memorial Hospital, and two years later was selected to oversee the Tata Memorial Centre (Tata Memorial Hospital and Cancer Research Institute) as well.

Throughout her tenure, she has been a driving force in establishing the highest standards, organizing and refurbishing all departments, providing modern instrumentation for diagnosis and treatment of cancer, and establishing modern management systems and computerization in the hospital.

One of her earliest initiatives was fostering an integrated team approach to cancer treatment, encouraging radiologists and surgeons to review new patients in the Lymphoma Joint Clinic. Together, the doctors established clinical protocols, and now channel cancer patients into appropriate treatment programs according to set guidelines—in the context of ongoing clinical trials. A vibrant scientific review committee and hospital ethics committee monitor and guide all research programs in the Tata Memorial Hospital.

A new facility housing the Advanced Centre for Treatment Research and Education in Cancer (ACTREC) opened just last year. The Cancer Research Institute at ACTREC will focus on molecular genetics, molecular epidemiology, immunology, virology and newer areas of genomics and drug development. The Clinical Research Centre aims to introduce translational research from the bench to the bedside and will focus on specific clinical trials. Validation by sophisticated laboratory methodologies, predictive and prognostic assays, and tumor markers will bridge intense interaction between scientists and clinicians. Indigenous development of teletherapy units and models will also be addressed at ACTREC, which is expected to be a hub of excellence in the region.

"Between the hospital and the research centre, we are strongly positioned to provide leadership in all areas of medical services, education and research," she says. "While we have concentrated on providing the best patient service, we are also interested in all aspects of basic and clinical research, and in providing post-graduate training. We place emphasis on teaching and using our wealth of excellent clinical material for research." ■