N E T W O R K

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INCTR

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THE PRESIDENT'S MESSAGE

KNOWLEDGE AND CANCER

by Ian Magrath

"Real knowledge is to know the extent of one's ignorance."
Confucius, 551-479 BCE

In spite of Plato's scepticism, most Western philosophers have been satisfied with the definition of knowledge as belief that is both true and justified. Plato recognized that the meaning of the word *knowledge* is inextricably entwined with what constitutes sufficient *justification* for belief. All knowledge, however, derives ultimately from a set of assumptions or beliefs for which there is no formal proof - a difficulty that lies at the heart of philosophy, and which Descartes, (often referred to as the "Founder of Modern Philosophy") attempted to address via his famous principle *cogito ergo sum*. Epistemologists (philosophers who study the nature of knowledge) must also address the range (or field) of meaning of the word itself. Knowledge of *what is* (descriptive, or propositional knowledge), for example, is not the same as knowledge of *how to* (procedural knowledge) although either, without the other, is of limited, if any value. Unprovable, but justifiably true beliefs (such as Euclid's five axioms or postulates that apply to *plane* or *Euclidean* geometry) provide a point of departure for the construction of the entire edifice of scientific knowledge - through mea-

"The School of Athens", a fresco painted by Raphael between 1509 and 1510 in the rooms now known as the Stanze di Raffaello in the Apostolic Palace in the Vatican. The painting depicts some of the greatest philosophers and mathematicians of antiquity, including Plato (center left) and Aristotle (center right). The face of Plato is actually that of Leonardo da Vinci. The figure leaning over a blackboard on the right may be Euclid. Published with permission of the Photo Vatican Museums.

surements of natural phenomena or made in the course of experiments and interpretation of their meaning. Such measurements, which require procedural knowledge, constitute, in effect, quantified experience. It is, however, precisely because scientific knowledge is based on evidence (scientific justification) that it is subject to a degree of uncertainty. This arises in part from the quality, quantity and completeness of the evidence, and in part from the psychology or "world view" of those who draw conclusions from it. Opinion, unsubstantiated statements, incomplete information or tradition do not provide sufficient justification for belief, an issue that Plato addressed two and a half thousand years ago. His concept of Forms - the universal truths that underlie the material world - demonstrates that perfect knowledge implies the possession of absolute truth which, in practice, can never be achieved.

INCTR

EDITORIAL STAFF
Ian Magrath, Editor
Marcia Landskroener, Managing Editor
Bénédicte Chaidron, Assistant Editor
Sophie Lebedoff, Tractor, Lay-out

ADDRESS CORRESPONDENCE TO:
INCTR at the Institut Pasteur
Rue Engeland 642
1180 Brussels • Belgium
+32 2 373 93 23 • bene@inctr.be
www.inctr.org *or to*

NETWORK: INCTR Newsletter
c/o Marcia Landskroener
3817 McGinnes Road
Millington, Maryland 21651 USA
mlandskroener2@washcoll.edu

All "knowledge" is subject to caution and caveat; new or more accurate evidence, or reinterpretation of existing evidence, may demonstrate even long held beliefs to be partially or wholly false. Euclidean geometry and Newtonian physics, for example, provide approximations to physical reality which continue to serve us well in many contexts, but which are inadequate formulations in the realms of the very large or the very small - where relativity and quantum physics reign supreme. In contrast, the longstanding belief that the sun revolves around the Earth was shown by Copernicus to be entirely unfounded. The constant remodeling of what is considered to be known is familiar to mathematicians and scientists, who recognize the external and internal determinants of the quality of what might be called "practical" knowledge (propositions in which belief is more or less proportional to the evidence of their validity) and therefore the seemingly paradoxical uncertainty that is inherent in justified belief - perhaps because it is, after all, merely a product of the human mind.

FROM AXIOM TO ALGORITHM

In 1900, David Hilbert, a brilliant German mathematician set the course of mathematics for much of the next century by listing 23 major mathematical problems that remained unsolved. His own goal, or program, as it became known, was no less than an attempt to demonstrate that all of mathematics could be shown to follow from a finite set of well-chosen axioms (Hilbert provided 20 such axioms in place of Euclid's), stated and manipulated according to a set of formal rules and comprising a complete, self-consistent system. Such a system would contain no mathematical contradictions and would allow the formulation of algorithms from within its own formal structure that could determine whether any mathematical statement were true or false. Demonstrating the completeness and, in essence, infallibility of mathematics, seemed to be a natural corollary to its blossoming, in the minds of a serious of outstanding European mathematicians (starting with Descartes himself), to the point where quantitative description had become possible, in algebraic or geometrical notation, of phenomena in fields as diverse as fundamental physics, biology and economics. It seemed logical to assume that using an axiomatic approach (the term *axiom* now being expanded to include a range of formal logical statements from which other statements can be derived), contradictions in any field of knowledge would be impossible, and the need for intuition (the basis, for example, of Euclid's axioms) would be eliminated. In 1931, however, Gödel, a 25 year old Viennese mathematical logician, published his *undecidability* or *incompleteness theorems*, which provided mathematical proof that Hilbert's conjectures were false, and that for any formal axiomatic system involving the natural numbers (and therefore, for the whole of mathematics) there exist true statements that cannot be proven to be either true or false using the axioms inherent to the formal system. In effect, Gödel showed that to prove that mathematics is consistent, one had first to assume that it is! This seemingly arcane conclusion is a demonstration of the existence of mathematical versions of propositions of the kind: "this statement is false."

To prove it correct is to prove it false and vice versa. It is also, perhaps, ironic, if also tragic, that Gödel, one of the greatest logicians of of the 20th century, a man who was for many years a close friend of Albert Einstein, suffered from paranoid delusions. He believed that strangers were trying to kill him by poisoning his food and for much of his life would only accept meals prepared by his wife. Eventually, in a final attempt to avoid being poisoned, he starved himself to death.

Although Gödel's theorems appeared to rock the very foundations of mathematics, it eventually became clear that a good deal of Hilbert's program could, after modification, be salvaged, while a restatement of the incompleteness theorems in 1936 by Alan Turing, an English mathematician, led to the concept of the *Turing Machine* (a thought experiment rather than an actual machine) and Turing's proof that such machines could perform any mathematical manipulation as long as the latter could be expressed in the form of an algorithm. Turing had developed, in essence, stored computer programs, and recognized, via his concept of a *Universal Turing Machine*, i.e., one able to perform the functions (execute the programs) of any other Turing machine, that a single machine, suitably programmed, was all that was needed to carry out or control almost any conceivable task. Turing, who had played a major role in deciphering the German military codes used in World War II, and whose work had provided the logical foundation of computer science, was arrested in 1952 after admitting to a homosexual relationship. He died two years later after eating an apple laced with cyanide.

KNOWLEDGE ACQUISITION

Computers, as their name suggests, are ultimately dependent upon computations - i.e., the manipulation of data according to precisely defined rules. Philosophers have discussed, since the time of Plato, whether the world consists of mathematical objects waiting to be discovered, or whether mathematics is a purely human invention imposed upon the world. Whichever is correct, every aspect of the world we live in can be quantified. Even sentences can be expressed mathematically, particularly when in the form of a proposition, i.e., a statement or assertion that can be determined to be either true or false. Thus, the language of mathematics permits more precise - sometimes exquisitely precise - description and provides a connecting matrix for the seemingly separate entities around us and the changes that occur in them. The simplest of entities are the elementary units of knowledge. Language, including mathematics, allows representation of these elementary units and exploration of the relationships among them, leading to the construction, fact by fact, of a more or less complete picture, or *theory*, of one or more aspects of reality. Knowledge, in the computer age, can be seen to be well-substantiated answers to a series of questions, which must be correctly structured if the ultimate goal - truth - is to be achieved. In Einstein's words: "The formulation of a problem is often more essential than its solution."

Data, which is a plural word derived from the Latin for "a given," are the propositions that represent reality, i.e., measurements or observations of a variable (something that can be quantified). Data can be in the form of numbers, words or images, all of which can be expressed in binary code and thus "digitalized" for analysis by computer. The quality of data depends upon many factors. An essential prerequisite is a precise definition for each data element (e.g., age, complete response). Such definitions are often compiled in a *data dictionary* and must be identical in different *data sets* if the latter are to be accurately compared. This resembles the need to use standard definitions of words used in specific contexts in order to understand and to be understood. It is also essential that data are collected with great care, and that for any meaningful interpretation of data derived from a controlled experiment, such as a clinical trial, the experimental protocol must be closely adhered to. Meaning emerges when data are analyzed and expressed symbolically as text, graphics or sound. Processed data (as opposed to the original or *raw* data) are usually referred to as *information*, which,

The Chinese character for "Listen" contains several of the elements relevant to both knowledge acquisition and management. The contained characters for heart, eye and ear imply both a deeper understanding and shared learning.

when used to determine the truth of a proposition or hypothesis, is referred to as *evidence*. Such propositions must be formulated so as to be *falsifiable*, i.e., they can be shown to be either "true" or "false." The degree of confidence in the truth of the hypothesis, if necessary, is assessed by statistical analysis, which varies with respect to its *power* to confirm or refute the hypothesis according to the amount of available data. And ultimately, sufficient evidence leads to justifiable belief in the proposition - i.e., knowledge.

But knowledge, in spite of the claims of some mathematicians and scientists, is not the final goal; knowledge without consequence, in the words of the Chinese epithet, is "thunder without rain." And regardless of the motives of the creators of knowledge, sooner or later it will have practical value to the community. Moreover, just as propositional and procedural knowledge are complements of each other, so action is essential to the creation of knowledge. The greater the knowledge, the more effective can be the action, and the greater the action, the more knowledge can be accumulated. Sufficient information (comprised of a web of individual facts, or validated propositions) leads eventually to *understanding*. This implies an ability to recognize the linkages between the known elements of a system, to derive its informational content and to be able to reproduce and use such information (Figure 1). Knowledge, it can be seen, lies somewhere between - and overlaps - information and understanding. And understanding, of necessity, includes a liberal seasoning of knowledge with intuition. For imagination is required to perceive the linkages among seemingly disparate units of knowledge - a process that is both dependent upon and complements the formal systems which provide the logical structure essential to the strength and endurance of the whole. And while intuition will often prove to be incorrect, identifying what is not the case is as important to understanding as recognizing what is. Intuitive assumptions provide the foundation on which all knowledge is built. They play a critical role in formulating the right questions to ask and in the process of inductive reasoning (such as generalization). Eventually, they lead to the slow dawning of understanding and the consequent validation of entire mental constructs. Paradoxically, it required Gödel's logical genius to prove that this is so.

CANCER RESEARCH

In the health sciences, the purpose of collecting data is to create evidence that can serve as the basis for action designed to improve the health of individuals or populations. It should be recognized that sound evidence and effective action are not dependent upon understanding. Empirical observation, in which there may be limited mechanistic understanding, provides perfectly legitimate evidence - for example, of the effect of treatment on a tumor or the observation of a decrease in the incidence of a cancer when exposure to an associated environmental agent is reduced. But understanding can lead to novel interventions, which are much more specific and likely to be much less toxic. In the last several decades great progress has been made in unraveling the molecular pathways that lead to cancer, and we are now beginning to reap the

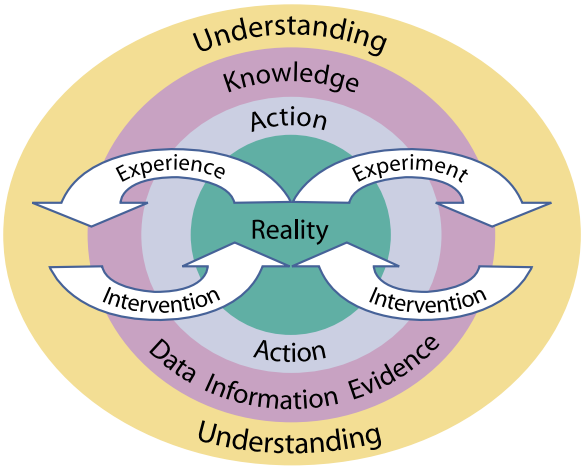

Figure 1. A knowledge mandala: reality is understood via actions that create knowledge through a process of data gathering, analysis and assessing the evidence for or against a proposition or hypothesis. Once there is knowledge and/or understanding, interventions (action) can be undertaken to modify reality.

benefits of the new understanding that has derived from the simultaneous advance of propositional and procedural knowledge; a large fraction of new drugs under development (including antibodies) are targeted to the molecular lesions which cause cancer and which, for the most part, are specific to cancer, or to molecules highly expressed in particular cancers. The broad sweep of progress in molecular biology has also allowed the development of new vaccines that prevent infection by microorganisms which cause diseases associated with the development of cancer.

While everyone uses knowledge as a part of everyday life, the acquisition of specialized knowledge, - whether at the level of data collection or interpretation -, itself requires expertise. This means that the majority are dependent upon evidence collected by the minority - i.e., knowledge transfer is essential. In the case of health care professionals, most have limited or no research training and have neither the necessary skills nor incentive to participate in high-quality research. One of the consequences of this is that in most high-income countries only a small percentage of patients participate in clinical trials. This is a serious problem, for it leads to a marked reduction in the speed with which knowledge can be acquired. An obvious, but often overlooked source of knowledge is the developing countries, where more than 50% of all cancer occurs, along with novel opportunities to understand more about cancer (sometimes via simple, inexpensive research) and to utilize this knowledge to the benefit of all. Unfortunately, the limited infrastructure means that the amount of research conducted is markedly less than in high-income countries and the abundant sources of knowledge in developing countries remain, to a large extent, untapped. The lack of the procedural knowledge required for research leads not only to a dearth of propositional knowledge relevant to the local situation, but also to a less than scientific approach to patient care and a negative impact on professional education. As a consequence, the numerically large populations of developing countries are unable to realize their potential and medical care and cancer control are significantly less efficient than need be, even within the constraints imposed by socioeconomic circumstances. This situation is compounded by the continuous leak of human resources to higher income countries (most often the best educated members of the population), where economic and professional rewards are greater.

The limited evidence base derived from research in the developing countries themselves means that the bulk of the evidence used for cancer control comes from high-income countries, not all of which is pertinent to the developing countries - or even meaningful in the specific circumstances they face. Major differences in populations and environments lead to different patterns of cancer and a broad set of problems that negatively influence access to care. Incidentally, these differences in the cancer patterns - an essential foundation for cancer control planning - are poorly documented because of the paucity of cancer registries (which also have an important role in the assessment of the impact of interventions). It is clear, however, that cancer is much more advanced at the time of presentation in developing countries, due to poverty, ignorance and limitations in cancer services; consequently, early diagnosis and palliative care should be assigned correspondingly higher priorities. Finally, the techniques used to detect and treat cancer in high income countries may be too expensive, not feasible because of the limited resources, or less suited to developing countries for cultural or other reasons. In order to begin to remedy these problems, to the extent possible within the existing socioeconomic constraints, it will be important to establish the size and quality of the existing evidence base pertaining to all aspects of cancer control in developing countries, to make it more accessible and to identify effective methods of expanding it. Only by improving the acquisition and management of propositional knowledge, which will require the transfer of the necessary procedural knowledge, will resource-poor countries be able to develop and sustain cancer control programs that are more specifically targeted to their needs. This topic is dealt with in a subsequent article in this issue of *Network*.

KNOWLEDGE MANAGEMENT

Knowledge management is a term most often used in the context of business, where the most effective use of knowledge is likely to lead to maximum profit. Knowledge can also be bought and sold as a commodity. Hence, businesses have a strong incentive to accrue, store, classify and exchange knowledge, and to ensure that staff members are kept well informed, at least with

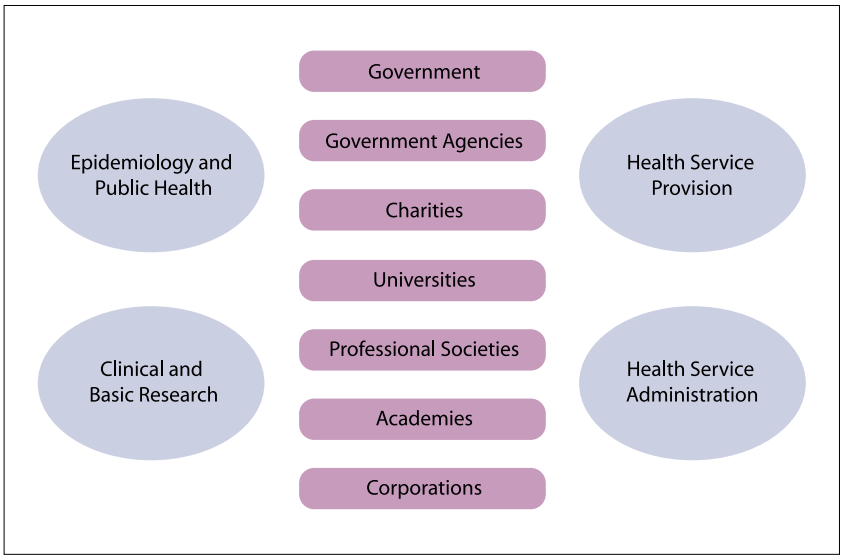

Figure 2. Components of the community concerned with cancer control - each has its own knowledge base and methods of knowledge management. The effectiveness of cancer control would be greatly enhanced if the intervening divides could be bridged.

respect to the knowledge areas in which they work. And while knowledge of products or services must be widely disseminated, the withholding of knowledge, even if not in the interests of the community at large, can lead to considerable economic benefit or political advantage. Indeed, patents, which permit short-term monopolies, were introduced centuries ago to provide incentive to inventors while not indefinitely withholding valuable information or products from the community. In non-profit situations the incentives may be different but the need for knowledge is equally great. Frequently, civil society is the only source or purveyor of information that is critically important to the public good. But no matter what their origin, whether or not messages directed to various sectors of the community are received and acted upon is often critically dependent upon the way in which knowledge is presented; optimal presentation requires understanding of the psychological factors that influence its reception. These differ widely in different populations and age groups as well as in men versus women.

A major problem with respect to knowledge management in cancer control is its compartmentalization. A broad range of experts is required to train and educate the workforce, develop the products and equipment required to undertake the range of necessary interventions and to collect, review and make available the knowledge derived from research. It is not possible to encompass in one organization, even less in a single individual, knowledge of each of these areas, but there is a need for the divides that separate the various components, some of which are shown in Figure 2, to be bridged if maximal benefit is to be gained from available knowledge. Such bridges would lead to increased understanding of the way in which the various components of the cancer control web fit together and to the possibility of "tuning" the system such that greater harmony is achieved among its parts.

KNOWLEDGE DIFFUSION AND TRANSFER

Even technically advanced countries derive information from other countries, but developing countries obtain a disproportionate amount of information in this way. In order to select the appropriate knowledge to transfer, it will be necessary to establish a dialogue between those who have knowledge and those who would like to use it, and to identify the most effective approaches to transfer it. Knowledge diffusion implies a non-targeted process, whereby information is made available through books, journals, the Internet and a variety of meetings. While this approach may be reasonably effective in societies where the majority of health professionals have access to such sources, particularly when requirements for continuing education are in place, the implementation of research findings in health care has, in the past, taken as long as two decades even in the most developed countries. This results from poor knowledge management coupled to the lack of a research ethos, which doubtless has its roots in medical education and the structure of health services. In developing countries the situation is far worse. Knowledge transferred from more developed countries may fall upon "deaf ears" because of differences in the knowledge base or in the perspectives of the messenger and recipient. Sufficient knowledge of the subject matter is required if a message is to be understood, and

appropriate resources and opportunity if knowledge is to be translated into action. Insufficient attention is paid to these issues.

The consequence of the knowledge deficit in developing countries is that, with the exception of occasional centers of excellence, the majority of patients are likely to be treated with outdated techniques or treatment regimens. The situation is compounded by frequent failure to complete therapy because of poverty and ignorance, while accurate measures of outcome are, for the most part, entirely lacking. Prevention and early detection are underplayed because all available resources are used to deal with the overwhelming number of patients with advanced cancer and because of the lack of knowledge, expertise or advocates. These problems will need to be addressed in a logical and stepwise fashion, and research will be an integral element in their resolution.

CLINICAL TRIALS AS A MULTIVALENT SOLUTION

Clinical trials directed towards the early detection and primary management of cancer, while addressing important questions in the setting of the local resources, the patient population and the local cancer pattern, also represent an effective means of providing more efficient and effective patient services and an effective platform for the training and education of health professionals. This follows from the fact that clinical research demands accurate diagnosis, knowledgeable treatment design (using sound scientific and ethical principles), discipline with respect to the administration of treatment and meticulous documentation of results. In addition, appropriately designed trials must take into account the available resources (human, financial and material) and may have as an objective, the development of cost-effective or resource-sparing approaches to care. Since research is more difficult to undertake in developing countries, many advocate the use of clinical practice guidelines. While these provide a useful source of information, they are, of necessity, largely based on evidence collected in high-income countries. Moreover, they are unlikely to be as valuable, from the perspectives of patient care and education, as the conduct of carefully selected clinical trials (see Table 1). Finally, the conduct of relevant clinical research will gradually lead to the establishment of a culture of scientific, evidence-based medicine, i.e., one based on effective knowledge acquisition, management and dissemination in settings, including major cancer centers or university hospitals, where this is presently absent or very limited. Eventually, improved professional circumstances should help to staunch the loss of talent to high-income countries.

Clinical Trials	Clinical Practice Guidelines
Designed for a specific population in the context of available resources	Based on available evidence, which may be out of context
Requires disciplined adherence to the planned protocol on the part of all participating investigators	May be modified at the discretion of each individual user
Usually entails collaboration and mutual learning	Rarely entails collaboration or learning that leads to understanding
Associated with quality assurance and ethical review	Not routinely associated with quality assurance; no ethical review
Identifies deficiencies in care and data management via audit and monitoring	Generally unsupervised, such that problems go undetected
Encourages measures to improve follow-up	No incentives to improve follow-up
Associated with outcome measures	No outcome measures
Generates new information	No new information generated

Table 1. Comparison of Clinical Trials and Clinical Practice Guidelines.

Plato's concern as to what constitutes sufficient justification for belief is as pertinent today as it was two and a half thousand years ago. Incomplete information may lead to false belief, and false belief to inappropriate action. To avoid this, knowledge will need to be harvested from wherever it is to be found - including from the developing counties, which accounts for more than 80% of the worlds people - and managed efficiently and with equity. Information technology, set in motion by the recognition of the limits of logic, will play a vital role in the next stage of the voyage of discovery which comprises, surely, the destiny of the human race. ■

THE EVIDENCE BASE FOR CANCER CONTROL IN DEVELOPING COUNTRIES: WHAT IS TO BE DONE?

In July 1945 an article entitled "As We May Think" appeared in the journal *Atlantic Monthly*. Written by Dr Vannevar Bush (the US wartime Director of the Office of Scientific Research and Development) the article dealt not with the arbitrary power of military science to shape the future of civilizations, but a far older problem: how to retain, and benefit from, the accumulation of knowledge. Even allowing for his insider knowledge of the early development of 'big brain' computers to which his post made him privy, Bush's predictions, were as visionary as those proffered to earlier generations by Jules Verne and H.G. Wells. Specialized electronic databases accessed through personal desk top computers, the development of the Internet and the World Wide Web are all outlined in his article. *"Wholly new forms of encyclopaedias will appear, ready-made with a mesh of associative trails running through them… The physician, puzzled by its patient's reactions, strikes the trail established in studying an earlier similar case, and runs rapidly through analogous case histories, with side references to the classics for the pertinent anatomy and histology."* The article is 'a good read' and contains a useful maxim: "A record, if it is to be useful to Science, must be continuously extended, it must be stored, and above all, it must be consulted."

Sixty years on, how much of Bush's vision has been achieved in the struggle to establish effective cancer control in developing countries? Access to most of the information hardware and infrastructure that Bush predicted has become commonplace in the developed countries but remains a relative rarity within the resource-poor populations of developing countries - a privilege of the well-placed few. More crucially, we lack data and the means to collect data. We still do not have a comprehensive picture of cancer in developing countries, and which health care interventions have proved to be effective.

Data begets evidence; evidence supports knowledge. Knowledge of the distribution of particular types of cancer, and the efficacy and cost-effectiveness of various interventions in each cancer type, is critically important. There are still not enough cancer registries in developing countries, and some of those that do exist currently produce sub-optimal data. There has been even less effort expended in the proper evaluation of the effects of cancer control interventions in developing countries; i.e., the preparation of systematic reviews of studies relevant to cancer prevention, screening, diagnosis, treatment and supportive and palliative care.

Effective cancer control requires a solid foundation of evidence on which to base the selection of priorities and the choice of interventions. At present, more than half of incident cases and 70% of global cancer deaths occur in the less-developed regions of the world. By 2020, the WHO predicts that there will be at least 16 million new cases of cancer per year, 70% in developing countries. Time is not on our side. In March 2006 volumes I-VIII of Cancer Incidence in Five Continents were made available via the Internet by the International Agency for Cancer Research. (http://www-dep.iarc.fr) Volume IX is in preparation and is due to be published around late 2007. Despite the acknowledged deficiencies in cancer registry coverage, these must perforce be our

TOPIC	Bangladesh	Bhutan	India	Maldive Is.	Nepal	Pakistan	Sri Lanka	TOTAL
Prevention	0	0	0	0	0	0	0	0
Risk	0	0	5	0	0	0	0	5
HPV related	0	0	23	0	0	0	0	23
HIV related	0	0	4	0	0	0	0	4
Diagnosis	0	0	11	0	0	0	0	11
Screening	0	0	24	0	4	3	0	31
Treatment	0	0	39	0	1	0	0	40
Secondary cancers	0	0	8	0	0	0	0	8
Psychosocial	0	0	1	0	0	0	0	1
Palliative care	0	0	0	0	0	0	0	0
Other	1	0	95	0	0	4	0	100
TOTALS	**1**	**0**	**210**	**0**	**5**	**7**	**0**	**223**

Table 1. Reports of cancer research relevant to cervical cancer originating from South Central Asia indexed in Medline and Embase databases between January 2001 and February 2006.

source documents for prioritizing which cancers require the most urgent control, along with the ever present need for tobacco control.

Once these priorities have been determined, the evidence from all previous relevant research conducted on the local populations should be identified, collected and made as accessible as possible. Placing the focus on the evidence for the effectiveness of interventions 'on the ground' in the developing countries is important. Approaches to cancer control in developing countries need to be adapted to specific national needs and resources. The applicability of the much larger, and generally better known, body of evidence derived from research conducted in the developed countries is likely to vary. High- and low-income countries differ with respect to the patterns of cancer, genetics, environments, socioeconomic status, literacy rates and behavior of populations as well as with respect to the resources they can command (human, physical and financial).

Identifying and collecting evidence is not straightforward. A preliminary survey conducted by the Cochrane Cancer Network has shown that the evidence originating from developing countries in the various fields of cancer control appears limited and is difficult to access. Searches of the Medline and Embase databases for reports relevant to uterine cervical cancer in South Central Asia published between January 2001 and February 2006 identified just 223 reports. Manual searches of conference proceedings (ESMO 2002/2004; ECCO 2003/2005, ASCO 2003-2005) and electronic searches of the INDMED database identified a further 40 reports (18%) not indexed in either Medline or Embase. The importance of identifying relevant conference proceedings in order to reduce the effects of publication bias been acknowledged. What is less well recognised is that electronic copies of conference proceedings generally do not allow search by addresses, making manual searches for abstracts originating from developing countries the only viable option. Neither are the major databases consistent in the way in which they index the countries of origin in their address fields.

SYSTEMATIC REVIEWS:

- **Establish a reliable and comprehensive knowledge base**
- **Identify gaps in research knowledge**
- **Prevent duplication of research & waste of resources**
- **Identify methodological difficulties and enable us to benefit from the experience of previous investigators**
- **Identify adverse effects of interventions**
- **Protect patients from unnecessary or inappropriate research**

Box 1. Benefits of systematic reviews.

New standards are being set for the registration of human medical research with the construction of the International Clinical Trials Registry Platform. The establishment of an accessible register of all relevant studies conducted in developing countries, identified by systematic searches of databases and non-indexed journals, the grey literature (conference proceedings, dissertations and industry reports) and sources of unpublished trials provide the foundation stone of the evidence base for global cancer control. This data source – which should include all types of research (translational research, epidemiological studies, as well as controlled clinical trials) will facilitate the preparation of systematic reviews of the effects and effectiveness of interventions, which should be used by NGOs (acting in alignment with national governments), health professionals and hospitals to guide improvement in clinical practice and to inform the cancer control research agenda in developing countries.

WHAT IS TO BE DONE?

In order to establish a comprehensive evidence base for cancer control in developing countries therefore, in addition to providing more and better data coverage by cancer registries, we need to build two new resources: (1) A register of studies and trials conducted in, or relevant to high-incidence cancers and tobacco control in developing countries (2) A database of systematic reviews of effectiveness of cancer control interventions in developing countries.

The benefits of systematic reviews are outlined in Box 1. Once developed, the register of trials and the database of reviews can used to generate a third resource: an evidence-based atlas of individuals and institutions located in developing countries contributing to cancer research, listing their areas of study

and the methodology used. Linked up with the country profile database being developed by the International Union Against Cancer (UICC), this useful by-product will enable NGOs and national governments to identify the appropriate centers of research effort and, equally important, those developing countries where no cancer control research appears yet to have been done.

The identification of the source data – the primary research conducted in the developing countries – and the preparation of the systematic reviews of effectiveness will require the recruitment and training of content experts throughout the developing world. This knowledge transfer is a sensible strategic investment. As Bush's maxim indicates, the continuous extension of the scientific record through the ongoing collection of data is essential. Updating the cancer registry data and the reviews of effectiveness of interventions will enable decision-makers to measure the success (or otherwise) of cancer control programs and to identify trends in cancer incidence and mortality which may influence changes in cancer control priorities or methodologies. A maintained body of research evidence is required in order for improved or more cost-effective methodologies to be developed.

In conclusion, the comprehensive collection of cancer registry data, the register of studies and trials, the database of systematic reviews of effectiveness, the cadre of content experts trained in preparing reliable analyses are all essential components in the building of a reliable evidence base for cancer control in developing countries. Clinical investigators have an ethical requirement to ensure that the outcomes of their clinical research are made as accessible as possible. All relevant sources of evidence, especially systematic reviews, should be carefully considered prior to undertaking new research or formulating health care policy. Clinicians and health care professionals in developing countries should be offered the skills and training to enable them to prepare and maintain systematic reviews which are both reliable and relevant to the circumstances in their own countries. ■

Mark Lodge
Cochrane Cancer Network
Headington, UK

BILIARY TRACT CANCER IN NEPAL

INTRODUCTION AND EPIDEMIOLOGY

Cancer of the biliary tract can be divided into cancer of the bile ducts (cholangiocarcinoma) and cancer of the gall bladder. Cholangiocarcinoma, at a global level, is uncommon – less than 01% of global cancer falls into this category. However, it can be difficult to obtain precise figures, since in most cancer registries it is included with hepatocellular carcinoma, which arises from the liver cells themselves. Cholangiocarcinoma arises either from the bile ducts within the liver or the larger ducts outside the liver that transport bile to the intestine. Gall bladder cancer arises from the gall bladder and is generally more common than cholangiocarcinoma, but still, overall, a rare cancer. However, these diseases, both of which are predisposed to by infectious or inflammatory diseases of the biliary tract, have a high incidence in particular world regions. Cholangiocarcinoma, for example, is known to have a high incidence in parts of south and east Asia, where there is a strong association with infection by liver flukes (*Opisthorchis viverrino* in Thailand and West Malaya, and Clonorchis sinensis in China), which infect many millions of people in these regions due to the common habit of eating raw fish, which unfortunately, are often infected by these parasites. The population registry in Thailand (Khon Kaen) reports a particularly high incidence of cholangiocarcinoma which accounts for 85% of all liver cancer and is believed to be primarily related to *Opisthorchis viverrino* infection. In this registry liver cancer has an incidence of some 32 and 15 per 100,000 in males and females respectively (Globocan 2002). Infectious hepatitis of types B or C, strongly associated with hepatocellular carcinoma, appear to play a limited, if any role, in the epidemiology of biliary tract cancer. Congenital abnormalities of the biliary tract may be associated with both types of biliary tract cancer, probably because of the irritant properties of some of the constituents' bile, or even of diversion of pancreatic juices, containing digestive enzymes into the biliary tract. Chronic inflammatory diseases involving the biliary tract (sclerosing cholangitis) and bowel (ulcerative colitis) predispose to biliary tract cancer, especially cholangiocarcinoma[1]. Exposure to toxic chemicals may also predispose to cholangiocarcinoma, and smoking has been implicated in gall bladder cancer.

Gall bladder cancer is related in the majority of cases to prior inflammation of the gall bladder, nearly

always associated with gall stones. It has a relatively high incidence in some populations and regions. In Northern India it is the commonest cancer of the gastro-intestinal tract in women (in whom it generally has a higher incidence, in contrast to cholangiocarcinoma, which has a higher incidence in men).[2] Predisposing factors to gall bladder cancer include diet and genetic factors – the disease has a much higher incidence in native American and Hispanic populations in the south-western USA for example, all of whom have a high incidence of gall stones. In the Pima Indians in Arizona, 70% of women have gall stones by the age of 30 years. Many develop gall bladder cancer, and there is a very high incidence of obesity and diabetes. Gall bladder cancer is also associated with chronic typhoid infection of the gall bladder. Smoking and exposure to other hazardous chemicals may be risk factors in some populations.

Little is known of the risk factors that pertain to the apparently increased incidence of this disease in Nepal, although they are likely to be similar to those in northern India. The most common cause of both cancers is probably chronic infection, most probably, bacterial; liver flukes are not known to be prevalent in Nepal, nor is the custom of eating raw fish. Primary sclerosing cholangitis, choledochocal cyst and ulcerative colitis are also believed to be rare. Having no proper cancer registration system, it is difficult to know the exact incidence of either cholangiocarcinoma or gall bladder cancer and there is no evidence of higher prevalence in particular regions, or in specific ethnic groups or occupations, although there is some indication that patients come predominantly from lower socioeconomic backgrounds. Whereas both cancers occur generally in older individuals (above 60 years), the average age at presentation in Nepal tends to be lower.

PREVENTION

Prevention of cholangiocarcinoma is clearly possible in populations prone to infection by liver flukes and in northern India, while dietary modifications, such as emphasis on fruits and vegetables, may lead to a reduction in gall-bladder cancer. Removal of gall stones has been suggested to be of value in the prevention of gall bladder cancer, and clearly, if congenital biliary tract abnormalities are present, early surgical correction may avoid the later risk of cancer.

PRESENTATION AND DIAGNOSIS

Both types of cancer of the biliary tract can present with similar features, since obstruction of the flow of bile is common, leading to jaundice and discomfort or pain in the right hypochondrium (the region below the right ribcage, where the liver and gall bladder are situated). The pain may be similar to that caused by gall stones, although tends to be more constant. Jaundice may be accompanied by severe itching, nausea and vomiting, and weight loss is common. A mass may be palpable in the right upper abdomen, either from distension of the gall bladder because its outflow is obstructed, or because of accumulation of tumor in this region. In advanced cases, ascites (fluid in the abdominal cavity) may occur, usually due to spread of disease to other parts of the abdomen or pelvis.

Before they come to hospital more then 80% of patients have been treated by traditional vaidas, quack (charlatans), faith healers, paramedics and even some non-specialist doctors. Jaundice in Nepal is always taken by patients to be caused by infectious hepatitis – by far the commonest cause and they are initially reluctant to go to hospital. Eventually, after at least several weeks or months have passed without improvement – and often with significant deterioration in spite of traditional medical treatments they may have received, they are finally referred to a specialist. Unfortunately, by then, their disease is usually too advanced to be cured, and complications such as ascites have often developed.

While liver function tests are available to all, imaging tests such as computed tomography (CT), magnetic resonance imaging and cholangiography are rarely available. Endoscopic retrograde cholangiopancreatography (ERCP) is and excellent means of demonstrating, by retrograde injection, the site of obstruction in the biliary tree while percutaneous transhepatic cholangiography (PTC), which enables the biliary tree proximal to the obstruction to be examined, but both are costly and beyond the reach of the bulk of the population. Ultrasound may be the most widely available and least expensive imaging tool, and in gall bladder cancer, it can identify a mass in most patients (perhaps 75%). It is also useful in detecting dilated bile ducts and the presence of metastases in the liver. The more sophisticated endoscopic ultrasound (EUS), which can be used to assess the degree of regional spread, is not generally available in Nepal. The tumor mark-

er, carcinoembryonic antigen, is frequently abnormal in cholangiocarcinoma but has not been shown to be of value in gall bladder cancer. In both cancers, however, carbohydrate antigen 19-9 is frequently elevated. Alpha-fetoprotein is not elevated in biliary tract cancer, and provides a distinguishing feature from hepatocellular carcinoma. Promising new "molecular" markers, using proteomics on serum, are not available in Nepal. Preoperative histopathological diagnosis, using CT or ultrasound-guided needle biopsy, the standard diagnostic procedure, is not widely performed because of the limited availability of the necessary expertise and equipment. Most biliary tract cancers, whether of the gall bladder or bile ducts, are adenocarcinomas.

STAGING

The extent of disease in biliary tract cancer, as in all cancers, is critical to outcome. The stage is determined by the usual criteria, i.e., size of the tumor and degree of local invasion (T), the extent of regional spread via lymph nodes (N) and the presence of distant metastases (M). Both types of biliary tract cancer are therefore amenable to the TNM system, which takes account of these features, and in which each element (T, N, or M) is given a numerical value, i.e., from T0 to T4, N0 to N1 or N2 (in gall bladder cancer and cholangiocarcinoma respectively) or M0 to M1 (i.e., present or absent) in the case of distant metastases. Patients with minimal local invasion, no nodes and no distant metastases are assigned to stage I, and patients with distant metastases to stage IV. Stages II and III and their subcategories include various degrees of tumor invasion with or without regional lymph node spread that differ somewhat with each disease. In Nepal, nearly all patients have stage III or IV disease at the time of diagnosis.

TREATMENT

Biliary tract cancer is curable only when the extent of disease is sufficiently limited as to permit complete surgical resection. Unfortunately, this is possible in perhaps no more than 10-15% of cases anywhere in the world, such that surgery is primarily palliative in intent. However, in rare cases of gall bladder cancer with stage T1N0M0 disease, a simple cholecystectomy may be curative. Less than 25% of the cases of biliary tract cancer in Nepal are operated on, even for palliation. The primary objective in these cases is to relieve biliary obstruction, either through surgical bypass or to insert a "T tube" into the biliary tract for external biliary drainage. T-tube insertion is the most frequently performed procedure. Relief of biliary obstruction by internal stenting is not available in the public sector, being a costly procedure. Neither radiation therapy nor chemotherapy are standard components of treatment anywhere in the world, although in some patients radiation therapy may be used to reduce the size of the tumor (in rare cases, to the point of surgical resectability). Few patients in Nepal are candidates for radiatiotherapy, which, in any event, is available only in four centers in the entire country. Chemotherapy also has a limited role in biliary tract cancer, although 5-FU or regimens including this drug, in which responses may be seen in up to 25% of patients with gall bladder cancer, may be recommended in high-income countries either after surgery or in a palliative setting. A role for chemotherapy in cholangiocarcinoma has not been established.

TREATMENT OUTCOME

Survival rates in patients with surgically resectable disease are very good, but since few patients fall into this category, survival rates are very low everywhere in the world. In Nepal, almost all patients die, and unfortunately, few even have adequate palliative therapy. Once a patient knows that the disease is incurable he or she is generally reluctant to return to hospital or even to go to a hospice (if available) for terminal care. This applies to many other cancers, and is likely to be ameliorated only by an expansion of home palliative care services which are presently extremely limited. This also means that assessment of the morbidity and mortality of biliary tract cancer is difficult at best, but it is probable that few patients survive for longer than six months. ■

Manohar Lal Shrestha
Nepal Medical College and
Teaching Hospital Atterkhel
Kathmandu, Nepal

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See also the INCTR Portal Educational site (http://inctr.ctisinc.com:9000/sites/inctr/Education/default.aspx) which includes a presentation on imaging studies (staging) in cholangiocarcinoma.

CHOLANGIOCARCINOMA IN NEPAL

A 56-year-old diabetic, chronic smoker and alcoholic male was admitted with a history of more than a month of progressive jaundice and right hypochondrium discomfort with loss of appetite and weight. There was no significant past and family history. On examination he had deep jaundice, a tender right hypochondrium, a palpable, smooth, liver edge four centimeters below the costal margin, and ascites.

Liver function tests were abnormal, with elevated bilirubin (total 15.5 mg/dl, direct 9.5mg/dl), alkaline phosphatase 6670 U/L, SGPT 320 U/L and SGOT 62 UL. Ultrasonography was inconclusive but a CT scan of the abdomen revealed hepatomegaly, dilated common hepatic and common bile ducts with an irregular area pf low attenuation and the presence of ascites. Endoscopic retrograde cholangiopancreatography (ERCP) revealed irregular narrowing of the proximal part of the common bile duct suspicious of cholangiocarcinoma with secondary spread to the porta hepatis. A sample sent to Cytology but was negative.

Laparotomy, performed on July 11, 2006, revealed a mass in the middle third of the common bile duct (3×5 cm) which was inoperable. A T-tube was placed proximal to the mass. Unfortunately, the patient expired on July 16, 2006.

DISCUSSION

Cholangiocarcinoma is a rare disease in Nepal. Parasitic infections, (*Opisthorchis sinensis* and *viverrini*, types of liver fluke), a recognized cause of cholangiocarcinoma, do not occur - the eating of raw fish, the usual source of infection - is not customary. Primary sclerosing cholangitis, ulcerative colitis and choledochol cyst, also predisposing factors, are very rare entities in Nepal. It would appear that the most prevalent etiological factor is chronic infection of the biliary tract duct, although congenital biliary-pancreatic abnormalities cannot be excluded. In spite of its rarity, most cases of cholangiocarcinoma in Nepal can be diagnosed because of the availability of newer diagnostic modalities such as CT scan and ERCP. Indeed, these imaging tools have probably led to more cases being recognized. The main difference in the presenting features of the disease from reports in the published literature is that patients in Nepal present very late. Jaundice is a common presenting symptom, but in Nepal, this is almost always assumed to be due to hepatitis – which, is, in general, correct. However this means that no further action is taken; patients are sent home to recover or they seek help from traditional healers, known as vaidyas (ayurvedic medicine practitioners) or even from faith healers.

If the patient's condition does not improve he will usually go to a medical assistant or non-specialist doctor with, again, limited, if any intervention. Finally, as the disease worsens – usually after a month or two has passed, patients are taken to tertiary level hospitals. By now, they will usually have developed ascites. Blood tests and ultrasonography, which are within the financial reach of everybody, are not sufficient to diagnose cholangiocarcinoma. Most ordinary Nepalis cannot afford the necessary diagnostic tests such as CT scan and ERCP. Tests for tumor markers such as carcinoembryonic antigen or carbohydrate antigen 19-9l, are not available in Nepal and it would be both expensive and difficult to arrange for such testing in other countries.

ERCP showing total obstruction of the common hepatic duct by cholangiocarcinoma (red arrow).

Most cases are palliated by percutaneous drainage of the bile duct (PTBD); a few are treated by internal stenting. Patients in whom surgery is performed are usually treated by biliary bypass or the insertion of a T tube into the common bile duct for external drainage. The mortality of the disease is very high and most patients die within six months. ■

Manohar Lal Shrestha
Nepal Medical College and
Teaching Hospital Atterkhel
Kathmandu, Nepal

References available on www.inctr.org

IAEA'S *PACT* MOBILIZES RESOURCES TO FIGHT GLOBAL CANCER EPIDEMIC

It is widely accepted that radiation medicine is a critical component in the diagnosis and treatment of more than half of all cancers, yet many developing countries still lack these basic technologies. A new initiative of the International Atomic Energy Agency promises to bring nuclear technologies for peaceful purposes to underserved countries, and to build comprehensive cancer control programs in the process.

Five years ago, a cancerous lung tumor left Mr. Wisdom Nutakor of Accra, Ghana, paralyzed from the waist down. Today, thanks to treatment at the Korle Bu Teaching Hospital, he is walking again.

Massoud Samiei, a nuclear engineer in IAEA's Department of Technical Cooperation for 15 years, was recently appointed to lead the agency's Programme of Action for Cancer Therapy (PACT). In its first year, Dr. Samiei secured support from a dozen key organizations, has received support through a WHO resolution acknowledging the urgent need for a comprehensive and integrated approach to fighting cancer, and is now working to develop public/private partnerships that will mobilize and direct resources to regions of the world where nuclear technology can have a measurable impact on cancer control. In addition to funding from IAEA's member states, PACT is looking to private sources for funding, particularly manufacturers and pharmaceutical companies.

"IAEA has long history with nuclear technology in the diagnostic and treatment areas, and we have over two dozen companies we deal with," Dr. Samiei says. "If the company produces equipment and technology in relation to cancer, for screening, treatment or palliative care, we encourage them to consider a donation to PACT ."

Samiei tells prospective donors that, as the number of patients increases and as their capacity for cancer treatment grows, emerging countries will be in a position to ask bilateral organizations to build and develop cancer systems requiring additional machinery, to the benefit of the donor.

The first Cobalt-60 machine, a gift from a private corporation that produces Cobalt-60 machines, is on its way to Tanzania as part of a demonstration project funded by IAEA. Three more machines - also gifts are in the queue.

The cost of radiotherapy includes capital costs of the building and equipment, maintenance costs, and staff salaries (and the initial training and education costs). A single Cobalt-60 radiotherapy machine costs well under $1 million but with the addition of buildings, treatment planning and quality control, trained staff and maintenance expenses, the price tag climbs to $2 to $3 million for a center. Still, if radiotherapy is used effectively - that is, for early treatment rather than palliative care - it is money well spent. Unfortunately, over 70% of cancers are detected too late in developing countries for an effective curative treatment.

"The current shortage is huge," Dr. Samiei says. "Although over 100 countries have been involved in the IAEA radiotherapy program in the past 20 years or so, still many countries have just one machine. To treat current cancer patients in developing countries, we need nearly 7,000 more machines, at a cost of several billion dollars. We could reduce that number by half if we also focused on prevention and widespread screening and early detection."

Around the world, the need is great. Only 20% of the population in Africa has access to radiotherapy cancer treatment; in Asia, only 40% and, in Latin America, only 50%.

Within the next three years, PACT is committed to building partnerships in as many as six countries where the prospects for success and sustainability are high. That means identifying cancer organizations with good leadership in countries that are committed to the idea of comprehensive cancer control.

"We want to encourage using radiotherapy to build a cost-effective cancer system that's longer term and to think about the need for trained professionals," he says.

PACT is looking first at cancer organizations in Africa and Latin America. "In Africa, the shortfall of radiation oncologists has been identified as

the most significant limitation to radiation oncology service delivery in developing countries - more significant than even the paucity of available equipment. For instance, we've analyzed how many staff they can train [a few hundred] and how many we need to train across Africa [a few thousand] in order to bring existing capacities to a level at which they can provide training for the region. The longer-term concept is development of cancer training through virtual universities and networking. This could partially address the issue of losing trained staff to more affluent countries."

PACT is working with the Institut Català d'Oncologia and the Universitat Oberta de Catalunya, which have developed an online e-ocology training program, to explore the possibility of using the IAEA-developed training material in radiation oncology or medical physics for future online courses. After completing coursework through e-oncology, participants would travel to recognized regional centers to complete their certification.

One of PACT's first pilot projects is slated for Nicaragua. "We are working on agreements and have discussed plans that focus on the long-term control of cervical cancer by vaccination, while continuing to treat patients for some decades until the effects of the immunization program can make an impact," Dr. Samiei says. This project has piqued the interest of the Gates Foundation, as well as the National Cancer Institute and WHO's Pan-American Health Organization. "My biggest concern is that there is not enough awareness of the world's growing cancer crisis at the political level," he notes, and he hopes that the international financial institutions will begin investing in cancer prevention. "When the G-8 begins talking about controlling cancer in developing countries, we'll know that we are moving forward." ■

Marcia Landskroener for INCTR

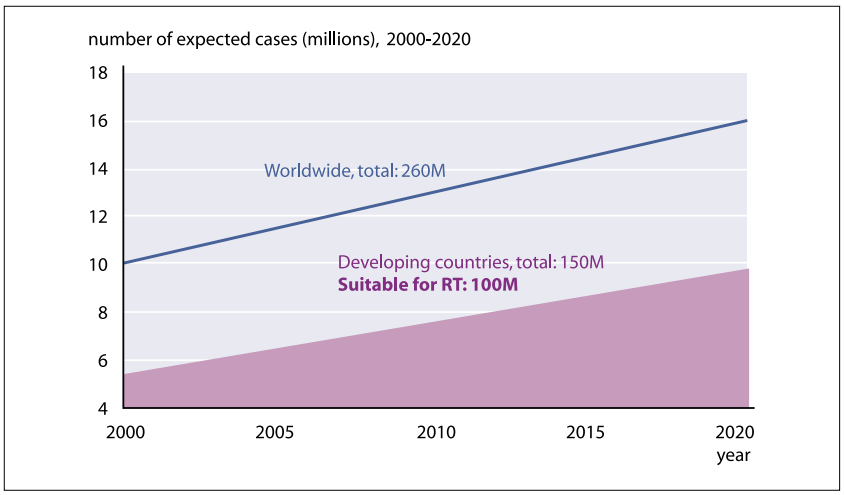

Figure 1. Between 2000 and 2020, some 260 millions people will develop cancer worldwide, 150 million in developing countries of which about 100 million will need radiation therapy as part of their treatment. As things stand on average less than 40% have access to services.

PROBLEMS FACED BY PATHOLOGISTS IN DEVELOPING COUNTRIES

Pathologists hold a key position amongst the medical professionals responsible for cancer management. They, unfortunately, face enormous problems and handicaps in discharging their vital role in the developing countries. This article enumerates many of them, particularly those at the lower end of the socioeconomic spectrum.

ESSENTIAL REQUIREMENTS FOR EFFICIENT PRACTICE

The efficient working of this important specialist does not solely depend upon his or her qualifications, training and competence alone, although these are important. Like most medical specialties, the pathologist is also dependent upon the adequacy of the facilities and infrastructure of his or her work environment.

It has not been determined how many pathologists are required per capita of the population for adequate health care, but the number in developing countries, overall, is clearly inadequate. It has been estimated, for example, that while England has 109 pathologists per million people, Pakistan has only 2.6. Pathologists in Pakistan are clearly overburdened and the quality of their work under these circumstances is bound to suffer. Unfortunately, there are some countries in the world that have no trained pathologists.

Pathologists in most developing countries have little or no access to continuing education programs or to the medical literature and there is often no requirement for licensing or any control over who can practice pathology. This results in widespread "quackery" and a general lowering of

confidence in the specialty, making the task of a pathologist to establish credibility a hard one.

Efficient medical technologists, who form the backbone of pathology laboratories, are even harder to find. Many of those presently practicing, particularly in the lower income countries, do not have a basic educational background and have received only "on-the-job" training.

Laboratory instruments are another essential requirement for any pathology practice. In the absence of the capability to produce equipment locally, most machines have to be imported, frequently from second-rate producers, in order to keep costs down. This then raises questions about the accuracy of results. Access to rapid and effective maintenance is also critical. In general, there are inadequate repair facilities and even when equipment is working the power supply is often unreliable, making an already difficult job even harder. Reagents are also often substandard. A WHO inter-country workshop to formulate policy regarding quality assurance in the context of diagnostic kits was organized in 2001. Most of the member countries have too limited an infrastructure and insufficient technical expertise to undertake the task of assuring the quality of diagnostic reagents. Only one had a national policy requiring routine assessment of the quality of reagent kits, while laboratories able to monitor quality existed in only two of the seven participating countries.

The handicap under which pathologists work is further compounded by the lack of financial resources and high cost of newer reagents and equipment. Immuno-histochemistry has become a routine element in the assessment of lymph node lesions in high-income countries. However to process a single case the cost is equivalent to some two weeks of the patient's wages. Since insurance is largely non existent for the poorer people, even if the pathologist has trained technicians and other necessary prerequisites, the diagnosis has to be made on morphology alone – often insufficient to establish a firm diagnosis, or to utilize current classification schemes.

Total Quality Management is the basis of the practice of modern pathology. Accreditation protocols have been developed by the International Standards Organization (ISO) and others. However with a few exceptions, pathologists in poorer countries are outside the purview of such plans. In India, for example, out of about 25,000 laboratories, only a few dozen participate in an accreditation program. The reason is the enormous financial cost, elaborate administrative structure and paperwork required for accreditation. This is beyond the reach of the vast majority of pathologists in countries such as Pakistan.

Country	Society	Membership	Population 1992 (Million People)	Ratio Members/ Million People	Rank (WASP) [2]
United Kingdom	The Royal College of Pathologists (Includes non-M.D. Doctoral Scientists)	6,300	58 [1]	109.0	1
Australia	The Royal College of Australasia	1,600	16.8	95.2	2
Italy	Associazione Italiana Patologi Clinici	3,330	58.0	57.4	3
Indonesia	Ikatan Ahli Patologi Indonesia	343	184.5	2.4	35
Colombia	Sociedad Columbiana de Patologia Clinica	72	31.8	2.3	35.5
India	Indian Association of Pathologists and Microbiologists	1,920	882.6	2.3	37

Table 1. Ranking based on Membership of National Pathology Societies Related to Population. [1] Figures for 1993, [2] WASP - World Association of Societies of Pathology.

WHAT CAN BE DONE TO IMPROVE THE SITUATION?

Given the breadth of problems faced, it is clear that significant improvement will require long-term programs designed to improve professional standards, including technical resources. Training programs and a regulatory framework designed to ensure the achievement of minimal standards are essential. However, a number of steps can be taken by the pathologists themselves with help from outside agencies to alleviate the situation. Very often, a reasonably well-trained pathologist will know best what is needed in the context of local realities.

A variety of educational and training programs could be established, supplemented, or even largely based on telepathology programs which, for this image-based discipline, is likely to lead to a more efficient use of the time available on the part of the teachers.

Such systems could also be used to obtain "distance" consultations and second opinions. To ensure that all pathologists meet minimal educational standards, a modified two-tier accreditation system could be devised, the lower tier being appropriate for smaller pathology laboratories able to undertake more routine analysis, thus freeing the more sophisticated laboratories to undertake more detailed analysis when necessary. Minimal guidelines for accurate diagnosis and standard reporting formats, including the classification schemes that will be used for each tumor throughout the country (preferably in line with the most widely used classifications internationally), should, ideally, be agreed upon and adhered to by all laboratories in the country. Such guidelines must recognize the limitations faced by the pathologist in developing countries and avoid unnecessarily exhaustive analysis. Inexpensive sampling techniques such as fine needle aspiration could be used in appropriate circumstances, but criteria defining an adequate sample will need to be created. Lists of "essential" instruments and tests could be drawn up and all pathologists would be required to comply in order for their laboratories to be accredited.

The challenges of overcoming the problems faced by the pathologists in developing countries are many and great. However they must be met if cancer care in developing countries is to improve, for without an accurate diagnosis, precious treatment resources may be squandered, and patients will not receive the treatment they need. ■

Manzoor Ahmad
Healthways Laboratories
Rawalpindi, Pakistan

IAEA MEETING

INCTR staff participated in a meeting with the International Atomic Energy Agency and representatives from participating developing countries in Vienna (from Feb 19th to 22nd) to discuss the implementation of a joint project in the treatment of breast cancer, with resource-sparing as an objective. ■

SIOP MEETING IN MARRAKECH

INCTR was represented at the African regional meeting of the International Society for Pediatric Oncology. One of the outcomes was a decision to explore how the two societies might work together to improve the management of Wilms' tumor in selected countries. ■

ACS ANNUAL MEETING

Dr. Magrath attended the American Cancer Society's biannual meeting in Washington (Jan 26th to 31st) to present the case for focusing more efforts on cancer in developing countries and to describe some of INCTR's programs. ACS and INCTR will continue to explore ways in which the two organizations can work together. ■

SANOFI-AVENTIS/UICC MEETING IN PARIS

INCTR staff members participated in a meeting held at Sanofi-Aventis headquarters to discuss the My Child Matters program, sponsored by Sanofi-Aventis and managed by UICC. This involves 14 projects in pediatric cancer in ten developing countries. INCTR is a mentoring organization for four of them. The program was launched via a ceremony held at the Musée André Jacquemart in Paris on January 31st at which the principle investigators briefly described their projects. ■

INCTR staff with Drs. Julius Lecciones and Twalib Ngoma in Paris for the meeting on February 1st after the inauguration.

ANNUAL GENERAL ASSEMBLY AND GOVERNING COUNCIL MEETING

INCTR's AGM and GCM took place on March 11th at the Brussels offices. ■

MEETING WITH ACS'S INTERNATIONAL PROGRAM STAFF

Nathan Grey, Dan McCormick and Johanna Ralston from ACS came to Brussels in March to further discuss joint ACS/INCTR activities in cancer in developing countries. ACS is already supporting a joint program with INCTR in palliative care in India. Additional meetings are planned. ■

NETWORK

DEPARTMENT OF MEDICAL ONCOLOGY, YAOUNDÉ GENERAL HOSPITAL

Cameroon is located in central Africa at the bottom of the gulf of Guinea at 2-13° northern latitude and 6-16° Eastern longitude. It has a surface area of 475.000 km^2, a maximum altitude of 4094 m and a population of 15.8 million inhabitants. It is bounded in the west by Nigeria, to the north and northeast by Lake Chad and Chad, in the south and southeast by Equatorial Guinea, Gabon, and Congo, and in the East by the Central African Republic. The most common diseases are infectious, the dominant infection being malaria. The health system of Cameroon is a pyramidal structure comprising three levels of care. In the periphery are the health centers managed by a nurse, health centers managed by doctors, and the district hospitals. At the intermediate level are the provincial hospitals, including some which come under the Ministry of Public Health. At the tertiary (central) level are the general hospitals, the central hospitals, the teaching hospitals and the main hospitals of the Ministry of Public Health.

Yaoundé General Hospital.

Cancer was, until recently, rare with little information being available on incidence, although hospitals have recorded an increase in referrals in the last ten years. Currently, cancer patients are managed only in tertiary care hospitals, of which there are five. Because of the larger number of patients being seen, a *National Committee for the Fight against Cancer* (NCCC) was created less than three years ago. A cancer registry was launched approximately two years ago. This report provides an overview of the Medical Oncology Service of the Yaoundé General Hospital (SOMHGY) which sees both children and adults.

In 2005, the three most frequent cancers seen in the SOMHGY were breast cancer, which accounted for 26.54% of all cancers, lymphomas (17.05%), and Kaposi sarcoma (4.19%). In women, breast cancer accounted for 42.14% of all cases, and in men, the most frequent cancer was lymphoma, which accounted for 24.06% of cases. In children, lymphomas were the most frequent cancer, and accounted for 50% of the cases.

The most prevalent risk factors for breast cancer are a family history of cancer, low parity and advanced age at the first childbirth. In some patients there are no recognized risk factors. Lymphoma and Kaposi sarcoma occur particularly in patients with HIV infection.

SOMHGY was opened in 1997 and is led by Dr. Paul Ndom, a medical oncologist (the only

INCTR staff accompanied by Drs. Paul Ndom (center left) and Anderson Doh (center right) and others on a tour of Yaoundé General Hospital.

one in Cameroon), assisted by three general physicians, seven nurses and three nursing aides. The facilities of SOMHGY are basic, and there is a need for improvements in various areas, including the protection of the personnel preparing and administering chemotherapy (there is no laminar airflow hood). There is a shortage of trained personnel. Cancer registration and campaigns relating to the prevention of cancer are organized by the NCCC, while an NGO, SOCHIMIO, provides public educational sessions on a monthly basis. The most difficult obstacle to the delivery of care remains the cost of treatment which, in spite of assistance granted by the Ministry of Public Health, remains high, thus limiting the quality of care available to the majority of the patients with cancer. The only external source of assistance to cancer patients is the PPTE Fund (Pays Pauvre Très Endetté).

After several international conferences on cancer held in the country and several awareness campaigns conducted by SOCHIMIO, the government accepted cancer as public health priority and after creating the NCCC ordered a National Cancer Control Plan to be created. The General Hospital of Yaoundé has formed a subcommittee against cancer and organizes regular multidisciplinary staff meetings on cancer management which practitioners from other hospitals also attend.

The Minister of Public Health for the Cameroon and the President of INCTR signed an agreement on April 5, 2006 to collaborate in the fight against cancer. The agreement calls for an INCTR branch to be established at the Yaoundé General Hospital. SOMHGY will likely begin to participate in INCTR clinical projects and educational programs. Additional assistance has been provided by the International Agency for Research on Cancer, which collaborated with Cameroon in the establishment of the Yaoundé Cancer Registry. Bilateral agreements also exist with the Centre Jean Perrin in France (which has sent antimitotics to Yaoundé) and the ERASME Hospital in Brussels relating to cancer management. The latter relationships have had a minimal effect in Cameroon, in part because they did not involve education and training or a continuing partnership. It is hoped that the relationship with INCTR will be more productive. ■

Dr. Ndom and his staff at regular departmental meeting.

MEDICAL RESOURCES

Additional departments at the Yaoundé General Hospital include: Gynecology/Obstetrics, Internal Medicine, Nuclear Medicine, Surgery, Radiotherapy, Pediatrics and Cancer Registry.

Beds devoted to cancer care	26
Human Resources:	
- Nurses	7
- Dedicated oncology nurses	7
- Pathologist	1
- Medical oncologist	1
- Radiotherapists	2
- Radiologists	3
- Pediatric oncologist	0
- Specialized surgical oncologist	1
- Oncologist in training	1
- General and specialized surgeons	6
Equipment:	
- CT Scanner	1
- MRI Scanner	0

PATIENTS

Total patients in the last full calendar year	486
Adult cancer patients > 16 yrs	457
Pediatric cancer patients < 16 yrs	29

Paul Ndom
Director of INCTR Cameroon Office

PROFILES IN CANCER MEDICINE

SLACOM'S PRESIDENT PROMOTES GLOBAL COOPERATION

Dr. Eduardo Cazap, President of SLACOM and member, INCTR's Special Panel, knew from a young age that he wanted to have some impact on the human condition. In choosing a career path in cancer medicine rather than law, Cazap was swayed by national pride and familial tradition.

In the sphere of cancer medicine, Cazap explains, Argentina was 20 years ahead of its time, conducting basic research in carcinogenesis and developing the first radiotherapy treatments between the 1920s and 1940s. Dr. Eduardo Cazap's father had been associated with the Roffo Institute, an early cancer institute established by Prof. Angel H. Roffo.

"In those days, at the beginning of our knowledge about radiation, the first radiotherapists came from different specialties," he says. "My father had trained as a dermatologist. Working with Dr. Roffo, he demonstrated, in 1947, the relationship between lip cancer and pipe smoking."

Eduardo Cazap was just 15 in 1963, when his father died of renal cancer. In the early 1970s, he pursued his medical training at University of Buenos Aires, completing his residency in internal medicine before seeking additional training in cancer medicine. This was an entirely new approach.

"The way to begin practicing oncology had been to become a medical doctor and then do radiotherapy or chemotherapy," he recalls. He believes his training in internal medicine made him a better doctor, and he took advantage of the fellowship opportunities that followed at Georgetown University's Lombardi Cancer Center

Dr. Eduardo Cazap.

and with the American Cancer Society. He was invited to become a principal investigator within the Collaborative Cancer Research Treatment Program of the National Cancer Institute in 1985.

Early in his medical career, he participated in a medical team in Argentina, conducting clinical cancer research that was instrumental in defining the role of medical oncology. The chief of the Military Center Hospital in Buenos Aires, Roberto Estevez, had been the first to publish a book on cancer chemotherapy in the Spanish language. Estevez's two-volume text, published in 1954, reflected the findings of international collaborators who were testing new drugs.

"I was mainly interested in oncology because it was a new specialty," he says. "A lot of the major questions were still unanswered. This specialty was known in Argentina as "chemotherapy". We were physicians providing treatment with drugs."

Cazap believes that to be a good oncologist, one needs to be a good clinician. He founded SLACOM (Latin American-Caribbean Society of Medical Oncology) four years ago to reinforce the idea of cancer specialization and to promote the concept of medical oncology throughout the region. With ASCO (American Society of Clinical Oncology) and ESMO (European Society of Medical Oncology), he has devoted considerable energy to promoting education and transfer of knowledge from country to country. The intent is to act as a global medical colloquium providing doctors with the necessary clinical skills.

With UICC (International Union Against Cancer), Dr. Cazap promotes cooperation and links for oncologists in Latin America, the Middle East and Africa - regions with more dissimilarities than commonalities. The medical oncology situation from region to region often reflects the political situation there, he says. In Africa, for instance, it's difficult to identify leadership. And forget the volume hotel discount when inviting cancer specialists from the United Arab Emirates - there are only five!

"You have countries with good radiotherapy units and some with none," Cazap says. "It's difficult to imagine ways in which physicians can treat patients with not even one of the main tools of the trade."

In July 2006, Dr. Cazap was designated a member of UICC's board of directors. His primary responsibility will be attracting new membership among organizations and individuals worldwide.

"The idea is to develop or promote regional blocks that encourage interaction among the people of that region," he says, "so that they have a voice in discussions about cancer control in their own part of the world." ■

Marcia Landskroener for INCTR