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THE PRESIDENT'S MESSAGE

THE CELL

Part 1. Discovery
by Ian Magrath

Omnis cellula e cellula (all cells originate from other cells); Francois-Vincent Raspail, 1858 ¹

Robert Hooke (1635-1703), in the densely worded preface to *Micrographia*, his magnum opus, observed that mankind is unique in being able not only to behold the works of nature and to sustain our lives by them, but also has the power of considering, comparing, altering, assisting and improving them to various uses. "This ability," he remarked, "varied greatly among men, and was far from perfect because of the limitations of the senses coupled to a willingness to speculate, to accept widely held beliefs, or to listen uncritically to others." He suggested that: "By the addition of such artificial Instruments and methods, there may be, in some manner, a reparation made for the mischiefs, and imperfection, mankind has drawn upon itself, by negligence, and intemperance, and a wilful and superstitious deserting the

Prescripts and Rules of Nature, whereby every man, both from a deriv'd corruption, innate and born with him, and from his breeding and converse with men, is very subject to slip into all sorts of errors."

Hooke went on to emphasize the importance of *Sense, the Memory, and Reason* – i.e., the scientific method. He had worked as an assistant to Robert Boyle (1627-1691) in Oxford University – he built the pumps used to establish Boyle's gas law – and became, in 1662, the Curator of Experiments of the Royal Society of London, whose Royal Charter had been granted earlier the same year. Hooke was an excellent choice and *Micrographia* was published in 1665, just three years after he had taken up his new post. Among the more famous illustrations in the book is a drawing of cork, in which he described pore-like structures similar to those he found in the tissues of several plants and the stalks of feathers (Figure 1). Hooke coined the term *cell* (from the Latin "cellula" meaning a small room) for the structures he observed. He suspected that cells had an important role



A microscope manufactured by Christopher Cocks of London, which is believed to have been used by Robert Hooke for his microscopic survey published in *Micrographia*. Courtesy of the Billings Microscope Collection, National Museum of Health and Medicine, Armed Forces Institute of Pathology, USA.

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to play in both animals and plants, although recognizing the limitations of his simple microscope, he did not explore this further. On page 116, he wrote:

"For in several of those vegetables, whilst still green, I have with my Microscope, plainly enough discover'd these Cells or Pores fill'd with juice, and by degrees sweating them out; ..."

Hooke could find no connections between the cells he observed, although he thought it likely that they were, in some way, controlling the passage of "liquors" in both animal and plant tissue and that:

"though me thinks, it very probable that Nature has in these passages many appropriated instruments and contrivances whereby to bring her designs and ends to pass, which it is not improbable that some diligent

Observer, if help'd with better microscopes, may in time detect."

In fact, it was almost two centuries before animal and plant cells became a topic of scientific pursuit, largely through microscopic observations, the importance of which, as a starting point, cannot be overestimated. *Micrographia* appears to have inspired a young Dutchman, Anthony van Leeuwenhoek (1632-1623), to undertake a similar microscopic survey. Unlike Hooke, Leeuwenhoek used single lenses that he made himself. He is reputed to have made more than 500, and achieved such skill as to reach a magnification of more than 200-fold (nine or so of his lenses and some of his specimens still survive) – some 10 times greater than that achieved by the earliest compound microscopes, such as that used by Hooke. Unfortunately, Leeuwenhoek kept to himself the methods he used to make his lenses and it was a century or so before such quality was achieved by others. Leeuwenhoek's survey was no more systematic than Hooke's, although he differed somewhat in his choice of subject matter. He examined, for example, the plaque between his own and other's teeth, including that of two old men who had never cleaned their teeth in their lives. In this material he observed bacteria for the first time. Subsequently he observed many "animalcules" in hay infusions and drops of lake water, his descriptions being sufficient to identify them as flagellates and ciliates (Figure 2), organisms we now know to be single celled. He also discovered spermatazoa, examined animal and plant tissue, and observed small multicellular organisms, some of which had been previously discovered, such as spirogyra, rotifers and

nematode worms. Leeuwenhoek started writing about his observations to the Royal Society in 1674 and his letters were published in the society's *Philosophical Transactions*, the world's longest running scientific journal, eventually leading to his election as a Fellow of the society in 1680. Like Hooke, Leeuwenhoek could not possibly have recognized the full significance of the organisms he had discovered – indeed, he lacked a scientific education (he was trained as a draper and spoke no Latin or English; his letters to the Royal Society had to be translated from Dutch). Nevertheless, his meticulous observations established the existence of a vast world beyond the reach of the human senses – a world that would, centuries later, provide a focus for speculation on the origins of life itself.

Leeuwenhoek also probably discovered the cell nucleus. In 1682, he mentioned *globules* in "oval structures" in codfish blood, but it was not until 1831 that such globular structures, the existence of which had, meanwhile, been observed by several other microscopists, were referred to as the cell *nucleus* (from the Latin meaning a kernel or small nut) in a paper read to the Linnean society in 1831 by a Scottish botanist, Robert Brown (1773-1858). Brown gave due credit to the botanical illustrations of the Austrian, Franz Bauer, in bringing attention to a structure that, he believed, must have functional significance. Robert Brown also observed the random movements of dust particles suspended in water (now known as Brownian motion) – a phenomenon later used by Einstein to unequivocally demonstrate the existence of molecules and atoms.

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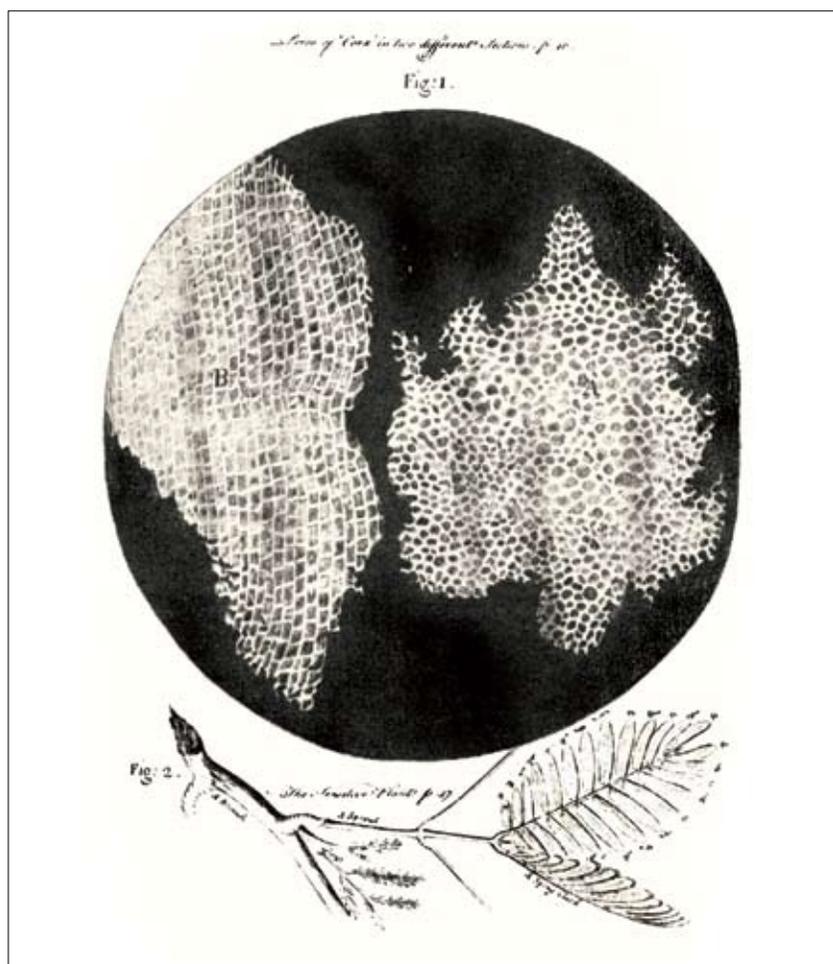


Figure 1. Hooke's illustration of the "cells" or "pores" of cork (*Micrographia*). Two sections are shown, cut transversely and vertically. Hooke comments that he found this same structure in many different kinds of trees, the stalks of vegetables and of feathers. He thought the cells in plants were related to the passage of fluids (sap), but could not prove this. He searched unsuccessfully for valves that might control the direction of flow, as occur in the heart and veins of animals.

THE CELL THEORY

Little attention to cells appears to have been given until the early 19th century. Ludolph Treviranus (1779-1864), discussed plant cells in the first chapter of his book *Vom inwendigen Bau der Gewächse*, published in 1806, mentioning that they appear to contain "grains" (nuclei?) (*Körner in den Zellen*) that others had also observed and suggested that cells are separated from each

other by an intervening space (*Zwischenräume der Zellen*). Johann Moldenhawer (1766-1827) was able to disrupt the cell walls of plants and thus separate individual cells from each other. He also showed that the pores of leaves and plant stems – critical for controlling transpiration and gaseous exchange – are comprised of a pair of cells, and identified several important plant structures, including vascular

bundles (xylem and phloem), and the cambium, from which the vascular bundles develop and which permits lateral growth of ligneous plants (e.g., of the trunks of trees). He also recognized the significance of tree rings. His pioneering work was brought together in the now classical *Beyträge zur Anatomie der Pflanzen*, published in Kiel in 1812.

The French botanist, Henri Dutrochet (1776-1847) discussed plant cells in 1821 in an article entitled *Recherches sur l'accroissement et la reproduction des végétaux*, published in the *Mémoires du museum d'histoire naturelle*, for which he was awarded the French Academy's prize for experimental physiology. In 1824 in *Recherche anatomique et physiologic sur la structure intime des animaux et des végétaux et sur leur motilité*, Dutrochet proposed that cells are the "fundamental unit of organization" of both animals and plants. He believed that cells in different organs secrete different substances, presumably giving the organs their distinct characteristics. In 1826, he described and named osmosis, showing that cells are surrounded by a cell membrane that permits the passage of fluids into or out of cells (endosmosis or exosmosis respectively), the flow being controlled by the internal and external salt concentration. This body of work and its interpretation would seem to qualify Dutrochet for primacy in the genesis of the cell theory, but this is not the case. In those days, the greater emphasis on books summarizing many years of work, and the small number of scientific journals, limited communication and slowed progress. Henri Dutrochet commented on this in the preface to his *Mémoires pour*

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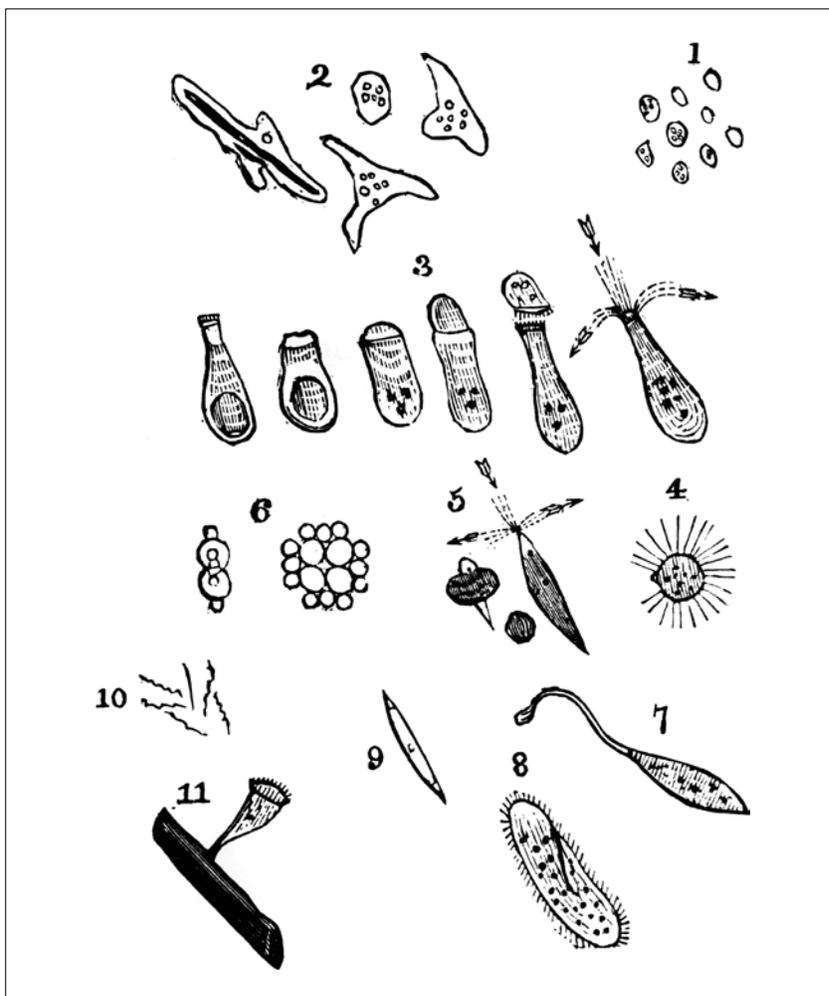


Figure 2. Some of Leeuwenhoek's animalcules. 1, Monads; 2, Forms assumed by the Ameoba; 3, Flask Animalcules, Enchelis; 4, Actinophrys sol; 5, Euglena viridis; 6, Gonium pectorale; 7, Trachelias anas; 8, Paramecium aurelia; 9, Navicula; 10, Vibrie Spirillum; 11, Vorticella Stentor — Goodrich, 1859. Source: S.G. Goodrich *Animal Kingdom Illustrated* Vol 2 (New York: Derby & Jackson, 1859) 2:646. Provided by Florida Center for Instructional Technology under its licence for educational use.

servir a l'histoire anatomique et physiologique des végétaux et des animaux, published in 1837. He bewailed the lack of familiarity of plant physiologists with animal physiology and believed – almost heretically for the times – that fundamental natural phenomena would be revealed by demonstrating similarities between animals and plants.

The cell theory is usually ascribed

to Matthias Schleiden (1804-1881) and Theodor Schwann (1810-1882). Schleiden had studied with the pioneering physiologist, Johannes Müller (1801-1858), in Berlin, many of whose students would subsequently make major contributions to medicine and the natural sciences. He subsequently became Professor of Botany at the University of Jena. Schwann was a zoologist

working at the time as an assistant to Müller. He later moved to Belgium, where he was professor at the University of Louvain before moving to Liège. The insights of Schleiden and Schwann regarding the fundamental nature of cells are said to have derived from a discussion they had over dinner in 1837 (the year, incidentally, in which the Czech physiologist, Jan Purkinje (1787-1869) discovered giant cells in the cerebellum, and commented, as had Dutrochet more than ten years earlier, on the fact that cells were present in both plants and animals. Schleiden was working on plant embryos, which he recognized as consisting of nucleated cells (he referred to the nucleus as the cytoblast, since he believed that new plant cells arose from the nuclei of old cells). In his work, which was first published in the journal *Müller's Archives* in 1838, he also referred to the frequent presence in the nuclei of some cells of internal "spots" of various sizes that Schwann later referred to as *nucleoli*. Schwann had, with Müller, identified nucleated cells in the *chorda dorsalis* (notochord) of tadpoles, and realized in the course of his discussion with Schleiden that they were basically similar to plant cells. Schwann's book, *Mikroskopische Untersuchungen über die Übereinstimmung in der Struktur und dem Wachstum der Thiere und Pflanzen*. ("Microscopic Researches into the Accordance in Structure and Growth of Animals and Plants") was published in 1839, making copious reference to Schleiden's work as well as to that of Brown and others. Schwann put great emphasis on the hypothesis that "all living things are composed of cells and

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cell products" and whether or not Schleiden and Schwann should be given credit as the originators of the cell theory, it was Schwann's book that drew attention to the remarkable similarity between plants and animals at a microscopic level.

THE CELLULAR ORIGIN OF CELLS

The theory, however, was incomplete since the origin of cells remained unknown. There were two main schools of thought – that cells budded off from the nuclear or external membranes of other cells, or that they arose from the intercellular matrix (or both). Schwann proposed that cells emerged from the intracellular matrix (which he referred to as the cytoblastema), in a manner analogous, although clearly very different, to the formation of crystals. Even when cell division had been observed, it was not seen as the exclusive mode of cellular proliferation. Barthelemy Dumortier (1797-1798), for example, in spite of the fact that he was the first to observe "binary fission" of plant cells (in 1832), continued to believe that cells could originate from the intercellular substance. Karl Wilhelm von Nägeli (1817-1891) described cell division in pollen (in 1842), while working, at the age of 25, in Schleiden's laboratory. Shortly afterwards he reported binary fission in unicellular algae, but still believed that, with this exception, new cells generally arose from the nucleus. Eventually the tide turned and by the mid-1940s Nägeli was convinced that all plant cells proliferated via a process of cell division.

It was yet another of Müller's students, Robert Remak (1815-1865), who provided unequivocal evidence

that in vertebrates, all cells arise from a single original cell – the fertilized ovum (*Untersuchungen über die Entwicklung der Wirbelthiere*, 1855). Remak, a Polish physician interested in embryology, first observed cell division in blood cells while studying the development of blood vessels in chick embryos in 1841. He subsequently showed that the fertilized frog ovum repeatedly divides as it develops into a multicellular animal with many different

**Lepidus: Your Serpent
of Egypt, is bred now of
your mud by the operation
of your Sun: so is your
Crocodile.**

**William Shakespeare
Anthony and Cleopatra
Act 2 Scene 7**

tissues' and postulated that all cells arise as a consequence of cell division. He also suggested that cell division permitted the spread of tumors, stating:

"These findings are as relevant to pathology as they are to physiology. I make bold to assert that pathological tissues are not, any more than normal tissues, formed in an extracellular cytoblastema (spontaneously) but are the progeny or products of normal tissue in the organism."

Remak was not initially supported in his conclusions by his friend, the eminent Rudolph Virchow (1821-1902), professor at the well-known Charité Hospital in Berlin. Often given credit with Schleiden and Schwann for the cell theory, it was some years before Virchow accept-

ed Remak's work as demonstrating that all cells arise from pre-existing cells by cell division. While this may seem surprising, acceptance of the full cell theory required overcoming an intellectual obstacle first propounded by Greek philosophers more than 2000 years before and summarized by Aristotle. According to this theory, life emerged spontaneously - usually from putrefying organic material. The spontaneous generation theory, discussed by Augustine of Hippo in *The City of God* and accepted by the Christian church, was widely (although not universally) believed well into the Renaissance period and beyond (Shakespeare referred, for example, to the widely held belief that snakes and crocodiles arise from the mud of the river Nile). Scientific experiments and observation for most of human history - even up to the present time - have not been considered the final arbiter of truth, and remain today open to different interpretations - quite apart from the possibility of specific instances that cannot be generalized. Some 200 years before the emergence of the cell theory, for example, the Italian, Francesco Redi (1626-1697), conducted many experiments relating to the spontaneous generation of insects and showed that the exclusion of flies prevented the appearance of maggots in rotting meat and that flies develop from maggots that hatch, in turn, from flies' eggs. Meanwhile, Leeuwenhoek's ability, around the same time, to observe animalcules in infusions of hay was taken by some (but not by Leeuwenhoek) to support evidence for spontaneous generation. In 1859, experiments conducted by Louis Pasteur, which

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improved on the design of earlier experiments carried out by others, demonstrated that microorganisms present in the atmosphere explain the putrescence of meat broth. His experiments are considered to have finally dispelled the spontaneous generation theory.

Rudolph Virchow' although originally skeptical of Remak's conclusions' eventually became a convert in the late 1850s and popularized Raspail's epigram *Omnis cellula e cellula* (although Raspail, like Dutrochet' was of the opinion that new cells arose from within old ones, not by cell division). Virchow expounded the idea that all diseases are disorders of cellular function in a series of lectures given in Berlin in the spring of 1858. These lectures were subsequently assembled into a single volume entitled *Cellularpathologie* (1859), which emphasized the origin of cancer from cells and was, therefore, an essential step toward the recognition that cancers could be differentiated from each other by histological examination. In spite of the promise of understanding, or at least, of classifying cancer at the level of cells, decades were to pass before histology became the primary approach to classification – for long it was simply one of the several descriptive characteristics of any given tumor. This is again rapidly becoming the case as more definitive molecular techniques evolve. Remarkably, in spite of his critical contributions, Remak was not mentioned in *Cellularpathologie*. Instead, the book was dedicated to Sir John Goodsir (1814-1867), a Scottish anatomist who had performed extensive work on cells in various tissues since the late 1830s.

Virchow is still generally credited, falsely, with being the first to recognize that all cells are derived from other living cells by a process of cell division. His notion that disorders of cells give rise to disease was, however a new idea, although not totally at odds with Giovanni Morgagni's (1682–1771) much earlier postulate that organs are the seat of human disease, or Marie-Francois-Xavier Bichat's (1771–1802) idea that diseases arose in tissues. Although partly right, all of these statements are oversimplifications arising from incomplete knowledge.

ANIMALCULISTS AND OVISTS

Recognition that plants and animals are comprised of cells raised the question of their relationship (or vice versa) to the rapidly expanding world of microorganisms discovered by the Dutch draper, Leeuwenhoek, almost 200 years before. These miniscule life-forms were considered by some to be an intermediate stage between the animate and inanimate, "explaining" how the spontaneous generation of life was possible. However, the discovery of spermatozoa, also referred to by Leeuwenhoek as animalcules, along with the other tiny creatures he saw through his lenses, also raised the possibility that individuals (whether animals or human) were generated from tiny copies of the adult form (homunculi) present in the spermatozoa. Supporters of this notion became known as *animalculists* while others (such as William Harvey), who believed that all animals develop from eggs (also from homunculi), even if such eggs (as was the case in humans) had not been identi-

fied, were referred to as *ovists*. The role of the egg was all too apparent in many animals - chick embryos, for example, had been studied by Malpighi (1628-1694) in the early 1670s - and the ovists saw no obvious use for sperm, except perhaps, to stimulate the egg to develop. These theories of preformation, as opposed to spontaneous generation, postulated either a male or a female origin of the offspring – an error of the kind referred to by Hooke in *Micrographia*, but due entirely to a complete lack of understanding of the process of inheritance. The animalculists assumed that microorganisms must be tiny animals and plants, but various theories existed about their origin and nature. In 1765 Horace Bénédict de Saussure (1740-1799) demonstrated that animalcules derived from plant infusions were able to divide into two equal parts, suggesting that these tiny organisms were not transmuted from vegetables, or gave rise to other organisms, but that the offspring were derived from and resembled their parents. Although never published, Saussure's experiments were widely disseminated, being described in detail, for example, in a letter written by Saussure to Bonnet in 1769, as recorded in *Animal Biography; or, Authentic Anecdotes of the Lives, Manners and Creation of Animals*, by the Reverend W. Bingley (3rd Edition, volume III, 1806). Many, however, greeted these results with skepticism.

Ernst Von Baer (1792-1876) is credited with the discovery of the mammalian ovum. His famous letter, *Epistola de Ovo Mammalium et Hominis Genesi*, published in 1827, described the microscopic appear-

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ance of the ovum, large enough in mammals to be seen with the human eye and contained within the Graafian follicles of the ovary, first observed in 1672 by Reinier von Graaf (1641-1673) and believed by him to be the ova themselves. In contrast, spermatozoa (except, in some algae) are tiny. It was Rudolf Albert von Kölliker (1807-1905), a friend of von Siebold' who realized in 1841 that spermatozoa are cells, likening them to pollen. Von Kölliker made major contributions to embryology but his recognition of the importance of the microscope to his studies stimulated him to improve the preparation of tissue for microscopic examination. He developed techniques of hardening, sectioning and staining of tissues (a field to which Paul Ehrlich (1854-1915) also made major contributions) which greatly improved the ability to separate cell and tissue types under the microscope. Progress in histology, based to a large degree on the pioneering work of von Kölliker' contributed greatly to medical diagnosis, particularly of cancer. In 1861, Karl Gegenbaur (1826-1903) proposed that all ova are single cells.

Surprisingly, recognizing both sperm and ova as cells did not immediately lead to the idea that fusion of the heritable material contained in each (although it was still unknown where in the cell it resided) would be necessary for the formation of a new individual organism – doubtless due to the almost total lack of understanding of the methods and nature of inheritance. Even Gregor Mendel's (1822-1884) laws of inheritance, discovered through a series of experiments conducted between 1856

and 1863, were ignored or actively rejected until their rediscovery in the 20th century.

A THIRD KINGDOM?

Karl Theodor Ernst von Siebold (1804-1884), like so many of his contemporaries, studied and taught a number of subjects, including zoology, physiology and anatomy. Von Siebold was co-editor of the two volumes of the *Lehrbuch der Vergleichenden Anatomie (Manual of Comparative Anatomy, 1846-48)* with Hermann Friedrich Stannius (1808-1883), a physiologist and entomologist. This work contributed greatly to the recognition of the relationships between various life forms, although in the absence of an overarching theory remained largely descriptive. Von Siebold was responsible for introducing the terms *Arthropoda* (insects and crustaceans) while limiting the use of the term *Protozoa* (from the Greek, meaning the first animals) to single celled organisms (although the latter were still considered to be tiny animals). The term *Protozoan* is believed to have been introduced by Georg Goldfuss (1782-1848) in 1817 in his book *Über die Entwicklungsstufen des Thieres (The Developmental Stages of Animals)*, prior to any knowledge of cells. It originally included a variety of "simple" animals including microscopic organisms, such as those observed by Leeuwenhoek in plant infusions and lake water, as well, for example, as sponges, corals and jellyfish. Ernst von Haeckel (1834-1919), who was responsible for the introduction of the terms *phylum and ecology* and strongly supported Charles Darwin's (1809-1882) theory of natural selection

(published in 1859 in *The Origin of Species by Natural Selection*) in Germany, believed that single celled organisms were worthy of their own kingdom, which he proposed, in 1866, should be called *Protista* (single celled) rather than each organism being arbitrarily labeled as either an animal or plant - terms which, he suggested, should now be confined to multicellular organisms, or *metazoans*. Since the latter develop from single cells, whether ova or sperm, the cell theory - that all life is comprised of cells and derived from cells - implies that life also began in primordial cells which, through the process of natural selection, evolved into the myriad life forms that subsequently developed. Modern molecular studies of a broad range of life forms suggest, in fact, that life, in all of its tremendous diversity, derives from a single cell that arose some three and a half to four billion years ago, within a billion years of the formation of our planet.

In 1665, Hooke had predicted that the "designs and ends" of nature might well be hidden in the cells he had discovered and that they might someday be uncovered by a diligent observer helped with better microscopes. Prescient though this statement was, he could surely have had no idea quite how vital to the designs and ends of nature the cells he had discovered would prove to be.

Part 2 of *The Cell* will be published in the next edition of NETWORK. ■

¹ This epigram is usually ascribed to Virchow, but in fact Virchow quoted it, without reference, from Raspail

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INCTR SUPPORTIVE CARE HANDBOOK

At the time of the August 2007 thematic workshop held in Tanzania, the Supportive Care Working Group created an outline for a supportive care handbook.

In the interim period between the August 2007 workshop and the follow-up workshop, it was considered essential to refine the purpose of the handbook and to identify the intended users of the handbook so that content would be relevant for the users. Although it was originally thought possible to create a handbook relevant to both adults and children with cancer, since there are differences in

approaches to providing supportive care to these patient populations it was decided to develop separate handbooks for each. It was agreed that the handbook for pediatric supportive care would be developed first.

The handbook will be useful to health care professionals involved in the care of children with cancer such as pediatric oncologists, pediatricians, hematologists, fellows, residents, medical students, both pediatric and pediatric oncology nurses and social workers. It is intended to provide information of particular value to the care of children undergoing cancer treatment in resource-limited settings, but is likely to

be of value to a much broader readership.

A general outline of major topics has been created and the structure and content for preparing information related to each topic has been defined.

In November 2008, pediatric oncologists from low- and middle-income countries including Brazil, Mexico, Morocco, Algeria, Tunisia, Nigeria, Tanzania, Jordan, Turkey, India and Pakistan attended a two-day workshop to work with INCTR staff and pediatric oncologists from major U.S. university hospitals in discussing and preparing content for the handbook. It was considered essential to obtain the input of investigators facing a range of resource limitations to ensure that the handbook contains information relevant to situations ranging from those where only basic care is possible, to centers where optimal care (or close to optimal care) is feasible.

By early December 2008, first drafts of many of the planned sections were completed. Further work on the Handbook was undertaken in the Thematic Workshop in January 2008 in Tanzania (see report in this edition of NETWORK). All of this material is available online for viewing and discussion (<http://inctr.wikidot.com>). All site members can make comments on the relevant pages by clicking on "discussion" at the bottom of the page, or by contributing to a specific discussion thread (theme). Such comments will be taken into account in the preparation of the final handbook. ■

*Melissa Adde, INCTR,
Brussels, Belgium*

The purpose of the Pediatric Supportive Care Handbook is:

- to improve the outcome and survival of children with cancer by providing guidelines for the management of tumor and treatment-related complications
- to provide basic guidelines for pediatric pain management and palliative care
- to provide guidelines for blood and blood component therapy
- to address psychosocial issues facing children and their families during and after treatment

The major topics covered include:

- Structure of the Pediatric Cancer Care Unit
- Pediatric Oncological Emergencies
- Co-morbidities Common to Low- and Middle-Income Countries
- Management of Treatment-Related Complications
 - Febrile Neutropenia
 - Prevention and Management of Infections During Treatment
 - Common Side Effects of Chemotherapy
- Pain Management
- Acute and Late Effects of Radiation Therapy
- Blood Component Therapy
- Psychosocial Support
- Basics of Pediatric Palliative Care

SECOND THEMATIC WORKSHOP IN TANZANIA

What progress has been made since the first Burkitt Lymphoma workshop was held in Tanzania 18 months previously? For five days in January 2009, members of INCTR's African network met in Dar es Salaam to analyze and assess the current situation. The meeting had several components, all relating to INCTR's ongoing project for the treatment of Burkitt Lymphoma in multiple institutions in African countries.

STRATEGY GROUP MEETING

The strategy group meeting included:

- An update on the present status of the project: patients accrued, survival, toxicity and data management.
- A report on the use of the salvage regimen and initiation of discussions regarding its inclusion in primary therapy for high-risk patients (to be defined).
- Protocol modifications necessary for the capture of data from HIV+ and HIV- patients.
- The development of a central pathology review process.
- The expansion of the range of

drugs to be provided.

- The employment of a nurse dedicated to the project at each center.
- Increasing the number of participating centers.

FOCUSED WORKSHOP FOLLOW-UP

As a follow-up to the workshop held in August 2007, the second focused workshop included:

- A report of progress made in each of the thematic areas previously identified.
- A discussion of what additional steps would be possible, based on the recommendations that were made at the first meeting (and published in INCTR's Network).
- A discussion on establishing a training program associated with consultation in pathology, initially confined to hematological malignancies and associated with the central review process for BL and HIV-related BL.
- A discussion on how best to publish a more detailed report of the August and January meetings in the East African Journal of Medicine, and elsewhere.

The pathology program was attended by approximately 35 pathologists from Uganda, Kenya and Tanzania. Eleven persons from new participating centers in East African countries attended the training sessions for new data managers and investigators, conducted by Melissa Adde. The palliative care group consisted of Dr. Mmsemu and his staff of some 20 people, as well as Dr. Robert Burton and Dr. Ian Magrath. The BL strategy group session was attended by representatives from all participating and new centers in the equatorial African INCTR Network. Approximately 50 people participated in the thematic workshop held on Friday.

The several elements of the workshop included:

1. A meeting of INCTR's strategy group for the treatment of BL. Participants included the principal investigators and clinicians responsible for the care of African patients with Burkitt Lymphoma.

Presently the participating centers include:

- Ocean Road Cancer Institute, Dar es Salaam, Tanzania
- Kenyatta National Hospital, Nairobi, Kenya
- University of Obafemi Awolowo University, Ile Ife, Nigeria
- Ibadan University, Ibadan, Nigeria.

In addition, several prospective members attended. These included:

- New Nyanza Provincial General Hospital, Kisumu, Kenya
- Aga Khan Hospital, Nairobi, Kenya
- Lacor General Hospital, Gulu, Uganda
- Kemri Research Center, Kilifi, Kenya
- Two additional centers in Tanzania

2. A meeting to assess the progress made and to develop future plans in several thematic areas previously identified — access to care, pathology, supportive care (including blood transfusion) and palliative care.
3. A monitoring visit with ORCI staff participating in the BL project.
4. Training of newly appointed data managers and new investigators from the hospitals that will be joining the BL project and to discuss management of the expanded network.

NETWORK

ITINERARY:

Monday, 19th January

Monitoring and auditing visit with ORCI staff participating in BL project, INCTR Office, ORCI

Tuesday, 20th January

Monitoring and auditing visit with ORCI staff participating in BL project, INCTR Office, ORCI

Wednesday, 21st January

PATHOLOGY PROGRAM

- Visit to Pathology Dept., Muhimbili Hospital and Pathology Lab, ORCI
- Pathology meeting at ORCI:
Improving pathology facilities and developing central pathology review for protocol patients

TRAINING PROGRAM

- Training sessions for new data managers and new investigators

Thursday, 22nd January

BL STRATEGY GROUP MEETING

- Welcome and introductory remarks: Twalib Ngoma and Ian Magrath
- Progress report of the present protocol (results and obstacles)
- Relapse protocol/incorporation into primary protocol for high-risk patients
- Treatment guidelines for BL (Twalib Ngoma)
- Inclusion of HIV-positive adult patients (and needed modifications to the protocol)
- AIDS Malignancy Consortium and International Trials Research (Ronald Mitsuyasu)
- Project Coordination, including development of central pathology review

PALLIATIVE CARE MEETING AND DISCUSSION

- Visit to ORCI Palliative Care Ward and meetings with PC staff.
Discussions led by Msemo Diwani, Robert Burton, Angela Rappaport

Friday, 23rd January

FOLLOW-UP OF FIRST THEMATIC WORKSHOP

- Opening session by the Ministry of Health. Chair: Twalib Ngoma
- Plenary Session: Report of progress made since Focused Workshop in August 2007.
Chairs: Twalib Ngoma and Ian Magrath
- General Discussion/Working Groups:
Report of progress made since Focused Workshop in August 2007.

HOW TO MOVE FORWARD?

- Plenary Session
- Working group sessions on access to care, palliative care, supportive care and pathology
- Brief reports/recommendations of working group sessions (rapporteurs) and discussion
- Conclusions (plenary session)

PATHOLOGY

This workshop was part of a follow up of the workshop held in Dar es Salaam on 22-24 August, 2007. The 2007 workshop dealt mainly with problems of pathology in Tanzania rather than the wider problems facing pathology services in East Africa. The recommendations of the 2007 Working Group were:

- The Muhimbili National Hospital Laboratory should be designated as the National Institute of Pathology and given its own director and dedicated budget. It would have responsibility for pathology services throughout Tanzania. (This change is designed to give the Pathology Department a national responsibility, rather than the current responsibility to the hospital).
- Current academic restrictions applied to applicants for training posts in pathology should be lifted, allowing the appointment committee to judge whether the applicant was suitable for training.
- Pathology training should include a period in clinical pathology before embarking on a single specialty. Ideally this should be the pattern of training in all East African countries. (This is the program already in place in Kenya).
- The sharing of resources (material and educational) between the East and Central African States would be to the benefit of all. The hope was expressed that the Association of Pathologists of East, Central and Southern Africa might act as a catalyst for this collaboration.

At the meeting on 21st January 2009, Dr. Mgaya made it clear that there had been no progress on these proposals. He also stated that the manpower situation in histopa-

thology had become more precarious with no further recruitment of trainees and the impending retirement of several of the established pathologists.

At the pathology session three presentations were given:

- Lorenzo Leoncini: ***Incidence and outcome of lymphoma in developing countries.***

In this presentation support for trainees was discussed, as well as the possibility of workshops on immunohistochemistry and international collaboration on training and research projects.

- Nina Hurwitz: ***Telepathology as an option for continuous support in haematopathology diagnosis and education.***

The use of the iPath system, developed at the University of Basel both as a diagnostic aid and a teaching method, was outlined. The basic equipment needed for the operation of this system is relatively cheap and much of it is already available in some laboratories.

- Manzoor Ahmad: ***Overview of pathology in developing countries.***

The problems of providing a reliable pathology service in developing countries were discussed with emphasis on the provision of laboratory services by untrained and unsupervised practitioners. The following needs were identified: A national or regional academic body to oversee training and standards; development of centers of excellence; "south-to-south" collaboration.

HOW TO MOVE FORWARD

The Group endorsed the recommendations of the 2007 Workshop and added others:

Telepathology. Centers wishing to participate should register with Dr. Nina Hurwitz. It is possible that INCTR will be able to provide funds to purchase the necessary equipment for some centres.



Workshop participants.

INCTR Centers studying Burkitt Lymphoma will, in many cases, make the diagnosis on FNA preparations. A biopsy should be taken where possible (protocol for fixation to be provided by Prof. Lorenzo Leoncini). H and E and Giemsa will be used as standard stains. The most helpful immunohistochemical stains will be CD20, BCL2 and Ki67. Centers without immunohistochemistry should find a partner center. Additional slides should be made available for FISH, if possible.

Central review of Burkitt Lymphoma cases.

The review panel should visit participating laboratories in rotation. A visit to East African pathology labs is proposed for later this year. The Centers currently identified are: Lachor-Uganda, University of Nairobi-Kenya, Aga Khan University Nairobi-Kenya, Muhimbili Hospital - Tanzania. Nigerian centers will be included in a second step.

OTHER DEVELOPMENTS

It was announced at the meeting that there is an East African Division of the International Academy of Pathology. Collaboration with this

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body might be helpful, for example, in the collection and distribution of pathology journals and books.

It was also announced that the establishment of an East African College of Pathologists is in its early stages. This college should play a major role in organizing the training and validation of pathologists throughout East Africa. INCTR should establish contact with those setting up this new college in order to provide any assistance that we can.

This session was attended by Yetunde Akenova, Muheez Durosinmi, Jesse Githanga, Edward Mgaya, Lorenzo Leoncini, Nina Hurwitz, Dennis Wright, Manzoor Ahmad, Shaheen Sayed, Riyat Malkit and Mostafa Nokta.

SUPPORTIVE CARE

In the course of the January 2009 Thematic Workshop, doctors involved in the care of patients with Burkitt Lymphoma in Africa met to discuss two of the most important topics in the handbook. The primary goal was to ensure that the proposed guidelines were practical and feasible in the African context (basic resources). The draft version of *Prevention and Management of Tumor Lysis* was discussed in detail and revised to include practical guidelines for doctors and nurses to follow prior to and during the start of initial treatment for newly diagnosed patients, particularly if nursing staff numbers are low. These guidelines address the critically important issue of ensuring that patients receive adequate hydration and have adequate urine output prior to the initiation of treatment and following treatment, as well as the monitoring of laboratory

values. It was felt advisable, except in urgent situations, not to initiate therapy in the evening hours or on Fridays if necessary tests are not available after hours or on weekends. Given the major shortages of nurses in some institutions, discussion turned to how to involve parents in monitoring fluid intake and output.

The management of febrile neutropenia was discussed in terms of what would be the most appropriate and basic care that could be provided with consideration given to the types of antibiotics, antifungals and antiviral agents available (and affordable), the difficulties in obtaining cultures and antimicrobial sensitivities in cases of documented infections. The majority of investigators stated that their institutions did not have "standard" guidelines for managing febrile neutropenia and many could not obtain bacterial antibiotic sensitivities.

It was further suggested that the

Pediatric Supportive Care Handbook should complement and be part of the Tanzanian National Guidelines for the Treatment of Burkitt Lymphoma in Children.

Melissa Adde gave the interim progress report. Dr. Parth Mehta chaired the working group discussion session related to the prevention and management of tumor lysis and the management of febrile neutropenia.

This working group discussion session was attended by Trish Scanlan, Jane Kaijage, Paul Ndom, O. Adeodu, Michael Mawanda, Moses Odongkara, Janet Mwilllo, Mohammed Shebe, Jamilla Rajab, Esther Kiwira, Ronald Mitsuyasu and Melissa Adde.

ACCESS TO CARE

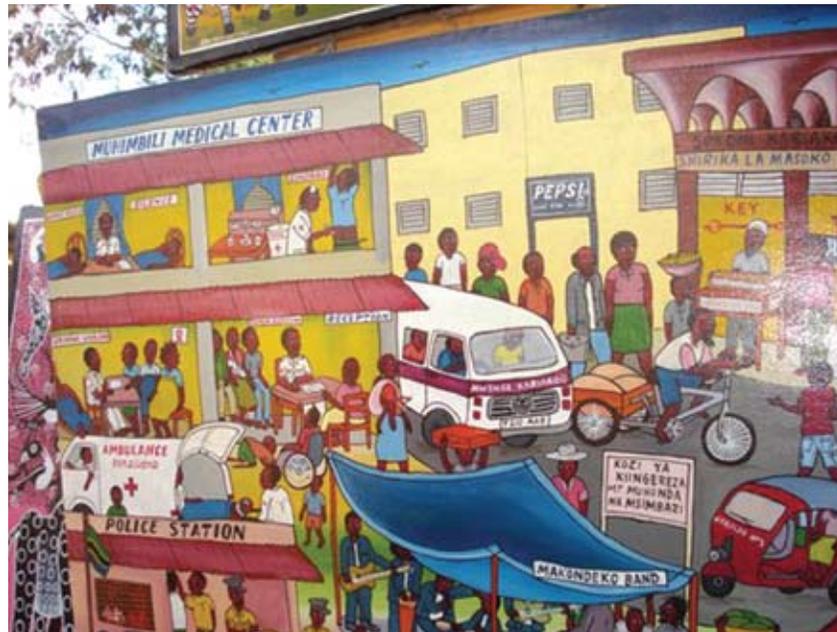
Dr. Twalib Ngoma chaired the session on access to care. The group briefly reconsidered the issues discussed at the previous focused workshop.



Dr. Nina Hurwitz explains the proposed iPath program.

One suggestion had been the appointment of cancer coordinators, who would visit various health centers and hospitals, provide education regarding the early signs of cancer and ensure that any suspected cases bypass the lengthy referral system and are sent for immediate biopsy to the district hospital, or even, if considered appropriate, referred directly to ORCI. Dr. Ngoma reported that the Tanzanian government had declined to support a large number of cancer coordinators to liaise among community health centers, district hospitals and ORCI. It was suggested, therefore, that a small feasibility project be established whereby either one or two cancer coordinators are trained to work in a specified district within realistic geographic reach of ORCI. It would be necessary to decide upon the training required of such an individual, and to gain the approval of the community centers and district hospitals that he or she would visit to function in this capacity. One possible approach would be to hold a meeting of all relevant parties to discuss the idea and provide an opportunity to ask questions. Such a meeting would also serve to provide education to primary care givers about the early signs of cancer. In addition, it might be possible to develop a pictorial brochure (or possibly even a video) that could be displayed in waiting rooms to provide education about the early signs of cancer. Such information could also be more widely distributed beyond the health care system.

A second potential solution for aiding navigation through the health service system for cancer patients that had been previously discussed was the use of health passports.



Typical African painting depicting Muhimbili Medical Center.

These are small booklets kept by the patient, and completed at every medical visit, such that a record of the dates of occurrence of symptoms, possible diagnoses, reports, recommendations and treatment would be available to any medical practitioner that the patient might see. This idea is being implemented in South Africa by the Medical Knowledge Institute (MKI), which would be willing to collaborate by providing a copy of the health passport they have developed for use as a model for a similar passport to be developed in Tanzania – or alternatively, if found appropriate, the MKI passport could be used as is. At some point, this system could be replaced by a computer system, whereby clinical data is held at a secure central data bank accessible by password in association with a specific patient identifier. Such a system would clearly take longer to develop and might be contemplated only after testing the feasibility

of the health passport proposal. MKI is exploring this possibility in South Africa.

Considerable discussion was held on the reasons for late diagnosis, and it was resolved to develop a questionnaire that could be applied to patients or family members to identify the major causes of late diagnosis. INCTR has experience in designing questionnaires and collecting information of this type, including retinoblastoma (an international project conducted in ten countries) and nasopharyngeal cancer (about to begin). Such a questionnaire could be constructed in basic form, and modified where there is a need for questions that relate to specific diseases (e.g., because of differences in the early symptoms). The group decided to initiate this program with breast cancer and also to develop a program in retinoblastoma awareness. These programs will be developed in the coming year.

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Group photograph of workshop participants.

PALLIATIVE CARE

During the first thematic workshop in 2007 a number of challenges were identified as major obstacles to access to oral morphine and to the scale-up of palliative care in Tanzania. ORCI was asked to use its unique position in the government to help solve these problems. The Board of Trustees of Tanzanian Palliative Care Association (TPCA) approved the palliative care curriculum developed by ORCI to be used as the standard palliative care training curriculum in Tanzania. ORCI, however, was faced with a shortage of funds since most palliative care donors are primarily interested in HIV/AIDS rather than cancer (even though ORCI's program was designed to include HIV/AIDS patients). It was resolved that TPCA and APCA would work together with ORCI and subcontract some of their activities to ORCI because ORCI had the expertise but not the financial resources, while TPCA/APCA had the financial resources but lacked the human resources.

STEPS TAKEN

A number of developments have taken place since the last thematic workshop. Palliative care policy will soon be a reality after the Ministry of Health and Social Welfare endorsement of the National Cancer Control Program (NCCP) document (which gives palliative care a high priority). The NCCP was spearheaded by ORCI together with other external agencies, i.e., IAE and its PACT partners. ORCI was contracted by TPCA/African Palliative Care Association (APCA) to carry out training on behalf of TPCA as per suggestions made during the thematic workshop held in 2007.

Two weeks of palliative care training for 40 health professionals from the Ilala municipality was successful carried out, resulting in the establishment of palliative care services there. During this period additional trained health professionals joined the the ORCI palliative care team. Two doctors and two nurses completed their palliative care distant learning diploma course in Uganda, thereby making the ORCI palliative

care team the largest (in terms of trained personnel) in the country. ORCI took another step towards scaling up palliative care in the country by conducting two-week palliative care training sessions for health care professionals from four main referral hospitals in the country, namely KCMC, Bugando, Mbeya and Muhimbili. All of these hospitals have, as a consequence, been able to establish palliative care services.

Increases in human resources for palliative care have been coupled to the acquisition of an oral morphine permit from the Tanzania Food and Drug Authority (TFDA) for the Kilimanjaro Medical Center and the Bugando and Bombo hospitals, the latter being the regional hospital for Tanga. Country-wide, additional health professionals have been trained in Tanga (Muheza hospice), Arusha (Selian hospital) and PASADA, an NGO based in Dar es Salaam. Unfortunately, evaluation systems are not yet in place, and data on oral morphine consumption is not yet available. We hope to rectify this in the near future.

CONCLUSION

ORCI still remains the national leader in palliative care due to its unique relationship with the government as well as the palliative care infrastructure it built over a decade ago. Lack of finances has been a great challenge to the ORCI palliative care program. Most of the existing funding for palliative care comes from HIV/AIDS program such as PEPFAR, which do not support services for cancer patients. Given more financial resources, ORCI could do more to fulfill its mission of making universal access to palliative care in Tanzania a reality. ■

BUILDING A FRENCH-SPEAKING CANCER CONTROL NETWORK

Cancer is not yet a public health priority for the governments of many developing countries. In fact, it remains a taboo subject for many people, and in Africa, most languages have no name for the disease. A high fraction of patients see traditional healers in the absence of access to standard medical care. Many patients never reach a competent facility, while others may be sufficiently delayed as to leave little possibility of treatment beyond palliative care. There is a lack of information, infrastructure and properly trained medical staff, and very low government expenditure on health-care. Thus, policy makers have little incentive or even the possibility of addressing the problem - even to develop programs on prevention and palliation. Therefore, non-governmental cancer control organizations have a particularly important role.

There is also a clear lack of communication and coordination with respect to support for cancer control provided by industrialized countries and international organizations to developing countries compared to what exists for HIV/AIDS. In part, this is due to the lack of a global fund equivalent to the several that exist for AIDS, tuberculosis and malaria, such that there is a chronic shortage of financial aid - a major problem given the complexities of cancer control programs. Given the severity of the problems in francophone Africa, the INCTR's branch in France (AMCC) is focused particularly on French-speaking Africa. AMCC

tries to share both knowledge and methods, provide training and participate in research. AMCC is helping to develop a network of African centers and European cancer organizations to facilitate this process.

With this in mind, the AMCC organized a colloquium entitled *You speak about the financial crisis: let us speak about cancer!* at the CRLC Val d'Aurelle (Regional Cancer Center)

in Montpellier, on April 3rd, 2009. This was the second colloquium of this type to be held in Montpellier and will be adopted as a regular event in AMCC's calendar. Medical experts and civil society representatives attended from Africa, Asia and Europe. AMCC's major purpose is to expand its network both within Europe and in French-speaking developing countries.

2^{ème} Journée Francophone de Lutte Contre le Cancer

en faveur des pays en voie de développement



**Vendredi
3 Avril 2009**

A Epidaure - Département de Prévention
CRLC Montpellier - Parc Euromédecine
Rue des Apothicaires
Montpellier

> Des conférences, débats, rencontres et ateliers sur les thèmes de la formation du personnel médical, l'organisation des soins, la nécessité de développer un réseau,....

> La présence d'intervenants des pays du Sud impliqués dans la lutte contre le cancer



organisée par l'Alliance Mondiale Contre le Cancer

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Among the 100 participants, two major questions emerged: how to expand the cancer control network in French-speaking countries and how to answer requests for information, training and partnerships from countries that wish to invest in cancer control.

In the morning, the AMCC and INCTR reports for 2008 were presented. African representatives and various NGOs discussed their cancer control efforts and difficulties they are encountering. The status of the three-year course on pain control and palliative care, developed in a partnership between the AMCC and the Bobo Dioulasso Hospital Cancer Committee in Burkina Faso, was discussed. This program, supported by the French National Cancer League and to the IAEA/PACT program, began with Burkina Faso and three neighboring countries - Senegal, Mali and Niger. More recently, Gabon, Ivory Coast, Mauritania and Benin were added. All participants in the training sessions stressed the need to organize additional training sessions on surgery, chemotherapy and radiotherapy. However, at present, among the West African francophone countries, radiotherapy is available only in Senegal, although it should be soon introduced in Niger.

In the afternoon, several workshops focused on topics raised by AMCC partners and collaborators in Africa. These included tobacco control, pediatric oncology, radiotherapy and pain management in developing countries.

A number of important points were made (see panel):

1. Tunisia is the first francophone country to ban smoking in the workplace.

2. Obtaining affordable anti-cancer drugs is a problem - even generic drugs can be beyond the financial means of many patients, although they are much less expensive.

3. In addition to financial constraints, many problems still exist with respect to drug procurement practices.

4. The delivery of radiotherapy can be immensely difficult in view of the shortage of equipment and trained personnel.

5. Data collection, e.g., by cancer registries is extremely limited.

One of the most successful workshops was on situation analysis, where participants were given a chance to learn how to conduct an initial assessment of the general health status of the population and the health system in their respective countries. A constructive debate on several key issues, such as *why conduct an analysis*, *how to prepare for an analysis* and *how to take advantage of opportunities and address challenges* were addressed.

In the course of the colloquium, side-meetings took place between participants, AMCC and the French National Cancer League to follow up on preliminary plans to form a network of African and Mediterranean French-speaking

cancer leagues. Participants felt it very important to create a network based on a common language, and francophone countries in Africa often lag behind Anglophone countries. AMCC and the newly formed Francophone cancer network plan to change this. There is strength in numbers: by banding together in the cause for improved cancer control, and calling for greater capacity-building with one voice, we are more likely to be heard by the various political authorities whose support is a key requirement for the improvement of health services, training and education as well as the availability of needed drugs and equipment. At present, cancer is largely considered an incurable disease by the African public. The only way to change this attitude is to demonstrate that this is not necessarily so: that for some cancers, incidence can be reduced by prevention, while for others, early detection will lead to better results, assuming prompt access to competent care is available. Even when there is no curable option, palliative care can provide comfort, and it will be critically important to ensure that these messages are delivered in a culturally sensitive way to the general public, as well as to primary health care providers and political authorities in developing countries.

Report of a meeting held in the Epidaure Department of Cancer Prevention, Val d'Aurelle Cancer Center, Montpellier in January 2009. ■

Sabine Perrier-Bonnet,
AMCC/INCTR, Montpellier, France
Julie Estal, INCTR,
Brussels, Belgium

THEMATIC WORKSHOP ON BREAST CANCER CONTROL AT EMRO CAIRO, DECEMBER, 2008

As part of the launch meeting of the WHO Eastern Mediterranean Regional (EMR) cancer control program which INCTR had helped to prepare, a thematic workshop was held on breast cancer – by far the most common cancer in the region. The workshop was jointly organized by INCTR, the EMR Office (EMRO) and the Association Lalla Salma Against Cancer. It consisted of a plenary session of overview lectures, followed by group discussions. On the second day, working group discussions and conclusions were reported and action items identified.

PLENARY SESSION

In his introduction to the workshop, Dr. Ian Magrath (INCTR, Belgium) pointed out that in addition to breast cancer having the highest incidence

of all cancers in the EMR, half of those diagnosed die from the disease. Post-menopausal women, as in most developing countries and Japan, have a markedly lower incidence than in the West, which has implications for screening and epidemiology. Awareness campaigns and early detection strategies must be associated with effective treatment programs if they are to be successful in reducing mortality. Given cultural and behavioural differences, it is critical to develop local evidence, including data on the treatment and outcome of screen-positive women. INCTR has developed templates for model data collection forms (modules) that can be used or adapted as required. There is one summary module (19). These could be incorporated in a system for data flow from screening, diagnostic and treatment centers to the data center – both for research and evaluating the impact of projects.

Dr. Robert Burton (Monash University, Australia) provided an overview of

breast cancer control, pointing out that survival from breast cancer in women has improved in many countries, especially in North America, Europe and Australia. Much of this is a result of improved awareness resulting in a reduction in tumor size (with most patients presenting in stages 1 and 2) at presentation and improved treatment. The room for improvement of survival in technically advanced countries is now very small. In low- and middle-income countries, however, a much higher fraction of women present in stages 3 and 4. Therefore, the first aim of an early detection program in such countries is to promote diagnosis in stages 1 and 2. This is not the objective of mammography, which is to find impalpable breast cancers in stage 1, and it misses many invasive breast cancers in younger women. Even in high-income countries, the value of mammography in reducing mortality may be small. Reduction in breast cancer mortality in the UK seems almost entirely due to treat-

The objectives of the workshop were:

- To promote actions directed towards breast cancer control in the EMR region.
- To identify obstacles to effective action that exist in the EMR, or areas where more research is needed.
- To propose approaches to overcoming known obstacles.
- To emphasize the value of an integrated approach from early detection to treatment and to discuss how this might be achieved, at least in the context of pilot projects.
- To emphasise the need to evaluate program outcomes and to consider how best this can be done:
 - Cost: financial, human capital, potential negative impact
 - Benefit: increased survival/decreased mortality
- To identify tools that aid decision-making re: priorities, methodologies, data collection and program evaluation.

The anticipated outcomes included:

- Learning from each other.
- Identification of obstacles and potential solutions as well as areas where more assessment is required.
- Exploration of possibilities for regional cooperation in breast cancer control.
- Promotion of pilot programs in breast cancer control that are integrated and effectively evaluated.
- Identify tools that could help, e.g., the draft model data collection templates created by INCTR.
- Preparation of a report of the group discussions and recommendations and eventual dissemination, as a basis for future actions and assessment of progress.

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ment, while in Australia, reduction in breast cancer mortality was greatest in women aged 40-49, a group not targeted for breast screening by mammography! In contrast, improvement in therapy response through the introduction of National Clinical Practice Guidelines was substantial.

Dr. R. Bekkali (Association Lalla Salma Against Cancer - ALSAC) provided some insights into screening strategies in Morocco. In the ALSAC study the target group for screening is women aged 45-65, as many cases are identified in women age 45-49, a population subset of more than 2 million women. The mean age of detection of incident cases is 48 years. Morocco has higher reported breast cancer incidence than Tunisia and Algeria, but a much lower incidence than in the West. Because of limited radiological resources, a tele-mammography pilot project was first conducted using digital mammography, with second reading of images in Brussels. Among the first 1000 women, five cases of breast cancer were found but three had clinically detectable disease. Consequently, the Scientific Board of the Lalla Salma Association recommended that screening be undertaken by clinical breast examination. Following this recommendation, a screening program was initiated through the primary health care system. Women are invited to be screened by clinical breast examination (CBE) conducted by physicians and nurses trained in CBE. Diagnosis is carried out at the secondary health care level where CBE is repeated, and mammography, ultrasound, biopsy and pathology can be performed if necessary. If breast cancer is confirmed, treatment is performed at the tertiary level. Dr. Bekkali also pointed out that in Morocco it

is difficult to persuade women without symptoms to be examined. In an attempt to overcome this, a media campaign, using print and television, was initiated in May 2008 to provide the necessary health education. This campaign, which was the first time in Morocco that breast cancer has been talked about in public, was led by women affected by breast cancer. A well-known singer acted as a celebrity advocate. In implementing the screening process in the public health system, 2,300 family physicians were trained, 120,654 CBEs performed, and 1284 women identified as suspected of having breast cancer.

Dr. Anthony Miller (University of Toronto, Canada) discussed the pros and cons of different methodologies relating to early detection: education alone, CBE/breast self examination (BSE) and mammography. He pointed out that mammography screening is less effective in women under age 50, and the technical and personnel requirements for population-based mammography screening are very substantial. An IARC working group (2002) determined that the reduction in risk of death from breast cancer by mammography screening was 12% in women aged 40-49 and 25% in women aged 50-69. In a large, more recent, UK trial among women aged 39-41 on entry, the ratio of breast cancer deaths at mean follow-up of

10.7 years in the intervention arm relative to the control was 0.83 (95% CI 0.66-1.04), i.e. a non-significant 17% reduction in breast cancer mortality. He pointed out that there has been only one trial that was specifically designed to evaluate the role of mammography over and above annual breast examinations and the teaching of BSE - the Canadian National Breast Screening Trial among women aged 50-59. In this trial, no breast cancer mortality reduction was found in the mammography-containing arm. A model-based analysis however suggested a benefit from CBE/SBE of 20% compared to no screening, and an extension of this observations suggests that breast examination is far more cost-effective than mammography screening. Although in Western countries breast cancer mortality has been falling, the timing of this recent fall is compatible with improvements in therapy, but is not compatible with an effect of mammography screening. Moreover, the lack of any reduction in mortality prior to 1990 suggests that early detection is not effective in the absence of effective treatment.

Dr. Miller also described a trial of breast examination as a means of screening in Cairo. The pilot study included 4000 women, and 10,000 women were subsequently randomized using the cluster method in two

WHO's recommendations for low- and middle-income countries are:

- Evaluate the importance of breast cancer.
- Evaluate the available resources.
- Ensure the availability of early diagnosis.
- Ensure the availability of therapy.
- Introduce early detection based upon evidence.
- If there is insufficient evidence to support early detection, screening should be used as a demonstration project, to collect more information.

other areas. There was a high rate of breast cancer detection with good compliance with diagnosis and preliminary evidence of a stage shift to an earlier stage at diagnosis in the BE group. The experience is now being replicated in Khartoum, Sana'a and Yazd (Iran), with projects designed to be compatible with local resources. Dr. Miller feels that BSE should be taught as part of BE and used as a means of contributing to breast cancer awareness, but should not be used by itself.

It was emphasized that a beneficial population impact requires an organized approach and a high compliance rate, not only with screening, but with diagnosis and recommended treatment. Opportunistic screening has been shown to be ineffective. There are detriments from early detection and screening, and we need to ensure they are not hidden, and that women are not coerced into screening.

Dr. Manzoor Ahmed (President, College of Pathologists, Pakistan) discussed the importance of rapid and accurate diagnosis in the control of breast cancer. This requires excellent communication, particularly between the surgeon and pathologist. The latter must distinguish between benign and malignant lesions and provide all information required to facilitate treatment planning. There should be quality assurance and standardization of practices. Minimally invasive needle biopsy is simple and inexpensive and can be done as an outpatient but requires carefully trained staff. Core-needle biopsy provides more information than fine needle aspiration and has the advantage that enough tissue is obtained to determine hormone receptor status. Pathology reports should include, tumor size, information on whether or not the margins are free of tumor, the degree

of nodal involvement of the axillae (based on lymph node biopsies), histological subtype and, where possible, hormonal status. Inaccuracies in diagnosis can be reduced by supervision, better training, and academic involvement.

Dr. H. Khalid (Vice President, Cairo University) discussed clinical management, pointing out that after a tissue diagnosis has been made, the next step is to assess the extent of disease (stage). Tumor size can be assessed by ultrasound (preferred in women under 30 years) or mammography (preferred with older women in addition to ultrasound if necessary). In Egyptian women with early stage disease, breast conserving surgery is preferred; this usually involves post-surgical radiation therapy, and in a few cases, additional systemic chemotherapy. Systemic treatment is necessary for locally advanced breast cancers, and is most generally given after surgery, although neoadjuvant therapy (prior to surgery) also improves outcome. In technically advanced countries, survival of advanced breast cancers has improved with combination chemotherapy regimens. Multidisciplinary care is essential, as it formalizes discussions and decisions about diagnosis, stage and plans for the right combination and sequence of treatment. Treatment guidelines have been produced by the Breast Global Health Initiative, in addition to other organizations, and recently updated (2008). Local (Egyptian) guidelines have also been produced. A unusual form of breast cancer – inflammatory breast cancer, which progresses rapidly, comprises 8% of breast cancers in Egypt and is particularly difficult to manage. This form of cancer is extremely rare in Western countries.

Dr. R. Sankaranarayanan (Head Early Detection and Prevention Section and Head Screening Group, International Agency for Research on Cancer) discussed the evaluation of any breast cancer control program.

Measures of processes used in evaluation include:

- Participation in screening
- Screening quality
- Screen positivity
- Compliance with referral
- Breast cancer/benign tumor detection rates

The quality of screening mammography is evaluated using the following criteria:

- % with radiographically acceptable mammograms (should be $\geq 97\%$)
- % undergoing a technical repeat screening test (should be $< 3\%$)
- % undergoing additional imaging at the time of screening (should be $< 5\%$)
- % of women recalled for further assessment
 - Should be $< 7\%$ for initial screening round
 - $< 5\%$ for repeat rounds

Intermediate outcome measures include:

- % screen-detected cancers that are invasive ($\sim 90\%$)
- Stage distribution
- Proportion of women with breast cancer ≤ 2 cms
- Proportion of node-negative breast cancers
- Proportion of ER +ve tumors
- Proportion of patients completing the prescribed course of treatment
- Proportion of cancers treated

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- with breast conservation
- Case fatality rate
- 2- and 5-year survival rates

Final outcome measures:

- Incidence of early and advanced breast cancer
- Mortality from breast cancer
- Adverse effects
- Quality of life

Obtaining these indicators requires a program database. The quality of the program can be assessed by linking with an appropriate (population-based) registry. Official death records often need to be supplemented with data from other sources (e.g. church and other registers) in order to obtain as complete information as possible. In CBE studies it is essential to identify the fraction of cancers missed by follow-up of screened women. This may add considerably to cost.

Dr. Sankaranarayanan discussed two recent studies. In Trivandrum, a cluster-randomized breast cancer screening study, designed to evaluate the extent of stage shift, survival improvement and mortality reduction in the context of a package of interventions consisting of breast awareness, CBE and improving public and professional awareness on breast cancer, its early clinical diagnosis and prompt treatment was carried out. Over 90,000 women were divided between the two arms. In the control group, education on cervix cancer and cervix cancer detection were offered in clinics. In the intervention arm, education on BSE, early detection of breast cancer, CBE, FNAC, biopsy, staging and treatment were offered. Thirty-four breast cancers have been detected in the intervention arm, and 26 in the control arm,

of which 60% and 42% are stage I and IIa, respectively. These findings, that show that education alone can result in down staging, are now being used to inform the regional breast screening program.

In Sarawak it has been possible to demonstrate that a simple health awareness program, without screening, can result in patients presenting for treatment with less advanced cancer. Similar observations have been made in South Korea. These findings should be taken into consideration by cancer control committees in determining optimal approaches to breast cancer control in the context of available resources.

Dr. N. Elsaghir, from the American University of Beirut Cancer Center, discussed the prevention and early detection of breast cancer in Arab countries. Unfortunately, tertiary prevention – i.e., the treatment of advanced disease, is the primary form of cancer control in Arab countries. Given the cost of treating advanced disease in the majority of patients, there is a need to move to secondary and primary prevention. In Lebanon and other countries, the incidence of breast cancer is increasing, in part from improved detection, and also from changes in lifestyle: increased fat in the diet, limited exercise among women, the increasing age of the mother at first birth and the frequent use of hormone replacement therapy (HRT); there is clearly a role for primary prevention. In Tunisia, approximately 5-7% of newly diagnosed cases are inflammatory breast cancer. The prevalence of mutations in genes that predispose to breast cancer (BRCA1 and 2) is unknown. Misdiagnosis, and/or negligence by primary physicians often leads to

delays in diagnosis, but other factors contributing to advanced disease at the time of therapy include:

- A low index of suspicion, especially in young women
- A “don’t worry” attitude, and presumptive diagnoses such as infection, engorgement “from pregnancy,” or engorgement “from breast feeding”
- Repeated treatment with antibiotics
- Low level of liability and accountability for medical errors in Arab countries

WORKING GROUPS: OBSTACLES AND SOLUTIONS

In the afternoon a series of working groups took place. These included:

1. Access to care/documentation (screening programs, guidelines, education/public awareness, navigation, data base)
2. Screening approaches: CBE/BSE/mammography, analogue and digital
3. Diagnosis of breast cancer: imaging and pathology obstacles and solutions
4. Treatment: developing standard multidisciplinary approaches

Each group created a report and made extensive recommendations. A complete report, including discussions and recommendations of the working groups, is available at <http://cancer-control.wikidot.com/focused-workshop-on-breast-cancer>. ■

Adapted from a report by Anthony Miller, University of Toronto, Toronto, Canada

BILATERAL EXTRAOCULAR RETINOBLASTOMA PRESENTING WITH BUPHTHALMIA AND PHTHISIS BULBI

A 2-year-old girl was referred to the JP. Hospital Garrahan from a distant province in Argentina with a diagnosis of suspected retinoblastoma. Her mother reported that she had been aware of leukocoria in the child's right eye since she was four months of age. The child lives in a rural area in a small house with her seven siblings. There is no family history of ocular malignancies. According to the mother's report, the girl was taken repeatedly to the primary care physicians, as well as ophthalmologists, none of whom recognized the potential serious implications of the finding. One month before being referred to the hospital, a rapidly growing, painful orbital mass developed and the child became blind. On physical examination, the child appeared to be in pain and severely malnourished, but neurological examination was normal. There were no enlarged lymph nodes (including the cervical and pre-auricular areas) or hepato-splenomegaly. A presumptive diagnosis of bilateral extraocular retinoblastoma was made. Investigations were performed to determine the extent of disease (i.e., disease stage). An ophthalmological examination revealed the presence of a right orbital mass and left phthisis bulbi (shrinkage of the eye) (Figure 1). Orbital and brain CT scan that showed an extensive orbital mass with calcifications in the right orbit and no evident CNS dissemination. Several skull periosteal lesions were evident on the CT scan examination. Abdominal ultrasound and bone scintigraphy were normal. A



Figure 1. Clinical appearance at presentation. Massive right orbital mass and left eye phthisis bulbi.

bone marrow examination, including bilateral aspirates and a biopsies, showed massive infiltration by non-hematopoietic cells that occasionally formed rosettes. These cells were positive for the ganglioside GD2 by immunocytology. Lumbar puncture and examination of the cytospin failed to show any malignant cell in the CSF. Other laboratory tests were normal, except for mild thrombocytopenia ($110,000/\text{mm}^3$).

The child was categorized as Stage 4 (metastatic) retinoblastoma and treated initially with chemotherapy including cisplatin, cyclophosphamide, vincristine and etoposide as per the US Children's Oncology Group (COG) protocol.

TEACHING POINTS

1) PRESENTATION WITH EXTRAOCULAR RETINOBLASTOMA

This patient presented with concomitant phthisis bulbi and an orbital mass, suggesting extraocular retinoblastoma. Extraocular retinoblastoma is distinctly uncommon in developed

countries, but it is the most common presentation in low income countries¹. However, in middle income countries like Argentina, less than 5% of cases have retinoblastoma that has extended beyond the eye. Most patients with extraocular dissemination of retinoblastoma have unilateral retinoblastoma, bilateral retinoblastoma with extraocular dissemination being less common. Even more uncommon is the presentation with concomitant orbital mass and phthisis bulbi, as in the present case. This was reported in fewer than 1% of cases in a recent series². Phthisis bulbi occurs after an ocular inflammatory episode possibly related to intraocular tumor infarction. In most cases the tumor is not visible because of intraocular disruption. The majority of patients with extraocular disease, however, present with painful orbital masses. Pain, usually a consequence of long-standing glaucoma, leads to irritability and contributes to poor nutrition. Sometimes, irritability is a

NETWORK

sign of increased intracranial pressure, such that a careful evaluation of the CNS is mandatory. Advanced extraocular disease is probably the consequence of delayed diagnosis of retinoblastoma, as is clearly the case in the present patient, who was seen by several physicians (including ophthalmologists) who failed to make an accurate diagnosis. In many countries, campaigns for increasing awareness of the presenting signs of retinoblastoma in order to promote earlier diagnosis have been launched³.

2) STAGING OF RETINOBLASTOMA

The metastatic pattern of retinoblastoma includes involvement of the CNS, which the tumor may reach either through the optic nerve or through the systemic circulation. Systemic dissemination usually presents with metastases to the bone and the bone marrow. Other sites of dissemination include the liver. Therefore, staging of extraocular retinoblastoma should include CNS imaging. Magnetic resonance imaging (MRI) is preferred in order to avoid the radiation exposure associated with a CT scan, since patients with retinoblastoma are predisposed to the development of second malignancies, particularly with irradiated sites. In our case, the more rapid access to CT scanning was felt to outweigh the benefits of MRI, since it was important to initiate therapy immediately. Bone marrow examination is mandatory and should preferably include at least two biopsies from different sites since involvement may be patchy and tumor invasion may be missed with a single aspirate⁴. The use of immunocytology examination, e.g., using GD2 as in the present case, may

increase the likelihood of finding retinoblastoma cells and confirming their identity⁴. Occasionally, circulating retinoblastoma cells may be detected in advanced cases⁵. Bone marrow involvement was suspected in this case because of thrombocytopenia, but there were no evident circulating cells.

Until recently, there was no consensus staging system for retinoblastoma and many staging systems have been developed, such that comparison of results in published data can be difficult. However, a recent international group developed a new staging system and most cooperative groups involved in the treatment of retinoblastoma have agreed to adopt it⁶. This initiative also includes the procedure, arrived at by consensus, for the pathological examination of enucleated eyes in order to have common definitions for whether there is involvement of the various layers of the eye (choroid and sclera)⁷. Complete work-up for metastases must include bone scintigraphy in extraocular cases or where there is a clinical suspicion of bone metastasis (e.g., persistent localized bone pain or swelling)⁸.

3) TREATMENT OF RETINOBLASTOMA

Patients with retinoblastoma should be evaluated by a multidisciplinary team and treated in tertiary care centers. Mutilating surgical procedures such as orbital exenteration, leading to facial disfigurement without therapeutic benefit, should be strongly discouraged⁹. Since retinoblastoma is a chemosensitive tumor, initial chemotherapy is the treatment of choice. Standard chemotherapy normally includes a platinum derivative such as carboplatin or cisplatin¹⁰, an alkylating agent such as

cyclophosphamide or ifosfamide¹¹ and etoposide^{10, 11}. Other active drugs include anthracyclines¹² and topotecan¹³. Presurgical (neoadjuvant) chemotherapy will generally permit more limited surgery - usually after three or four cycles - to be performed, e.g., orbital exenteration can be avoided^{14, 15}.

Despite being a chemosensitive tumor, extraocular retinoblastoma usually relapses with conventional treatment¹⁶, so metastatic retinoblastoma was considered to be incurable until more intensive regimens, including high-dose chemotherapy and stem cell rescue^{17, 18} were explored. A current international initiative led by the COG involves the use of high-dose chemotherapy and stem cell rescue. Such treatment is expensive and requires appropriate facilities and knowledge, which is not widely available in the developing world (it is available at the Garrahan hospital and will be used in this child). The prognosis of children with CNS dissemination, however, remains dismal, even with high-dose chemotherapy, and most cases are treated palliatively in less developed countries.

4) PREVENTION OF METASTATIC RETINOBLASTOMA

Metastatic retinoblastoma is more frequent in less developed countries, almost certainly as a consequence of delayed diagnosis¹⁹. This is a social problem with multiple causes. The INCTR retinoblastoma strategy group is conducting a survey of affected families to try to identify the factors that influenced delayed diagnosis. Many countries have launched campaigns directed towards raising public awareness that leukocoria may be an early sign of cancer³. However, it is difficult to estimate their impact, and

such campaigns need to reach a high fraction of the population to be successful. In addition, awareness of the early signs of retinoblastoma among primary care physicians, pediatricians and ophthalmologists needs to be raised. Screening of retinoblastoma would imply ocular examinations under anesthesia, which is not generally feasible in less developed countries and since retinoblastoma occurs only in 1/17,000 cases, the cost-benefit ratio is unlikely to be favorable. Screening of children in families known to be predisposed genetically to retinoblastoma, however, should be done, but even in mid-income countries only some 45% of children in this situation are screened – a sub-optimal situation²⁰. More emphasis should be given to the screening of children in afflicted families.

Delayed diagnosis is not the only factor predisposing to metastatic disease. Treatment refusal is another quite common phenomenon in less developed countries²¹. This problem requires a different solution, particularly education about the existence of prosthetic eyes (and making such prostheses available). Demonstrating their use in enucleated children could greatly allay fears of disfigurement, and sufficient time to adapt to the idea of enucleation (which is provided when neoadjuvant therapy is given first) could also be helpful. Above all, sensitivity and training of staff in discussing options and consequences with the parents is a vital component of ensuring that treatment is accepted promptly and metastasis and death, hopefully, avoided. ■

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NETWORK

A JUDICIOUS COMBINATION OF COMMERCE AND PHILANTHROPY

After congestive heart failure that put him in intensive and critical care in 2007, Raj Shah has been diligent about living under a protocol with proper diet and exercise. But even more important than his lifestyle choices that include meditation and the regimen of drugs he takes throughout the day, he says, is the personal electronic health record he carries. In the event of another medical emergency, responders can see his medical history in an instant and know how to contact the doctors who manage his chronic disease.

For Raj Shah, Chairman of Capital Technology Information Services, Inc. (CTIS) in Rockville, Maryland, information sharing is critical to effective health care, and technology holds the key, especially for chronic disease patients like him. Among the many applications of health IT are proper data collection, data management, data mining, clinical trials management, patient tracking, secure information sharing and messaging using handheld and other convenient devices for patients and family with healthcare providers.

"Information between patients, physicians, health providers and health workers needs to be shared for better care management," Mr. Shah says. "You cannot do that without interoperable health IT, and it can happen anywhere in the world."

Educated in chemistry, process engineering and business management, Mr. Shah spent the first part of his business career focused on management consulting for energy and the environment. But after three of his aunts died of cancer with-

in a three-year span, the IT expert decided to move into health care. He purchased a small company within Montgomery County's Technology Corridor in 1986 and began servicing the informatics needs of the National Institutes of Health. In subsequent years Mr. Shah developed an increasing interest in international health, which led to his relationship with the International Network for Cancer Treatment and Research (INCTR); he became a member of its Governing Council in March 2004.

Mr. Shah has a keen interest in addressing health disparity issues, both in the United States and abroad. His company has built the informatics systems for the National Cancer Institute, National Heart Lung and Blood Institute and National Institute of Allergy and Infectious Diseases. CTIS customizes and donates the software, after suitable modification, to support cancer and other chronic disease research in developing countries. Over the last several years, INCTR's Clinical Trials Office, has used this Web-based software for managing data collected by the leukemia study group in India.

"Regulatory compliance is key," says Mr. Shah. "Because of what we did for NIH, we had already developed the best practice and standards to support in-depth clinical research, including those related to patient safety, clinical practice management, adverse event reporting, and how to store and protect data. Now it is being applied to developing countries."

Mr. Shah would like to see INCTR benefit further from his efforts. "We have \$400 million invested through our NIH contracts, in the systems we've built, and they are all reusable," he says. "Everyone conducting clinical research needs health IT. A judi-

cious combination of commerce and philanthropy may be the best way to move quickly forward. India, in particular, provides new opportunities of this kind. Who would have thought ten years ago that India would be as advanced in IT as it is today?"

In addition to providing software training and support, CTIS has funded several small projects such as palliative care in Nepal and a communication portal for all INCTR offic-



Raj Shah of CTIS, Inc.

es. Most recently, in a joint project with several other organizations, CTIS worked with INCTR as lead in the area of cancer education known as the Open Educational Resources for Cancer (OREC), which will help provide online educational materials to cancer health professionals in developing countries.

Over the last ten years, counting in-kind donations and real dollars, CTIS has contributed nearly \$10 million to support international cancer research and to INCTR more than \$1 million. But Mr. Shah's assistance is not confined to finance and applications. His counsel is also of great value. Mr. Shah has advised Tata Memorial Hospital, Rajiv Gandhi Cancer Institute, Bhagwaan Mahaveer cancer hospital and research center, The Gujarat Cancer & Research Institute and other cancer institutes in his native India, smoothing bureaucratic bottlenecks

in the Ministry of Health and the Indian Council of Medical Research. He is a member of the Health IT group for the Indian Knowledge Commission.

His office walls are covered with awards recognizing his community service activities in the United States and abroad. Among his pet projects is *Community Ministry of Rockville and MobileMed*, a nonprofit organization that provides medical care to the uninsured of Montgomery County. Healthcare professionals from several local hospitals volunteer their services, and CTIS supports the IT system that maintains the electronic health records of nearly 40,000 patients.

"This is my model approach to health care in the developing world," says Mr. Shah. "The idea is to start at a grass-roots level and get local professionals to make a commitment and bring in some funds."

As part of a similar program in India, health care workers are being trained to operate mobile clinics in rural areas where there are no doctors. Trained workers will provide basic services and refer patients to government hospitals, as needed. Just as importantly, they will be able to keep track of their patients via health IT.

"The truth is that in the years ahead personalized medicine will become a reality and prevention will be a key in successfully managing healthcare costs," promises Mr. Shah. "The desire is that human beings will all come together to find solutions to our medical challenges. When a drug is developed in the U.S., Europe or India, for instance, researchers have to understand that it's needed worldwide. If patient cohorts from developing countries are not included in clinical trials, it's just not good science." ■

Marcia Landskroener for INCTR



Active and Governing Council members at the February meeting.

INCTR ANNUAL GENERAL ASSEMBLY AND GOVERNING COUNCIL MEETING 7th February, 2009

INCTR's Active Members and Governing Council gathered in Brussels early in February of this year to discuss the financial state of INCTR, progress made in 2008 and plans for 2009. Two new active members were elected (Dr. Sidnei Epelman, currently President of INCTR, Brazil, and Dr. Ahmad Manzoor, chairman of INCTR's Special Panel (an Advisory Board comprised exclusively of persons from developing countries. An important decision made by the Governing Council was to examine



View of the Bellagio Center.

and improve INCTR's use of the World Wide Web with respect to all of its activities. A special meeting will be held in 2010, to celebrate the opening of INCTR's office in Brussels. ■

MEETING IN BELLAGIO, ITALY 21st February, 2009

Dr. Magrath attended a small meeting at the Rockefeller Foundation Bellagio Center, which provides "space for framing debates on world issues, for translating theory into action and for devising creative responses to some of the most pressing issues of our time, especially those directed at alleviating poverty and vulnerability." The meeting was organized by Dr. Peter Mauch, and, in line with the decision taken by the Governing Council, Dr. Magrath was invited to speak about INCTR's work, and in particular, the use of the internet on knowledge dissemination and communication with its members and collaborators. ■

NETWORK

SARAWAK GENERAL HOSPITAL KUCHING, SARAWAK

Even on the remote island of Borneo, the incidence of cancer is on the rise. According to the most recent report from the National Cancer Registry (2003-05), nearly 68,000 new cancer cases were diagnosed among the people of Malaysia, a Southeast Asian nation of nearly 28 million people.



View of Sarawak General Hospital.

The Sarawak General Hospital, a government hospital that offers the peninsular nation's only cancer treatment facilities, devotes about 20% of its 765 beds to cancer patients. The hospital established its Department of Radiotherapy and Oncology, along with a nuclear medicine section, in 1985. Since that time, the Department has added outpatient chemotherapy, three linear accelerator units and a high dose rate brachytherapy unit, particularly useful for treating patients with nasopharyngeal cancer as well as gynecological malignancies. Although primarily a treatment facility, the oncology department also supports epidemiological studies, early detection programs and home-based palliative care, and participates in numerous international phase 2 and 3 clinical trials.

Malaysian women have a higher incidence of cancer than men (55 percent

versus 45 percent). Breast cancer is the most common cancer, followed by cancers of the large bowel and lung. In the state of Sarawak, breast cancer is the most common, followed by nasopharyngeal and cervical cancers.

NASOPHARYNGEAL CANCER

Nasopharyngeal cancer (NPC) is fairly rare in most parts of the world. In North America, it occurs in about seven of every one million people. According to a recent epidemiological study directed by Dr. Beena Devi, a clinical oncologist at Sarawak since 1992 and now senior consultant in the Department of the Radiotherapy, Oncology and Palliative Care Unit, the Bidayus in Sarawak have the highest incidence of NPC in the world. "We have seen a lot of this cancer in certain families," says Dr. Devi, "particularly among the Bidayus, one of the ethnic groups in Sarawak." Since 2002, Dr. Devi and her colleagues have collaborated with IARC, Lyon, and the World Health Organization on a genetic epidemiology study of NPC.

Doctors at Sarawak General see about 150-170 cases of NPC a year—a number that has remained relatively constant. This type of cancer is also prevalent among certain populations in China, Vietnam, Thailand, Singapore and the Philippines. In advanced stage, patients present with neck swelling; very early symptoms include unilateral nose and ear blockage and nose bleed.

"Over the years, we've been conducting an "Early Cancer Surveillance" program emphasizing the early signs and symptoms," says Dr. Devi. "We educated our rural health personnel so they could teach the people in the village. At a June 2009 meeting in Marrakech, we presented our findings demonstrating clinical downstaging in late diagnosis of nasopharyngeal cancer from 90% to about 60%."

In a study initiated by INCTR, Sarawak's oncology department is investigating barriers to late presentation of NPC, as well as the genetic aspects of the disease.

BREAST CANCER

Oncologists at Sarawak General Hospital are also seeing some progress in reaching women with breast cancer at earlier stages. Although the incidence of breast cancer is up from about 100 cases per year in 1998 to more than 250 cases per year, Dr. Devi attributes this to greater awareness of the signs and symptoms of breast cancer among rural populations. With more awareness, more women are coming forward.

"We have treated women whom I call our role models. These survivors go home to their villages and share their stories that you don't have to die of this disease."

"While Malaysia's government health care program does not support a mammography screening program — in part", Dr. Devi says, "because the disease typically strikes young, premenopausal women whose breasts are too dense to offer an accurate image — a strong community awareness program encourages women with early signs to go to the nearest rural clinic". Nurse personnel have been trained to refer patients to the nearest hospital; from there, they may be referred to Sarawak General.

"The population of Sarawak is pretty small for the size of our state [48,000 square miles]," notes Dr. Devi, "and the government hospitals in Malaysia will provide free treatment for Malaysian citizens who are unable to pay."

For patients traveling great distances to Sarawak, patients are treated and referred back to their respective referring doctors. Every six months, the smaller hospitals outside Kuching

PARTNER PROFILE

are asked to provide a list of patients who have come for follow-up. In cases of relapse, doctors in the peripheral hospital will arrange to refer patients back to the Sarawak's Department of Radiotherapy, Oncology and Palliative Care Unit for further treatment.

"The burden on the government is pretty high," Dr. Devi admits.

PALLIATIVE CARE

With her background—Dr. Devi trained in palliative care in Australia and was a hospice doctor for Singapore Cancer Society before joining the medical staff at Sarawak General—she was quick to put a home-based palliative care program into place.

"With our initial analysis in 1994, we saw that about 70% of our patients had advanced cancer," Dr. Devi recalls. "We set out to create awareness among nurses throughout the state, emphasizing pain management and nursing care. We wanted our nurses to be able to teach family caregivers. And we wanted to make sure pain medications could be delivered to the hospital or rural clinic nearest the patient's home. We began in 1995 with a small program of home visits, and began teaching families how to care for terminally ill patients."

Training sessions were initially conducted in Sarawak General Hospital, and extended to Sibu in 1996 and Miri in 1997. The program now extends to all four reaches of the state. "We know from talking to families that their main fear is not knowing how to care for the patient," says Dr. Devi. It was also up to her to negotiate with the pharmacists and the state medical director to make sure patients in even the most remote parts of Sarawak get the drugs they need for pain relief. Terminally ill patients are provided a one-month supply. If the patient dies before the end of that month, the family returns



Staff of the Department of Radiotherapy and Oncology.

the drugs to the local hospital or clinic.

"It did not happen overnight," Dr. Devi admits, "but now people are more accustomed to the idea that morphine does not cause addiction in cancer patients, and understand why it's important that pain should be controlled. When I first came here, the use of traditional medicine was quite rampant, but now using morphine is more acceptable. Even some hospital

personnel were skeptical, but when they make the home visits and see the patient spending quality time with the family, they realize it actually works."

In September 2009, the accreditation committee of the European Society for Medical Oncology has designated Sarawak General Hospital a center of integrated oncology and palliative care.

WORKING WITH INCTR

One of the most important advances in cancer management in Sarawak is not a drug, but communications technology. INCTR members have been using the interactive software to share pathology slides and to consult on diagnoses and treatment management options across thousands of miles. Dr. Devi is beginning to use the iPath program at Sarawak General.

"We have very few pathologists on staff," she says, "and with some unusual cases we would like to have a second opinion. This program has been used with some success in Vietnam, where it became an excellent tool helping pathologists learn about diagnosis. If we can use iPath to improve what we are doing, I'd be thrilled." ■

Marcia Landskroener for INCTR

INSTITUTIONAL RESOURCES

Total Beds	765
Beds Devoted to Cancer Care	130
Staff Physicians	30
Nurses	1,262
Dedicated Oncology Nurses	95
Pathologists	6
Clinical oncologists (trained in radiotherapy and chemotherapy)	3
Pediatric oncologists	1
Specialized surgical oncologists	1
Oncologists in Training	2
General and Specialist Surgeons	30
CT Scanners	3
MRI Scanner	1
Cobalt Radiotherapy units	none
Linear Accelerator units	3

NETWORK

PROFILE IN CANCER MEDICINE

ADVANCING PEDIATRIC ONCOLOGY IN PAKISTAN

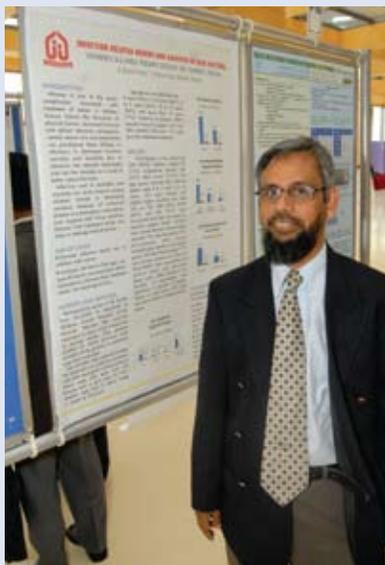
M. Shamvil Ashraf was a young medical graduate in Pakistan completing his pediatric rotation when he made himself a promise. "I looked after a few children with cancer and decided then to specialize in oncology because nobody paid any attention to those unfortunate children," he recalls. "It was my dream in 1985 that I would establish a facility for the treatment of childhood cancer in Karachi. By the grace of Almighty Allah this is now a reality."

Today, Dr. Ashraf is a consultant in pediatric oncology, chief executive of Children Cancer Hospital in Karachi, and founding CEO of the trust established to support the hospital's mission — treatment of every child with cancer regardless of a family's ability to pay.

Focused on his vision to establish a pediatric cancer facility in Pakistan, Dr. Ashraf pursued pediatric oncology training at three institutions in Ireland and the UK: the Hospital of Sick Children in Dublin, the Royal Victoria Infirmary in Newcastle, and the Alder Hey Children's Hospital in Liverpool.

"I learned the basics in Dublin and was impressed with Fin Breatnach's passion for pediatric oncology and his communication skills with parents," he says. "In Newcastle I had the privilege to work with people like Prof. Alan Craft and Andy Pearson. Working as Senior Registrar in Liverpool helped me groom myself a consultant."

Returning to Pakistan in 1995, Dr. Ashraf practiced at Shaukat Khanum Cancer Hospital, which had just opened in Lahore, and then spent two years at Ziauddin Medical University



Dr. Shamvil Ashraf presenting a poster at INCTR's meeting in Antalya, Turkey.

Hospital in Karachi. When families could not afford to pay for cancer treatment, doctors often reached into their own pockets and sought contributions from friends, relatives and other donors. In December 1999, Dr. Ashraf formalized this philanthropic instinct and established the Children Cancer Foundation to fund diagnosis and treatment and, a few years later, to establish a hospital. Children Cancer Hospital opened its first outpatient clinic in Karachi in June 2000 and soon added an inpatient facility. With a major expansion completed in July 2008, Children Cancer Hospital is now a 22-bed hospital with a 10-bed daycare and three outpatient clinics, in addition to a lab, pharmacy, departments for medical records and social services, and an emerging palliative care service.

From 1999 to 2004 Dr. Ashraf also worked with Child Aid Association to

establish a pediatric oncology unit at National Institute of Child Health, Karachi.

A founding member of the Pakistan Society of Pediatric Oncology and a member of the Pediatric Oncology Group in Karachi, Dr. Ashraf is working to define standard treatment protocols for leukemia and lymphoma in Pakistan, he notes. As a member of INCTR's pediatric oncology group, Dr. Ashraf is helping to prepare supportive care guidelines and a standardized protocol for Wilms tumor in developing countries.

In January 2008, the International Union Against Cancer (UICC) awarded Dr. Ashraf's foundation a "My Child Matters" seed grant for an outreach training program for pediatric oncology in the Sindh and Balochistan regions, to improve diagnosis and treatment of childhood cancers in Pakistan.

"The vision is to establish pediatric oncology units in the medical colleges and to develop shared care with Children Cancer Hospital," he explains. "Throughout Pakistan, we need to create awareness about childhood cancer and its excellent outcome, establish specialized centers for treatment, and make treatment affordable for everyone. These measures will help to address the major issues of pediatric oncology in Pakistan".

"Who will bring about these changes?" he asks. "Government alone cannot, as it is not its priority. The community and the philanthropists have to come forward. We should not only support treatment but also invest on cancer awareness, capacity building, clinical trials and research." ■

Marcia Landskroener for INCTR