Greetings from Donald W. Campbell,  
Ambassador of Canada.

On behalf of the Canadian Embassy in Tokyo, I would like to welcome the participants to Tokyo Medical College’s International Symposium, New Strategies in Cancer Treatment–Photodynamic Therapy.

Photodynamic therapy (PDT) promises to be an important new tool in treating cancer painlessly and effectively. Patients who, in the past, faced the ordeal of surgery, radiation treatment and/or chemotherapy may now look forward to an alternative course of treatment with a high probability of positive results. Moreover, I understand this new treatment approach reduces hospitalization costs and difficulties for patients. PDT offers new hope in mankind’s ongoing battle against cancer.

Canadian scientists have developed world class technology related to this exciting new field of medicine. The Canadian Embassy would like to extend its appreciation to Tokyo Medical College for its role in investigating PDT. After years of development PDT is now ready to revolutionize the way we treat cancer.

Canadian capability in the medical/health care industry is extensive. The government of Canada has included health care–medical devices in Canada’s Action Plan for Japan. This document is a blueprint for future development of technological and other relationships between Canada and Japan.

I would also like to thank Tokyo Medical College for hosting this symposium. I know that all of the participants will find New Strategies in Cancer Treatment – Photodynamic Therapy both interesting and informative.

2. Lecture

A Brief History and Current Status of Photodynamic Therapy

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The recent history of photodynamic therapy (PDT) began in 1972 at Roswell Park Cancer Institute when it was found that addition of fluorescein diacetate to a culture dish of tumor cells caused them to be killed when exposed to room light. This process of destruction by certain dyes and light was first reported by Raab in 1900, who noted that paramecium died in the presence of an acridine dye and light (1). Over the years various others noted similar effects and the possible application to treating cancers was explored by Tappeiner and Jesionek in the 1930’s (2) and also by Lipson in 1967 (3), However, the first clinical trial of PDT began with Mittelman and Dougherty in 1976 at Roswell Park Cancer Institute in Buffalo, New York (4). Over the next four years approximately 50 patients were treated at Roswell Park, most with various types of advanced cancers that had metastasized to the skin. The light source was a large xenon arc lamp filtered to emit red light (~590–670nm) and the photosensitizer was hematoporphyrin derivative (HpD), made and bottled at the Institute. HpD was first made by Swartz and used by Lipson for tumor detection (5). It was recognised in 1972 that HpD would be a better photosensitizer than fluorescein because of its absorption in the red (better tissue penetration) and its
high yield of singlet oxygen (60–70%), the putative cytotoxic agent in the photodynamic process. In 1978 we were visited by a group from Tokyo Medical College who were interested in obtaining our HpD for a clinical trial in lung cancer. In 1980 Hayata and Kato were the first to report endoscopic PDT to treat a lung cancer using a laser as the light source and delivery via fiberoptics through the bronchoscope. This patient achieved a complete response and many others were subsequently treated similarly. This, of course, stimulated a number of investigators to become involved in PDT. These groups also asked us to provide HpD for their trials and at one point we were supplying HpD to approximately 35 centers throughout the world. This became difficult for us, so we approached various pharmaceutical companies to become involved. No one was interested. Luckily in 1981 we were able to isolate and partially identify the active fraction of HpD which ultimately led to a patent, a key element in interesting pharmaceutical companies in PDT. However, since we still were unsuccessful in involving pharmaceutical companies, in desperation, in late 1981, several of us formed our own company (Oncology Research and Development, ORD) to manufacture HpD and the active fraction called Photofrin®. Ken Weishaupt, one of the original inventors of Photofrin®, and his father, Robert, literally with their own hands built a first class manufacturing facility in what was once a small liquor store. However, what we had not realized was that we would be frequently inspected by the U.S. Food and Drug Administration (FDA) and that each time they inspected we had to hire more people and buy more equipment. We did not have sufficient funds for this, so we brought business people into the company to help raise money. This proved very difficult, as at that time it required about $100 million to bring a new drug to market in the U.S. – it now costs about $400 million! We first tried to raise funds through the stock market but the success of new companies at that time became very low, so we again talked to pharmaceutical and laser companies. In 1985 Johnson & Johnson, one of the largest medical companies in the world, acquired ORD and moved the manufacturing to one of their plants in New Jersey. Ironically, they had great difficulty in preparing clean product. Ultimately they solved the problem and began Phase III clinical trials for approval. However, after two years they lost interest and ultimately sold the company to QLT (Vancouver, B. C.), who collaborated with Lederle Laboratories (part of American Cyanamid). This finally got the clinical trials going again and resulted in the first U. S. approval by the FDA in 1995 for obstructive esophageal cancer. The very first approval for PDT came in Canada in 1993 for treatment of bladder cancer. However, Lederle also lost interest when American Cyanamid was acquired by an even larger company, American Home Products. Essentially all control of Photofrin® was acquired by QLT (now QLT PhotoTherapeutics). Photofrin® is now approved in the U. S. (obstructive esophageal cancer; lung cancer approval is pending), Canada (bladder cancer, esophageal cancer), in The Netherlands (lung, esophagus), France, Germany (lung) and Italy (esophagus, lung) and for five early stage cancers in Japan (lung, esophagus, stomach, cervix and cervical dysplasia). Several other approvals are pending in Europe.

The success of PDT has spurred the formation of several new companies and brought existing companies into PDT, all with their own new photosensitizers. For example Phase III clinical trials for SnET2 (tin etiopurpurin) are being carried out by PDT Inc. (Santa Barbara, CA) in metastatic skin lesions breast cancer, basal cell carcinoma and Kaposi’s sarcoma, and Phase I/II trials are under way with mTHPC (metatetrahydroxyphenylchlorin) for head and neck cancer in Europe (Scotia Pharmaceuticals of Great Britain), ALA for actinic keratosis and acne (DUSA, New Jersey), a texaphyrin metallo complex (Lutex) (Pharmaceuticals, Sunnyvale, CA) for melanoma, Nep6 (Nippon Petroleum) for lung cancer, and BPD-MA (QLT PhotoTherapeutics, Vancouver, B. C.) for age-related macular degeneration. As time goes on, no doubt others will be added to this list. For example, at Roswell Park Cancer Institute we are entering a new drug, the hexyl ether derivative of pyropheophorbide-a (HPPH), into
Phase I/II clinical trials for skin cancer and advanced esophageal cancer. This chlorin type photosensitizer came out of a large study we carried out to find an optimum photosensitizer among pyropheophorbide ethers, HPPH was found to provide the optimum in vivo photodynamic activity in experimental rodent tumors and in veterinary patients (dogs/cats) and to induce the least normal tissue toxicity. It is activated at 665nm, compatible with existing diode lasers, and is predicted to produce cutaneous photosensitivity in patients for one week or less. These clinical trials will commence in late 1997.

Looking into the future is of course difficult. Certainly the type of information presented by others in this symposium, when widely known, will encourage both physicians and patients to consider PDT. The advent of diode lasers, to be used with Photofrin and other photosensitizers, will make PDT more acceptable to physicians. Some of the newer photosensitizers noted above may induce less cutaneous photosensitivity than does Photofrin, which also will increase the acceptance of this new therapy. However, this cannot be done at the expense of efficacy considering the benign nature of the photosensitivity problem. The real challenge for PDT, however, is to clearly demonstrate its superiority to existing treatments in certain types of cancers (early stage lung and esophageal cancers, for example) and to establish its place in the overall management of cancer patients.

REFERENCES


Photodynamic Therapy for Lung Cancer

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This study describes 41 patients with small lung cancers treated between January 1990 through April 1993, in a non-comparative open-label study. Conditions of treatment were homogeneous because all patients were treated in the same study center with the same laser and by only one investigator. Of the 41 patients, 38 (93%) were male and the average age was 63 years. All of the patients had superficial endobronchial carcinoma. All cases were 18 years age or older and presented histologically-proven inoperable non-small cell lung cancer which was radiologically occult (CIS or T1). The CT scan also failed to display any abnormalities. All lesions were accessible endoscopically.

Other modalities were excluded because of poor pulmonary function, inoperable general condition, recurrent multifocal lesions, failure to respond to conventional therapy or refusal of standard therapy. The majority of patients had only one tumor therapy. The majority of patients had only one tumor (83%) and most cases (81%) were squamous cell carcinoma. These included 6 CIS cases. Most tumors