I. INTRODUCTION

Photodynamic therapy (PDT) is a selective, experimental treatment for solid tumors. PDT consists of the activation of a photosensitizing agent by light. The photodynamic reaction induced by light causes damage to the tissue containing the photosensitizer in the presence of oxygen.

The idea of treating tumors by photosensitizers is as old as the early 1900's; already in 1903, the topical application of eosin and exposition to sunlight was known to produce a response in skin tumors. On the other hand, Policard, in 1924, reported reddish fluorescence in animal and human tumors observed under a Wood lamp. The presence of fluorescence was attributed to endogenous porphyrins accumulated after infection of the observed tissue by emolytic bacteria.

In 1942, Auler and Banzer reported animal tumor fluorescence after systemic administration of Hematoporphyrine (HP) and in 1960 Lipson and coworkers prepared the Hematoporphyrin derivative (HPD), a mixture of porphyrins obtained by treating HP with acetic and sulphuric acids. They demonstrated that HPD was selectively accumulated by malignant as well as by actively proliferating tissues, and demonstrated the first endoscopic diagnosis of malignant tissues by detection of fluorescence in the respiratory and in the upper digestive tract.

Since the development of the laser, diagnosis through fluorescence and particularly PDT have been intensively studied. Photodynamic reactions have different cellular targets: cross-linking of cellular membrane proteins, inactivation of mitochondrial membrane enzymes and DNA damage have been reported. However, in-vivo observations suggest that necrosis of malignant tumors may be secondary to a damage of the tumor vasculature.

The main parameters involved in PDT are: the photosensitizer, the light for activation and the selection of patients.

II. PHOTOSENSITIZERS

An ideal sensitizer should have low toxicity, specific absorption spectrum and tumor selectivity. Biologically photoactive agents can be
distinguished in (a) natural fluorochromes, such as porphyrins, (b) exo-
genous fluorochromes, such as acridine orange, fluorescein and rhodamine; and, (c) endogenous fluorochromes, such as flavoproteins and keratine. Most studies deal with the first group of natural fluorochromes and their derivatives, because they are activated by a wavelength (600-690 nm) which more deeply penetrates the biological tissues than the shorter wavelengths necessary to activate other fluorochromes.

Next to the use of HPD, Di-Hematoporhyrin Ether or Ester (DHE) is the most widely employed photosensitizer at present in clinical studies; DHE is considered the major active fraction of HPD. The drug is injected intravenously, and after an interval of 24 to 72 hours it is concentrated in malignant tissues at a variable rate of 3-4 times more than in normal tissue. HPD is administrated at dosages of 3 to 5 mg/kg body weight and DHE at 1.5-3 mg/kg body weight.

These drugs present two kinds of limitations which restrict the procedure to an experimental stage: skin photosensitization, and low tissue penetration of the light at the wavelength used for the activation of the sensitizer. The photosensitivity to sunlight, due to the drug retained by the skin, may be present for 4 to 6 weeks after the injection. Precautions must be taken to avoid exposure to direct sunlight for 30 days, and during this period patients are advised to stay indoors, cover exposed parts and protect eyes from sun rays and strong fluorescent or incandescent lighting.

Future efforts will be directed to improving the selectivity of photosensitizers, consequently allowing the use of smaller amounts of drugs, reducing cutaneous sensitization. An improved selectivity may be obtained by means of inclusion of the drugs into liposomes, or their linkage with monoclonal antibodies. Furthermore, the possible use of new drugs, now under investigation, having a high absorption coefficient in the near infrared, would improve light penetration into biological tissue, inducing necrosis of larger volumes of tumor.

Among the new drugs, some are compounds resulting from modification of porphyrins: modifying the structure of DHE by converting one or more of the porphyrin rings to chlorin (DHEC), or linking HP to chlorin, or modifying the ester and acid functions (Benzoporphyrine). Of great interest is also the use of phtalocyanines, which are porphyrin-like compounds with a main absorption band in the red; these have experimentally been demonstrated to be very efficient as photosensitizers. The action spectrum for chloroaluminium phtalocyanine (C1A1PC) is a narrow band centered around 680 nm. C1A1PC appears to be about 50 times more efficient than HPD, and the red-shifting of its action spectrum allows better light penetration into irradiated tumors.

III. LIGHT FOR ACTIVATION

There are various possibilities for obtaining sufficient amount of light to be useful for PDT. The activation of porphyrins is usually obtained with a 630 nm wavelength. This wavelength can be produced by filtered lamps, for surface application, but when an intracavitary tumor must be treated by endoscopic systems and light must be transmitted on fiberoptics, it needs special properties such as intensity, coherence and monochromacity, that are characteristic of lasers. Generally speaking, in PDT applications lasers are the most suitable sources because the photo-biological responses produced by laser-tissue interaction can be quantitatively and qualitatively superior to those caused by conventional light sources.