I. INTRODUCTION

The fluorescence of hematoporphyrin-derivative (HpD) or dihematoporphyrin ether (DHE), together with the property of attaining a higher concentration in malignant tumors than in most normal tissues, form a basis for diagnosis of cancer. Malignant tumors exhibit greater fluorescence than the surrounding nonmalignant tissue when excited by light of appropriate wavelength, and the tumor can be detected by a suitable imaging or nonimaging system. This paper discusses the fluorescent agent and background fluorescence, excitation systems, imaging methods, and nonimaging methods for diagnosis of cancer.

The photodynamic property of HpD and DHE is a nuisance in diagnosis. A nontoxic drug which is more fluorescent than HpD or DHE and less photodynamically active would be preferable, but so far none has been developed and approved for human use. Detection is limited to tumors accessible to irradiation with the exciting light, and where the emitted fluorescence can be detected, but this in principle includes a large number of carcinomas of the respiratory system, gastrointestinal system, urogenital system, eye and skin. Most of the clinical experience has been with bronchogenic carcinoma, but there is no reason why similar methods and instrumentation could not be applied to other sites.

Both imaging and nonimaging techniques have been used for detection and localization of small as well as large tumors. The imaging technique permits more precise localization, and contrast is independent of distance or angle. Nonimaging techniques suffer from field-averaging of the signal, but if compensated for variations in distance or angle, they can be made quantitative.

II. FLUORESCENT AGENTS

Hematoporphyrin-derivative, HpD, was marketed as Photofrin by Photofrin Medical, Inc. Because of a change in ownership, it is no longer certain that this agent will be available. Dihematoporphyrin ether, DHE, is still marketed as Photofrin II by the Photofrin Medical division of Johnson & Johnson. DHE is the photodynamically active main ingredient of HpD, which is a mixture of porphyrins. DHE is also
fluorescent, but there are other fluorescent porphyrins in HpD. The concentration of DHE in saline in Photofrin II is about twice the concentration of DHE in Photofrin. It appears that fluorescence emission from tumors is less with Photofrin II than Photofrin, if the dosage has been adjusted for equal photodynamic effect. The fluorescence can be increased by increasing the dosage, and as an approximate but useful rule, the dosage of Photofrin II should be about two-thirds of the dosage of Photofrin, for at least equal fluorescence yield. The photodynamic effect will be somewhat increased but acceptable. A typical dosage is 2.0 mg Photofrin II per kg body weight, or 3.0 mg Photofrin per kg.

The actual dosage required for fluorescence diagnosis depends on the amount of HpD/DHE required to exceed background from autofluorescence. Side effects from the induced photosensitivity of the skin to sunlight (or the irradiated tissue to the exciting light) also have to be considered. Most tissues fluoresce when excited by short wavelength light, e.g. violet. If the fluorescence extends to the region of HpD/DHE emission (600-720 nm, red), it will be impossible to reject all of the autofluorescence by a red barrier filter. Image contrast will be degraded, and it may be impossible to distinguish a thin, low contrast tumor from the surrounding normal tissue. Likewise, the fluorescent power collected by a nonimaging probe at a suspected tumor may be too close to the power collected from a normal or control site, compared to noise and other fluctuations. (Contrast or tumor/control ratio depends on the thickness of the tumor because a tumor thin enough to transmit some of the exciting light will emit fluorescence corresponding to the lower concentration in the underlying normal tissue, as well as higher concentration in the tumor itself.)

Figure 1 plots the spectra measured in a lung cancer patient, using a fused quartz fiber to conduct light to a grating spectrograph and EG&G-PARC Optical Multichannel Analyzer (OMA) with intensified silicon CCD detector. The tumor was large (several mm) and it is easy to discern the HpD fluorescence emission above the autofluorescence, with a spectrum