

COMMENTARY**CHROMOLYMPHOGRAPHY WITH "CHLOROPHYLL" REVISITED**

"Chlorophyll" was found to be highly useful in visualization of lymph nodes at the time of lymphadenectomy (1,2). In some investigations, however, the value of this preparation as a color marker has been questioned. These reports claimed that in several cases, dilation and stasis within lymphatics as well as rapid extravasation (24-48 hr post injection) of "chlorophyll" into adjacent tissues occurred (3,4). As a result, the application of Chlorophyllated Ethiodol (Lipiodol UF) for lymphadenectomy has remained controversial.

In recent years, new data have been collected which support the utilization of "chlorophyll" in chromolymphography. Watanabe et al (5) effectively employed Chlorophyllated Lipiodol UF, to guide the dissection of mediastinal lymphatics for surgical treatment of esophageal malignancy. Miyamoto et al (6), in animal experiments, successfully identified lymph nodes solely by endoscopic injection of an oil/water "chlorophyll" emulsion into the gastric submucosa. No complications due to the procedure occurred in these studies. Unfortunately, the generic term, "chlorophyll", was used in all publications noted here but the specified chemical structure and purity of the preparation were not described. In other words, it is uncertain whether the same preparation was used in the different investigations.

At the same time when most of the studies occurred, the main commercially available "chlorophyll" was chlorophyllin copper complex (CCC). This preparation has been known for years and is currently used as

coloring matter in the food and cosmetic industries. CCC is a mixture of a variety of chlorophyll derivatives, some of which have not been identified. Depending upon the sources of the raw material and production process employed, the composition of CCC differs widely. Moreover, contaminating substances of unknown nature may constitute up to 50% or more of CCC when the preparation is of poor quality (7). Our studies conducted with individual chlorophyll derivatives may clarify which "chlorophyll" yields the best results for chromolymphography. The compounds investigated were selected on the basis of chemical features correlated with reduction of their hydrophobicity. They included copper pheophytin, structurally similar to chlorophyll and hemin-like copper chlorophyllin identified as one of the main components in CCC. In animal experiments, none of the tested compounds, incorporated in Lipiodol UF, induced toxicity of the lymphatics. Copper chlorophyllin failed to keep the lymph nodes stained for a period of more than 2-3 days after injection. The more hydrophobic copper pheophytin, however, displayed a brighter tinting and resulted in a vivid and stable visualization of the lymphatics. A prominent borderline between lymph nodes and adjacent tissues was detected for up to 4 weeks after administration of this compound.

Clinical trials were conducted in Russia in patients suffering from gynecological cancer. 0.12% solution of copper pheophytin in Lipiodol UF was instilled gradually in lower extremities with an automatic injector.

Excellent identification of the lymphatics and the lack of adverse effects indicate that copper pheophytin is an effective and safe color marker for lymphadenectomy (8, unpublished results).

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Editor Comments:

*In recent years, there has been a resurgence of interest in the use of coloring matter to visualize the lymphatic system and particularly to highlight regional lymph nodes. It is noteworthy that more than 50 years ago McMaster summarized the first attempts in patients to gain insight into lymph dynamics with disease states including renal and cardiac failure [McMaster, PD. *Lymphatic participation in cutaneous phenomena. Harvey Lecture (1941-42)* 37:227-268]. Subsequently, Kinmonth extended this "dye test" to facilitate cannulation of peripheral lymphatics and ultimately brought to the clinical arena the technique of conventional oil lymphography. As Dr. Chernomorsky indicates, staining lymph nodes to help visualize them at operation ("chromolymphography") has been popular in some clinics to make nodal resection more accurate. Ironically, others have suggested to limit removal of lymph nodes after intradermal injection of a vital dye by identifying the sentinel nodes in the groin and axilla to stage, for example, malignant melanoma or breast cancer. Thus, if after intradermal injection of a vital dye the immediate draining or sentinel node is colored and on frozen section is negative for metastasis, then further resection of the regional lymph node chain is averted. [Giulano, AE, DM Kirgan, JM Guenther, et al. *Lymphatic mapping and sentinel node biopsy for breast cancer. Ann. Surg.* (in press).] If this technique proves reliable, that is with few false negatives and false positives, it would substantially reduce the sequelae of peripheral lymphedema that follows in the wake of radical groin or axillary dissection. [CLW]*

Also see Editorial by Hirnle in this issue.