Unproven Methods of Cancer Management

The following statement was recently distributed to the 58 Divisions of the American Cancer Society for their information:

Lewis Methods

After careful study of the literature and other information available to it, the American Cancer Society does not have evidence that treatment with the Lewis Coupled Tumor Protein Antigen (CTPA) results in objective benefit in the treatment of cancer, or that the Lewis Test is a proven method of diagnosing cancer in human beings.

The following is a summary of information on the Lewis Methods, including the Lewis Coupled Tumor Protein Antigen (CTPA) and the Lewis Test, in the American Cancer Society files as of November, 1971:

Therapy

The Lewis Coupled Tumor Protein Antigen (CTPA) or "Human Tumor Diazo-Rabbit Protein Complex" is described in a leaflet distributed by Lewis Laboratories, Inc., in June, 1971, as consisting of "a soluble extract of human tumor protein chemically coupled to purified rabbit serum protein by bis-diazotized benzidine." Administration is by injection. The leaflet adds: "The injection is to be administered by BOTH the intramuscular AND the intradermal routes. The injection is administered into the properly prepared site on the anterolateral aspect of the patient's thigh by injecting 0.8 ml intramuscularly, partially withdrawing the needle, and then injecting 0.2 ml intradermally. Intradermal injection is assured by the formation of a small bleb. The patient should receive an initial injection followed by subsequent injections seven days apart. Each injection is given after the patient's serum has been tested for circulating antigens (Lewis Test) and circulating anti-tumor antibodies (Lewis Anti-Tumor Antibody Titre Test).
When the Lewis Anti-tumor Antibody Titre demonstrates that the patient’s serum has circulating antibodies greater than one part in eight (1:8) detectability, then subsequent injections should be suspended until the antibody level diminishes. . . .” (Capitalization in leaflet.)

In a section titled “Adverse Reactions,” it noted: “Patients may develop an Arthus-like reaction at the sites of injection. . . . Latent local exacerbations of the injection sites may occur. Since a foreign protein, i.e., rabbit serum, is employed in the production of Lewis CTPA, one should be aware of the possibility of systemic allergic-type reactions. . . . In addition to the local reactions, a fever of short duration may occur and the use of aspirin usually suffices to control this. . . .”

In 1966, Andrew J. Lewis, President of the Lewis Laboratories, Inc., was involved, as Director of the Laboratory of Cancer Virology and Immunology of the Rand Development Corporation, in the development of the Rand Coupled Fortified Antigen (RCFA), also identified as Human Izo Antigen-Diazo-Rabbit Hetero Antigen Complex, or Human Tumor-Diazo Rabbit Gamma Globulin Complex. This vaccine was reported to be an extract of soluble proteins from homogenized tumor tissues obtained from biopsies and autopsies, coupled with rabbit gamma globulin. It was prepared by the Rand Corporation and administered by injection, both intradermally and intramuscularly, into the anterior lateral aspect of the patient’s leg.

Test

According to an undated brochure, distributed in 1969 by Lewis 3-D Test, Inc., and designated by Andrew J. Lewis, President, as giving factual information, the Lewis Test, also known as the 3-D Test and the Delayed Double Diffusion (3-D) Test, utilizes a modified Ouchterlony technique with a reagent manufactured from horse plasma containing antibodies against human neoplasma. Known positive and negative human sera are used as controls. The test is an immuno-diffusion procedure which requires a specially prepared agar with inoculating wells pre-cut in a pattern prescribed by the developer, with four central wells, each surrounded by four smaller peripheral wells. "The peripheral wells receive unknown test sera or controls and the central well the test reagent. Diffusion is allowed to proceed for up to 24 hours, at which time the plate is examined using a hand lens and a diffuse light source. Precipitin lines which have formed between the peripheral and central well indicate positive results. The absence of such precipitin lines indicate negative results." Test results, according to the brochure, "are reported as either negative, questionable, or positive with positive results quantitated as weak, medium, or strong." It also notes: "It is extremely important that the results of the Lewis Test be interpreted within the test parameters. The clinical status of the patient must be known before any conclusions are drawn. A positive result indicates the presence of cancer only when the patient is known not to have either any recent tissue damage, recent trauma or traumatizing surgery, or any infectious, inflammatory, or necrotizing tissue processes. . . . False negative tests may result from effective antigen suppressant therapy. Occasionally an unexplained false negative test result is encountered." (Underlining theirs.)
The brochure also contains a protocol recommended when a positive Lewis test is obtained on an apparently healthy patient, which includes: (1) a repeat Lewis test in 30 days; (2) "if the repeat Lewis test is also positive and criteria of a valid test are present," they recommend "a complete cancer work-up investigating the most common malignancies according to age and sex of patient. . . . Failing to establish a diagnosis of malignancy, the Lewis Test should be repeated every three months until a diagnosis is established or the Lewis Test is repeatedly negative." If the repeat Lewis Test is negative, they recommend repeating the test every three months for one year, then every six months for one year, then annually, "provided each test yields a negative result." If at any time the repeat Lewis Test is positive, the procedure under (2) above should be followed.

In a letter to prospective users of the test accompanying the brochure, Mr. Lewis stated that "whole blood is not acceptable for the Lewis Test. The test is conducted on unhemolyzed serums only. The serums should be at least one milliliter (1 ml) by volume. The cost of each Lewis Test to the patient is $10.00. Your per serum specimen collection and handling fee is twenty per cent or $2.00. The test may be conducted only on patients who are referred by Ohio physicians." A paper which appeared in Medical Lab, July 1968, stated: "The test requires two reagents; (made by him (Lewis) (A) anti-human abnormal antibody and (B) anti-human-malignant antibody. Reagent A absorbs low to moderate levels of abnormal serum constituents which seem to be the source of false positives in earlier attempts to detect cancer immunologically by Ouchterlony techniques. Reagent A is derived from horse plasma that has been immunized by non-neoplastic human tissue protein extracts. Reagent B contains anti-human malignant antibodies of horse origin, similarly prepared, using human neoplastic tissue as antigen. The 3-D Test also requires control sera from known positive cancer patients as well as normal healthy patients."

According to the Brochure, the Lewis Test is also recommended for evaluating therapeutic results during treatment of cancer patients. The Lewis Test was first described as the Rand Delayed Double Diffusion (3-D) Test in a preliminary report in Cancer Cytology, July-December 1966, by Andrew J. Lewis, B.A., H. J. Rand, D.Sc., and J. Ernest Ayre, M.D. According to the Medical Lab article in 1968, this test, developed by Andrew J. Lewis, "is called a delayed double diffusion or '3-D Test' by Lewis." In a communication to the Ohio Division of the American Cancer Society in August 1969, Norman H. Daily, Vice President of Lewis 3-D Test, Inc., reported that the corporation "acquired the legal rights to the 3-D Test from the Microlog Corporation of New York in the fall of 1968 and has since researched, developed, and further improved the test and assigned the name 'Lewis Test' in honor of its developer, Andrew J. Lewis."

Mr. Daily added: "On March 3, 1968, Lewis 3-D Test, Inc. was granted approval from the Department of Drugs, State of Ohio, to manufacture and distribute the Lewis Test reagents within the State of Ohio. Accordingly, our corporation is now engaged in the distribution and sale of the Lewis Test to pa-
thologist-directed laboratories in hospitals throughout this state."

The Lewis brochure contains a chart summarizing tests conducted on 3,981 patients, which included 961 cancer patients, and claimed the following result: "The test correlation with histopathology is 91.46%. Also included were 303 specimens from six, noncancerous or presumed cured cancer patients yielding a test correlation of 91.74%. Even if the 38 additional specimens from patients who exceed test parameters are included the correlation is 81.11%. In addition, 2,680 clinically healthy patients were tested and showed a correlation of 99.70%. Overall accuracy, wherein true results are divided by the total of true plus false results, is 96.20%."

A letter received from a Cleveland physician stated that in late September 1971 Mr. Lewis had reported that he was no longer marketing the Lewis Test as a cancer test, but rather as a test for C-reactive protein.

**Rationale**

In the Lewis CTPA leaflet, it states: "Lewis CTPA is designed for use in histopathologically proven cancer patients as a therapeutic. Hypothetically its efficacy results from the combination of soluble human tumor antigens in combination with antigen of a foreign species, namely rabbit serum protein. While undergoing CTPA therapy, the patient will develop an immune response to the rabbit protein portion of the coupled drug due to species differences. This immune response is manifest as human anti-rabbit serum antibody. Because the rabbit serum protein is coupled to human tumor protein antigen an immune response against the human tumor antigen portion of the drug also develops. This immune response is manifest as human anti-human-tumor antibody. Consequently these human anti-tumor antibodies precipitate, in vivo, those tumor antigens which are continuously being spilled into the patient's blood stream. When the rate of precipitation of tumor antigens (due to reaction with Lewis CTPA induced antibodies) exceeds the rate of tumor antigen being spilled into the blood, therapeutic efficacy of the drug is reflected in reduced quantities of new tumor antigens being introduced into the patient's blood stream. Such efficacy may also be demonstrated by lack of metastasis and regression of tumor mass, indicating that antitumor (CTPA) antibodies are attacking the tumor antigens at the cellular level."

In April, 1971, the (Cleveland, Ohio) *Plain Dealer*, describing the experimental studies conducted by Dr. Michael J. Phillip on mice with Lewis CTPA, reported: "Dr. Phillip said the team believes the vaccine helps the animal's system build antibodies against the gamma globulin. As a side effect, it works against the tumor antigen to which the gamma globulin is linked. In effect, it uses the mouse's immunity system to fight the invading cancer. He told the *Plain Dealer* that he believes this is a new approach to the problem."

A discussion of the Lewis Test in *Oncology* in 1971 stated: "It is possible that the positivity of the Lewis Test is related to some chemical stimulus directly related to the chemotropic properties of plasma cells. It is also possible that the degree of positivity may be due to the serum or plasma concentration of a protein factor with immunologic properties."
Whatever the nature of that factor, it is apparent that when the criteria of the Lewis Test are scrupulously observed and the test is made to aid in the detection of cancer, statistics indicate that a positive result shall be considered reason to suspect with better than 90% probability that the disease exists in the person being examined. "6

Proponents

According to an article in the Cleveland Press in June, 1971, Andrew J. Lewis, "37, graduated from John Carroll University in 1966 with a bachelor of arts degree. He majored in English and minored in chemistry. "7 The earliest reference to Mr. Lewis in our files was in a news item in the Health Bulletin in July, 1965, referring to him as the new Director of the Laboratory of Cancer Virology and Immunology of the Rand Development Corporation. "8 In a communication to the Ohio Division of the American Cancer Society in August, 1969, Norman H. Daily, Vice President of Lewis 3-D Test, Inc., reported that "Mr. Andrew J. Lewis resigned from Rand Development early in 1968 and has since May 6, 1968, been President of our own corporation, Lewis 3-D Test, Inc."

Norman H. Daily, B.Sc. was designated in a report in Medical Lab in July, 1968 as Laboratory Director for the Foundation for Oncological Research, Willoughby, Ohio. "9 In 1969, he signed correspondence as the Vice President of Lewis 3-D Test, Inc. In June, 1971, he was referred to as the Vice President of Lewis Laboratories, Inc.

Lewis 3-D Test, Inc. was established in May, 1968, according to Mr. Daily. In April, 1971, the Cleveland Plain Dealer referred to it as the Lewis Laboratory of Cancer Research. "5 The Cleveland Press in June, 1971, referred to it as Lewis Laboratory, Inc., "at 3756 Lee Rd., Shaker Heights," and added: "Employees include himself (Lewis), Norman H. Daily, the vice president, and their two wives. They sell no stock, financing the firm instead out of Lewis' income as a parttime real estate salesman and Daily's outside income as director of medical laboratories in Painesville and Willoughby, according to Lewis. Neither Daily nor himself is paid Lewis said. "17

Investigation

In April, 1971, an article in the Cleveland Plain Dealer stated that in a paper presented at the 80th meeting of the Ohio Academy of Sciences in Akron on April 23, 1971, Dr. Michael J. Phillips, Associate Professor of Biology at John Carroll University, reported that in a study of 100 mice in which adenocarcinoma was implanted, and which were then treated with CTPA, "13 showed no increase in tumor size. The remainder had tumors growing to a mean volume of .48 cubic centimeters. The growth rate in untreated mice was five times greater, to a mean volume of 2.58 cc. "15

A news release dated June 1, 1971 from John Carroll University began: "Clinical trials will begin in Ohio this month on a vaccine designed to fight cancer growth in cancer patients. The vaccine, developed and manufactured by Lewis Laboratory for Cancer Research . . . is available to Ohio physicians who request it for clinical treatment of cancer patients. "9 Identifying the vaccine as Lewis Coupled Tumor Protein Antigen (CTPA), the release stated that "it is a variation of an antitumor vaccine recently tested successfully..."
on research animals at John Carroll University here."

Cleveland newspapers in June quoted Mr. Lewis as stating that he had notified the Cleveland Academy of Medicine in March "of his intention to move into . . . clinical trials," and that "letters seeking physician investigators . . . went into the mail starting on April 19." He also stated that as of that date (June 14) ten to thirteen doctors were "participating in the experiments with humans throughout Ohio."

On June 14, 1971, the Cleveland Press reported that the Cleveland Academy of Medicine was critical of the methods of Lewis' solicitation of patients for clinical trials and questioned the value of the drug. The academy advised doctors to continue withholding their participation until the experiments meet standards to which the academy subscribes and until they are directed by competent doctors. The academy had neither accepted nor rejected the drug.

In reply, the newspaper quoted Mr. Lewis as stating: "We are soliciting physicians to act as investigators in treating their own patients who might have run the gamut of conventional therapy and who—in the opinions of their doctors—would be considered terminal patients." Academy President, Dr. John J. Gaughan pointed out that the random appointment of physicians in private practice as 'clinical investigators' did not meet the requirements for scientific investigation to which the Academy subscribed.

Prior to this, an evaluation of the Lewis 3-D Test was carried out by a subcommittee of the Cleveland Society of Pathologists, with Mr. Lewis conducting the test in his laboratories on samples provided by the Subcommittee. In June, 1971, a report was received that of 246 cases considered in the final evaluation, consisting of 161 benign and 85 malignant specimens, results were as follows: in the benign group, there were 81 negative and 80 false positive; in the malignant group, there were 42 positive and 43 false negative.

References

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