Portable Pumps and Controlled Drug Toxicity
Keep More Patients Ambulatory and at Home

The need for close monitoring of chronically ill patients has traditionally led physicians to hospitalize these patients. But advances in therapy and technology are allowing more M. D. Anderson patients to benefit from outpatient therapy either in the Ambulatory Treatment Center—the outpatient chemotherapy area—or even their own comfortable homes. It’s less expensive, more convenient, and, most important, just as effective as inpatient treatment.

"Physicians at many institutions are conservative in evaluating patients for hospitalization, but I think that's changing as a result of economic hard times, DRGs, and advances in technology," said Peter McLaughlin, M.D., associate professor, Department of Hematology, and member-at-large of the Patient Education Chemotherapy Committee.

Primary obstacles to effective outpatient treatment are toxicity and complex administration schedules of chemotherapeutic agents. The hydration needed for therapy with cisplatin, for example, once required patients to be hospitalized for close monitoring and hydration. Now the necessary supervision can be achieved during the patients’ treatment in the Ambulatory Treatment Center. Twenty-four-hour-a-day continuous infusion therapy with doxorubicin, for instance, can also be done by outpatients with the portable infusion pumps now available. Recent reports have suggested that the cardiotoxicity of doxorubicin is reduced if the drug is given as a continuous infusion over a prolonged period, McLaughlin said.

Complications Caused by Toxicity

Even though toxic effects generally can be reduced to allow outpatient therapy, some patients still need hospital monitoring. Patients who are debilitated by underlying diseases or by cancer-related problems may need inpatient monitoring. "A patient with congestive heart failure who is receiving cisplatin needs careful regulation of intravenous fluids. Overhydration could easily exacerbate the heart failure. On the other hand, another patient on the same protocol might be treated as an outpatient. Underlying medical problems affect our decision on whether or not to admit a patient to the hospital," McLaughlin said.

We’re always looking for ways to keep patients out of the hospital.

Similarly, diabetic lymphoma patients undergoing treatment with the ESHAP protocol (etoposide, methylprednisone [Solu-Medrol], cytarabine [high-dose Ara-C], and cisplatin) or other steroid-containing regimens may need careful inpatient monitoring. "The steroids can aggravate the patient’s diabetes," McLaughlin explained, "but non-diabetics can receive ESHAP as outpatients."
Chemoprevention of Colorectal Cancer

by Michael J. Wargovich, Ph.D.
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Consider the average individual at risk for colon cancer. What risk factors come to mind?

Certainly one recognizes age as a factor: cancer of the colon and rectum has often been called a disease of the elderly. The average age of the 150,000 Americans who will develop colorectal cancer in 1988 will be 50 years or more. In light of this association, persons over 40 are often advised to have a digital exam as part of an annual physical examination and, beginning at age 50, a periodic sigmoidoscopic exam.

But what other factors are associated with risk? Cancer of the colon is also considered a genetic disease, genetic predisposition often manifested by such premalignant syndromes as ulcerative colitis, familial polyposis coli, Gardner's syndrome, and Lynch family syndrome, each with diagnostic features familiar to physicians.

But the risks related to familial or genetic factors account for only 10% to 20% of colon cancer patients seen in the clinic. Cancer of the colon is also considered an environmental disease, and research has focused predominantly on aspects of the human diet as possible causes. Demographic and epidemiologic investigations have pointed to profound dietary differences among populations throughout the world. Largely, these investigations implicated amounts and types of macronutrients as risk factors in colon cancer. Ingestion of high amounts of dietary fat was suggested as a causal factor, for example, whereas the consumption of fiber-rich fruits and vegetables seems to confer protection.

Recent laboratory studies also identified micronutrients, substances included in the diet in small quantities, that have the ability to retard, inhibit, or in some cases reverse the neoplastic process. Active micronutrients that prevent or inhibit cancer have been called chemopreventive agents. In this sense, chemoprevention, which describes this new discipline of cancer research, encompasses studies involving prevention of cancer through use of naturally occurring agents.

Chemopreventive Agents

Compounds of potential use in preventing human cancer have been identified through in vitro, animal, and epidemiologic studies. This work, sponsored mainly by the National Cancer Institute's Chemoprevention Branch, has already yielded a number of agents that survived the rigorous journey from animal screening and efficacy studies to incorporation into clinical trials with patients at high risk for cancer.

Most of the current effort has concentrated on natural and synthetic forms of vitamin A. Trials of beta-carotene and its analogue, 13-cis-retinoic acid, are in progress at several medical centers. In our department, the first clinical trial using beta-carotene or 13-cis-retinoic acid will begin soon for patients with oral leukoplakia, a lesion that often precedes oral cancer. Waun Ki Hong, M.D., chief of the Section of Head and Neck Oncology, is the principal investigator.

Vitamin A is found in precursor compounds, carotenoids, in green and yellow vegetables, and in dairy products; it is stored in the liver. The carotenoids are active inhibitors of several carcinogen-induced cancers in animals, but at high doses both the carotenoids and retinoids have toxic side effects. The adverse nature of vitamin A compounds is being investigated, and new analogues that have low toxicity yet retain their chemopreventive activity are being made.

One phenomenon noted from the vitamin A studies represents a generalization of the chemopreventive agents' activity: high doses seem to be needed to attempt to reverse the neoplastic process. Because of the possibility of reaching toxic thresholds, human cancer chemoprevention trials are conservatively managed and the patients tightly monitored for adverse effects.

Other kinds of chemopreventive agents abound in foods. Vitamins C and E, present in citrus fruits and many vegetables, have been shown in laboratory studies to block the formation of nitrosamines, suspected to be etiologic agents in several types of gastrointestinal cancer in humans. In a current NCI-sponsored trial, physicians seek to determine whether large doses of both vitamins prevent the recur-
rence of rectal polyps in patients who have had "cleaning" sigmoidoscopy. Compounds under experimental investigation in animals include the minerals selenium and calcium, protease inhibitors (found in legumes), thioethers (in onions and garlic), terpenes (in citrus fruits), indoles and isothiocyanates (in cruciferous vegetables), phenolic acids (in many fruits and vegetables), and several forms of dietary fiber.

Evaluation of Chemopreventive Agents

Based largely on epidemiologic and natural product chemical studies, we are evaluating prospective cancer chemopreventive agents in a number of animal models. The first step in the evaluation is to test the agent in in vivo screening assays, which are designed to gain information rapidly, in weeks rather than months, about an agent's activity. The assays in this category include DNA-binding and damage assays and inhibition of such cytogenetic endpoints as micronucleus formation. Our laboratory is under NCI contract to perform these "first-pass" studies of chemoprevention agents.

Promising agents that pass the initial screening will be scrutinized in extended studies with animals. The tests, intended to determine the suppression of chemically induced cancers, require chronic exposure of animals to the potential cancer-inhibiting agent. Animal tumor models selected for these studies are those with high relevance to the most common human cancers, those of the colon, breast, lung, skin, pancreas, and prostate. Dosage and efficacy will be formulated, side effects noted, and a preclinical pharmacology assessment made. These data will permit the design of phase I clinical intervention trials, and this poses a larger question. Which groups of patients are candidates for cancer chemoprevention trials? How to identify the person at high risk for cancer is a significant challenge for clinicians and researchers.

Candidate for Chemoprevention: The Person at High Risk

Chemoprevention trials must necessarily involve persons at high risk for the common malignancies such as cancer of the breast, lung, or colon, diseases with long latency periods before they are diagnosed. These cancers share the problem of difficult clinical management when the disease has progressed. Cancer prevention trials using malignancy as an endpoint are unfeasible because of such trials' duration and cost. The more common cancers, however, often have associated premalignant indicator lesions—dysplasia of the cervix, actinic keratoses of the skin, and adenomatous polyps of the colon, for example—that could serve as endpoints. As mentioned, genetic predisposition often takes the form of recognizable syndromes. Familial polyposis is characterized by an autosomally dominant, inherited disorder that causes the formation of many polyps in the colon; familial polyposis patients, therefore, participate in several chemoprevention trials currently under way.

More work needs to be done to identify the asymptomatic high-risk individuals in the general population. New laboratory techniques may become available to gauge risk long before the appearance of an indicator lesion. At our institution, this approach might include initial screening in the Special Risk Clinic of the Community Oncology Program headed by Rodger Winn, M.D. After a patient's medical evaluation in the Gastrointestinal Oncology and Digestive Diseases Clinic, biopsy samples would be tested in research laboratories for biological markers of high risk. Parameters to be measured would include in vitro measures of cellular proliferation (thymidine kinetics and polyamine levels), DNA ploidy, expression of selected oncogenes, and expression of molecular markers for growth factors and differentiation. Researchers and clinicians could then judge—based on family history, health status, and biological markers—whether the individual indeed has a high risk of developing colon cancer. Then the patient could choose to enter a chemoprevention protocol or be assigned to rigorous follow-up, or both.

Promising New Agents

Work in our laboratory has focused on two promising agents for the prevention of colon cancer. Diallyl sulfide, a naturally occurring sulfur compound found in certain members (garlic and onions) of the *Allium* family, was shown in experimental trials substantially to protect mice from developing colon cancer, despite their exposure to a potent colonic carcinogen. We recently showed that the same compound completely inhibits experimentally induced esophageal cancer in rats; now we are trying to identify the mechanism by which the sulfur compound confers protection.

In investigations of calcium and its ability to control cellular proliferation induced by a fat-rich diet, we showed that calcium added to the diet regulates the cells' stimulus to proliferate; and in patients at high risk for colon cancer studied elsewhere, calcium was shown to modify mucosal proliferation. The mechanism may be linked to cancer prevention. Our clinical efforts include a recently begun protocol to examine the effect of added calcium carbonate on mucosal proliferation in patients who had polyps of the colon removed. By comparing proliferative markers before and after introduction of calcium, we hope to add to the accumulating information that increased calcium intake may help to prevent colon cancer.

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Clarifications of Tumor Cell Diversification
Bring New Ideas for Stopping the Process

Two UT MDAH scientists who last fall were awarded Outstanding Investigator Grants by the National Cancer Institute discuss their work from somewhat different views, but the central point is the same: Isaiah J. Fidler, D.V.M., Ph.D., chairman of the Department of Cell Biology, and Garth L. Nicolson, Ph.D., chairman of the Department of Tumor Biology, test new ideas to learn how cancer cells diversify and move to new sites in the body. Both are concerned with the heterogeneity of these mechanisms and with translating the knowledge to treatment.

The National Cancer Institute awards are encouraging to the scientists and their teams because the grants are a generous recognition of long-standing productive cancer research and because the sums—$3.35 million to Nicolson’s research group and $2.45 million to Fidler’s for the next seven years—relieve the scientists of some of the administrative burden of frequently renewing grant support for their work.

Among Fidler’s many recent publications is a review written with Charles M. Balch, M.D., head of the UT MDAH Division of Surgery, “The Biology of Cancer Metastasis and Implications for Therapy,” in the March 1987 issue of Current Problems in Surgery.

In it the authors emphasize that the major goal of surgical and clinical oncologists “remains the prevention or eradication of cancer metastasis,” and in some 70 pages of fairly brusque, clear prose they explain what is known about the development and spread of metastatic cells.

Patterns of cancer growth and spread are not random, although many of the genetic and biochemical processes are not yet understood. What is known now, however, is that by the time a tumor is diagnosed, it may be biologically heterogeneous and may already have spread to regional or distant sites. This biological diversity has important implications for research and for therapy.

Obstacle to Treatment
The emergence of metastases in organs distant from the primary tumor is the most devastating aspect of cancer, Fidler said in an interview, and the biologic heterogeneity caused by the constant evolution of tumor cells is the greatest obstacle to successful treatment. This implies that effective treatment must result in the eradication of all cancer cells, which so far has not been possible.

Fidler and his group are now studying freshly isolated human neoplasms to identify their normal and neoplastic cell populations and the genetic and epigenetic mechanisms of tumor progression. In these studies in vitro and in investigations with mice, the researchers hope to clarify both the diverse characteristics of metastatic cells and their growth in different organ environments.

One promising approach to eradicating tumor cells that resist conventional therapies is the systemic activation of macrophages, which are cells engaged, among other functions, in recognizing and disposing of aged cells, cellular debris, and foreign invaders.

The tendency is to treat with acute methods a disease that took years to incubate.

“We hope to learn, generally, the role of macrophages in the pathogenesis of cancer metastasis and to understand how activated macrophages discriminate between tumorigenic and normal cells. Specifically, we want to achieve maximal stimulation of appropriate macrophages in patients to destroy treatment-resistant tumor cells, and some of these methods are now being tested in the clinic,” Fidler said.

Information gathered on cell heterogeneity and tumor spread, so far, he said, leads to questions that may be bothersome to clinicians because “the human tendency to categorize things, to put things in boxes, has led to broad cancer categories that may be inadequate for developing effective treatment.”

The etiology of colon cancer, for example, is likely to be different in a patient who is 20 years old from one who is 70—the
20-year-old person has not had time to develop diet-related disease, Fidler said. As for melanoma, "10 different patients with the same type of melanoma of the skin may represent 10 different stages of disease, and each tumor may be heterogeneous within itself."

By the time they are diagnosed, Fidler said, melanomas and many other cancers contain diverse cell populations with different characteristics of growth rate, karyotype, cell-surface properties, immunogenicity, marker enzymes, sensitivity to cytotoxic drugs, response to radiation, ability to invade and produce metastasis.

**Take Advantage of Differences**

Treatment protocols might be designed to take advantage of the cellular and developmental differences of neoplastic diseases. Certainly, a malignant tumor that has an incubation period of two to three weeks and is in an explosive phase requires rapid treatment, Fidler said. But the "mirror image of this is that chronic forms of cancer may not be amenable to acute treatments."

Most cancers do not develop in days or weeks, in some cases not even months, he said. "We suspect a prolonged etiology of years. Melanoma, for example, may occur in individuals who were exposed to UV light during their early childhood. So when an infant runs on the beach naked, the initiating events of melanoma may take place then, but the disease may develop years later. The tendency is to treat with acute methods a disease that took years to incubate. We want to see tumors melt away, regress in weeks. This may work in the case of some tumors, but for others it may not be the logical approach because the cells follow a different biologic schedule."

Data from his and Nicolson's laboratories, Fidler said, show that metastatic growth in an organ environment is a highly selective process that depends on both tumor cell properties and organ characteristics. Scientists in Nicolson's group, for example, are isolating metastatic tumor cell growth factors unique to certain organs, and in Fidler's laboratory researchers are looking for ways to short-circuit the contribution of the host organ to the growth of metastases.

That knowledge will lead to better subdivision and better classification of patients—"better rather than busier"—and to better treatments, Fidler believes. "We can now image some tumors with monoclonal antibodies. And we can identify the presence of some cancers by circulating carcinoembryonic antigens. I believe that when new ideas prove effective, they will be embraced."

**Cytotoxic/Cytostatic Therapy**

"Some of the ideas we are trying to develop here," Nicolson said, "are not so much new therapies as better use of existing ones. Right now cancer is being treated, for the most part, with cytotoxic agents to kill as many cancer cells as possible. But this allows the survival of certain cells, usually the ones that are most unstable and diversify rapidly. This leads to wave after wave of cytotoxic therapy against an ever more refractory and metastatic cell population."

To interrupt this process—to cause tumor cells to stop diversifying after they survive cytotoxic therapy—Nicolson and Reuben Lotan, Ph.D., are studying the alternation of cytotoxic and cytostatic treatment cycles, using as cytostatic agents biologic response modifiers like interferons, differentiation factors, and vitamin analogues. These can stop tumor cell division while the organism recovers (so far the work has been done in mice) before a new hard-line cytotoxic agent is used again. A patient might undergo this kind of two-sided treatment for years, unlike therapy solely with toxic drugs, which is limited by toxicity and the diversification of surviving tumor cells.

What looks like randomness...may actually be built-in diversification.

**Fetal Process Turned Back On**

In the case of cellular proliferation, Nicolson said, "we believe that what looks like randomness or heterogeneity may actually be built-in diversification. It's not accidental that fetal characteristics crop up in cancer development, because we are learning that genetic programs that encode these fetal characteristics are inadvertently turned on in cancer. Many cancer markers we thought were specific for cancer are actually developmental markers. Two of these are carcinoembryonic antigen and alphafetoprotein, which are expressed at high levels during embryonic diversification and differentiation of certain tissues."

Cancer cells often go back to a more "primitive state," he explained, which means that genetic programs that control diversification and heterogeneity somehow became active. "Ultimately, to really understand what's happening we need to understand the genetic basis of these mechanisms. Primitive tumors that diversify rapidly and take on more malignant characteristics seem to be similar in many ways to cells at early embryonic stages, which are times when they can literally metastasize to different parts of the developing organism. In adult tissues, these characteristics are believed to be inappropriate."
A reader survey in the April-June 1987 issue of *OncoLog* was designed to tell us who our readers are and how well the newsletter's content fits their interests.

We found that we have a substantial, enthusiastic audience of physicians, most of them specialists in private practice, located mainly in urban and major metropolitan areas of the Southwest but spread all over the globe. These readers want information on new developments in cancer research and treatment they can relate to the care of their patients. Seventy percent of the respondents treat cancer patients, and for about 40% cancer treatment is the major focus of practice. Readers like *OncoLog* as it is, though they made valuable suggestions for improving the editorial direction.

Among 465 respondents...

87% read every issue,
12% read two or three issues a year, and 1% read one a year.

We received 479 responses to the initial survey: 98% of the respondents said that they read *OncoLog*, and 2% do not. This kind of survey does not tell how many nonreaders we have, so to learn how many nonreaders correspond to our total mailing list of more than 31,000 names, we sent a separate survey to 100 people selected at random from the whole list. Of 37 respondents to that survey, 73% read *OncoLog*, 13.5% do not, and another 13.5% said that they do not receive it. (Since those names were all drawn from our mailing list, we can only assume that the newsletter gets lost in the mail or is filed or discarded before it is read.)

In the initial survey, the seven respondents who did not read the newsletter cited lack of interest or nonapplicability to their fields as reasons for not reading it. Some respondents said that they are retired and no longer interested; in contrast, others said they are retired and finally have time to do some leisure reading in medicine; for them and others, *OncoLog* serves as a quick review of the cancer field.

How Often, How Much, How Many?

Among 465 respondents who answered questions about how frequently they read *OncoLog*, 87% read every issue, 12% read two or three issues a year, and 1% read one a year. As expected, most (63%) read specific articles; the other 37% read the newsletter cover to cover.

We thought that readers might pass their newsletters on to associates, and 35% do. Those in group practice, hospital practice, and academic settings reported that they circulate their copies to about 473 others, including 273 physicians, 129 nurses, 71 students, and some interested spouses and relatives practicing or studying medicine. Conservative calculations cause us to conclude that we have about 23,000 pass-along readers, or about 1.5 readers per copy.

When we asked what readers liked, 84% liked articles on treatment, 64% liked articles on research, and 43% liked news articles; 27% appreciated information on conferences. Book reviews were generally disliked. Specific articles mentioned favorably included those on limited therapy for Hodgkin's disease, adjuvant therapy for breast cancer, alternative treatment for prostate cancer, natural killer cells, liposomal drug delivery, cell survival and radiotherapy, hereditary colon cancer, and advances in chemotherapy. Some readers cited volume and number, indicating that they filed their copies and looked them up for this survey.

The major theme of suggestions for future articles was practical clinical management of the more common malignancies.

Thanks to all readers who answered the questions. We like confirmation, and we understand criticism. ■

Colorectal Cancer continued from page 3

Epidemiologists, natural-product chemists, cellular and molecular biologists, and clinicians together are establishing new research programs in chemoprevention. The first trials must enroll individuals at high risk for the most common cancers such as colon cancer. Ultimately, physicians in the community will be in the vanguard of chemoprevention trials in the general population. ■

Physicians who desire additional information may write Michael J. Wargovich, Ph.D., Department of Medical Oncology, Box 68, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 1515 Holcombe Boulevard, Houston, Texas 77030.
At times patients may require hospitalization before they begin chemotherapy. “When a tumor obstructs the biliary tree, for example, we sometimes admit the patient to insert a catheter for draining the biliary tree before beginning therapy,” McLaughlin said.

Hospitalization may also be necessary to treat patients for threatening problems such as hypercalcemia or to observe patients at risk of developing tumor lysis, which occurs in some high-grade lymphomas. “Tumor lysis is a sudden breakdown of the tumor, usually as a result of a rapid response to chemotherapy. The breakdown products may overload the kidneys and result in kidney failure or heart-rhythm disturbances. These patients need careful monitoring and, occasionally, dialysis,” McLaughlin said.

Numerous Routes of Treating a Tumor

Chemotherapeutic agents may be administered by a variety of routes. Some lend themselves to home treatment more than others. Hormones for patients with breast cancer or chlorambucil for patients with low-grade lymphoma may be taken orally. Subcutaneous or intramuscular agents may be self-administered at home in the same way diabetics give themselves insulin injections. Currently, the treatment of hairy cell leukemia with interferon can be done in this way, McLaughlin said.

The most common route of administration, however, is intravenous, and if patients are to have intravenous chemotherapy at home, they need a portable pump and a central venous catheter to connect to the pump. Single-drug protocols or even multidrug protocols with simple administration schedules can be adequately administered at home with pumps currently available, but multidrug protocols with complicated schedules are currently not practical for administration in the home, according to Edward Rubenstein, M.D., medical director of the Ambulatory Treatment Center.

“Traditionally, an obstacle to outpatient chemotherapy was simply that people had to have several bags on a tall pole with a large pump attached to it,” Rubenstein said. “The logistics generally required inpatient care. Now we have smaller pumps that can dispense four drugs at once. We are just now examining how these more advanced devices can enhance cancer treatment. In the near future, many of our complicated multidrug protocols will be tested strictly on an outpatient basis.” Advances in outpatient therapy will depend in part on how effectively the new pumps administer several drugs several times a day.

“For instance, let’s say a patient has a particular protocol that calls for the infusion of a drug 24 hours a day over five days and a second drug given once a day,” Rubenstein said. “What if this protocol also called for a third drug given once a day, but at a different time than the second? That’s complicated. But if you have a programmable pump with four channels, you simply load all the channels with the drugs, program it the way the drugs should be given, and hook it to the patient’s catheter. The computer takes it from there. That technology is coming.”

Regardless of new developments in outpatient chemotherapy, Rubenstein said one thing is certain, “Whether it be with new technology or improved therapy, we’re always looking for ways to keep patients out of the hospital.”

Physicians who desire additional information may write Peter W. McLaughlin, M.D., Department of Hematology, Box 47, and Edward B. Rubenstein, M.D., Department of General Medicine, Box 78, The University of Texas M.D. Anderson Hospital and Tumor Institute at Houston, 1515 Holcombe Boulevard, Houston, Texas 77030.
Malignancy and Gene Expression

Nicolson’s basic studies of gene expression and malignancy show that some gene transcripts believed to be involved in the cell differentiation process are always present but are expressed at higher or lower levels when the cells change from an essentially benign to a malignant phenotype. “Such changes in gene expression seem to be quantitative, not qualitative. Knowing this may help us understand how to prevent the process from occurring,” Nicolson said.

His immediate goal is to develop cancer markers that will spot the stage of a tumor cell’s malignant progression and be specific for the highly malignant phenotype. “This will enable us to follow up breast cancer patients, for example, who have gone through their initial therapies and surgical intervention, with blood tests every few months to check for the presence or absence of markers for recurrent malignant disease,” he said.

Nicolson and his associates are working on a half-dozen patents, with more on the way, for new procedures they designed to test blood samples for these tumor markers. The reason for patents, he explained, is not to make money but to stimulate the methods’ commercial application.

“Unless a patent is properly registered and licensed to a company, the device will stay on the shelf,” he said.

Nicolson’s long-term goal is to understand what generates the malignant phenotype, “what goes awry genetically, and how this can be recognized early and controlled before it goes too far. For this we have to know what genes to look at. That is why our immediate goals are tied to our long-term ones: finding the malignant tumor phenotype, which is a more focused task than finding the cancer phenotype or the tumor phenotype. Under certain conditions, when the malignant tumor phenotype becomes a reality, the tumor is capable of invading, spreading to, and surviving at distant sites. Once we understand how these properties are controlled and regulated, we may be able to prevent tumor cells from progressing to more malignant phenotypes. Perhaps we can even learn to make them revert to less malignant states.”

Physicians who desire additional information may write Isaiah J. Fidler, D.V.M., Ph.D., Department of Cell Biology, Box 173, and Garth L. Nicolson, Ph.D., Department of Tumor Biology, Box 108, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 1515 Holcombe Boulevard, Houston, Texas 77030.