Chapter 12

Evaluating Unconventional Cancer Treatments

CONTENTS

Chapter 12

Evaluating Unconventional Cancer Treatments

INTRODUCTION

Chapters 2 through 6 of this report provide information about a variety of unconventional cancer treatments. To the extent possible, the composition of treatments and the ways in which they are used were described, the rationales and theories provided by their supporters discussed, and the evidence available concerning their effects on cancer patients presented and critiqued. In these treatment "portraits," there are pieces of information, ideas, various fragments that some might find provocative, or suggestive of a worthwhile approach, and other pieces suggesting that a treatment is groundless.

This report undoubtedly will be used selectively by individuals wishing to portray various points of view, in support of or in opposition to particular treatments. The reason this is possible is that, by and large, the treatments have not been evaluated using methods appropriate for actually determiningg whether they are effective. No amount of digging through descriptive information, theoretical discussions, laboratory tests, or individual case histories of exceptional patients can adequately answer the question of whether the treatment works—whether it prolongs or otherwise improves life, or affects a cure. The background information is useful, vital in some cases, to move the process to the point of evaluation. However, regardless of the nature of the treatment or of its intended effects, in the final analysis, except for those treatments whose effects are dramatic, gathering empirical data from clinical trials in cancer patients using valid, rigorous methods is the only means for determiningg whether a treatment is likely to be of value to cancer patients in general or to a class of patient. This fact is as true for unconventional as it is for mainstream treatments. For none of the treatments reviewed in this report did the evidence support a finding of obvious, dramatic benefit that would obviate the need for formal evaluation to determine effectiveness, despite claims to that effect for a number of treatments.

Pursuit of evaluation by practitioners and supporters varies considerably among the wide range of treatments covered in this report. As portrayed by members of the project Advisory Panel, it may be proponents of the "middle ground" (mainly psychological, behavioral, and dietary approaches used along with mainstream treatment) who would be most interested in testing and refining their treatments, but who apparently find the current system for doing so unsupportive (8). An additional difficulty is posed by the different orientations of evaluation in the social sciences (a source of middle ground approaches) as opposed to medicine. The former rests on a stronger belief in inference based on nonexperimental situations, though the methods have not generally been used to study medical endpoints such as life extension. A concomitant rejection of some experimental methods, particularly randomized trials, for psychological or multifaceted approaches for cancer patients by some psychological practitioners and researchers (7) is one of the factors that has led to relatively little mutually acceptable evaluation.

New evaluation methods, including any adapted from social sciences, should they be developed and validated, would apply equally to unconventional and mainstream treatments. That remains for the future, however.

This chapter ***discusses*** approaches ***to*** acquiring valid ***information about the efficacy and safety of unconventional cancer treatments, including some approaches for dealing with the practical problems of carrying out evaluations.***

THE NEED FOR EVALUATION

There is a demand on the part of cancer patients for information about the safety and effectiveness of unconventional treatments to validate the claims made for them. If they are contemplating spending time and money, and forgoing other options at a critical time in their lives, they want to know whether a treatment is likely to work for them. Many practitioners and their supporters believe that the information that exists already, the fragmentary evidence presented in this report, is sufficient, and do not pursue evaluating their treatments in a way that would produce valid evidence. Lack of development and evaluation through mainstream science, however, is axiomatic of unconventional treatments (with the possible exception of "middle ground"

approaches). Presumably, valid evidence from evaluations would either cause treatments to become accepted by mainstream medicine (if the treatment is effective) or to be abandoned once and for all (if the treatment is ineffective).

Individuals knowledgeable about unconventional treatments have their own explicit or implicit criteria, based at least partly on intuition, for choosing among unconventional cancer treatments (e.g., Ironer differentiates by such factors as the training of the practitioner, whether the treatment is completely "open' or has "secret' components, whether the charge for treatment is "reasonable, ' what claims are made regarding outcomes (530)). Other people have other approaches (e.g., McGrady's CANHELP computerized data bank (594)), and since every treatment has its adherents, there clearly must be conflicts among the lists of "good" and "bad." Without formal clinical research, however, it is not possible to get beyond this unsatisfactory status quo.

On a more pragmatic level, evaluation may also be important for legal and financial reasons. For unconventional cancer treatments that involve substances that would be classified as new drugs or biologics, evidence of safety and efficacy (and formal approval by the Food and Drug Administration (FDA)) are required before they may be offered legally in this country. In general, acquiring this evidence entails carrying out a series of prospective clinical trials, including randomized trials. For unconventional cancer treatments that do not involve substances that require FDA approval, e.g., psychological, behavioral, or dietary approaches, no regulatory requirement applies. However, health insurers may require evidence of efficacy and safety as a condition for covering those treatments. Evaluation may also be of benefit to health care professionals who are incorporating "middle ground" treatments into their practices, but who fear professional sanctions for doing so (218).

MAINSTREAM EVALUATION OF CANCER TREATMENTS

Legal approval and widespread ***use of medical drugs and biologics, and, ideally, the adoption of new medical practices, are based on evidence of efficacy and on knowledge and acceptance of adverse effects. A decision about whether to use a product requires weighing the risks against the benefits. In the ideal system, medical treatments do not become part of standard practice until adequate evidence exists. The system has not worked perfectly. There are probably many ineffective treatments, for cancer and for other conditions, that are believed effective on the basis of inadequate evidence. Some of these are being reexamined in new clinical trials, and the process of updating and weeding out treatments is likely to continue.***

Extension of life and improved quality of life are the hallmarks of a successful cancer treatment. Tumor shrinkage (antitumor effect) is an intermediate endpoint that is easier to study than is life extension, and is regarded as good evidence on which to proceed to studies that can measure life extension and quality. All conventional cancer treatments known to extend life thus far do, in fact, have antitumor effects, but some treatments with strong antitumor effects do not appear to be beneficial in the long term. It is important, therefore, that promising treatments eventually be studied directly for life extension and quality of life in randomized trials (discussed later in this chapter).

Before new cancer treatments are given to patients for clinical testing, in the current mainstream approach to evaluation, extensive "preclinical" laboratory and animal studies are carried out to establish a reasonable presumption that an agent might ultimately be of value to cancer patients. Both natural and synthetic agents are normally screened and tested in various animal tumor models (323,351). Preclinical studies are used to determine whether the compound is active against cancer cells, to attempt to learn about mechanisms through which the agent has its effects, to learn as much as possible about adverse effects, and to estimate the doses that might be tried in patients.

Screening and Preclinical Testing of Potential Anticancer Drugs

Until recently, the ***most common type of primary screening test*** for botanical products (and other substances) involved the ***use of*** tumor-bearing rodents—mice ***or rats with tumors that arose and were maintained in inbred strains. (Examples of such systems include P388 leukemia, L1210 leukemia, B16 melanoma, Lewis Lung carcinoma, Ehrlich ascites, Walker 256 carcinosarcoma, and Sarcoma 180 tumor models.) Generally, these animals would be treated with a range of doses of an***

experimental agent. An antitumor effect would be indicated by an increase in survival of the experimental animals compared with the untreated control animals. Cytotoxic (cell killing) or cytostatic (blocking further cell division) effects are measured in some of these tumor models, while others measure immunologic responses of the host animal to the experimental agent.

The National Cancer Institute (NCI) once used the L1210 mouse leukemia tumor model (from 1956 to 1971) and the P388 lymphocytic leukemia (from 1971 to 1985) as primary screening tests for new antitumor agents (841). Agents that tested positive in these tests were generally tested further in animal systems[1] before being considered for human trials. Those that tested negative might have been retested in the same or similar systems a number of times. For botanical products, such retesting might have involved the use of different parts of the original plant, different dose ranges, or different ways of administering or preparing the experimental solution.

Animal tumor tests can generate information about a new agent's biological properties, e.g., its immunologic and pharmacologic effects, in a whole animal system. The usefulness of such data depends on the degree to which they predict corresponding effects in human beings. The information gained from animal tumor tests can be used to select agents for clinical testing in human beings.

The limitations of animal tumor tests are well known. Their results do not necessarily correlate with results in human patients with cancer, although the degree of correlation varies with the type of test and the type of human cancer. There are many examples in which the response in an animal tumor system failed to predict a similar response in humans, in addition to examples in which animal results correlated closely with clinical responses. One way around this problem has been to use a variety of different tests to study each new agent. In general, the greater the number of animal tumor systems that show antitumor responses to a drug, the greater the chances that the drug will be active in humans. Activity in only one or two animal systems tends to correlate with little chance of activity in humans (99).

In 1985, NCI discontinued the use of animal tumor systems for routine, primary screening testing, in part because of these problems. In their place, a test system of human tumor cell lines grown in culture is currently being setup for initial screening of possible antitumor agents. The new system focuses on identifying substances that maybe active in specific tumor types. Substances that test positive in this new system would then be tested in human tumor-bearing athymic (nude) mice, and then in other whole animal systems for toxicology testing as a final step before use in human subjects (2,841).

Clinical Trials of New Anticancer Agents

"Phase I" clinical trials are often the first *time new anticancer treatments are given to human beings (except in cases in which new treatments for cancer have been used for other purposes). Patients with very advanced cancers, with virtually no hope of recovery, are asked to participate in these trials, as investigators attempt to determine appropriate dosages and learn about unwanted toxic effects, as well as to look for evidence of anticancer effects. These trials involve relatively few patients, usually in the range of 15 to 30, who are observed intensively.*

Phase II studies serve the purpose of generating information about antitumor effects and additional information on unintended adverse effects. These studies span a rather wide range, initially often including a number of different tumorsina"screening" study to see if any tumor types are particularly sensitive to the treatment, progressing to phase II studies focused on one or a small number of tumor types (phase III studies, if eventually undertaken with a particular agent, almost always include only a specific tumor type).

Patients eligible for phase II studies generally have advanced cancers and no available proven treatment options. Often, these patients already have had surgery, radiation, several different chemotherapy regimens, or a combination of these treatments. Anywhere from 15 to 30 or so patients are generally enrolled in single arm phase II studies, but they may include more patients. Accurate information about patients' clinical status and the status of their tumor (quantitative measurements) are obtained at the start of the trial, and patients are reassessed at specified intervals to determine changes in their status. While

[1]Animal tumor models commonly used for secondary testing include spontaneous or carcinogen-induced tumors (autochthonous tumor systems) or human tumors transplanted into athymic (nude) mice. These tests are considered impractical as primary drug screening tests.

survival data and 'quality of life' information may be recorded, without a control group the analysis of the information can only suggest that either the treatment has a positive effect, no effect, or a negative effect.

The vast majority of phase II studies are "single arm" studies, that is, they have no control groups, but they can be of other designs. It is the endpoints, not the design, that cast a study as phase I, II, or III. Several randomized phase II designs are available (see e.g., Carter, 1984 (172)). Once an agent has shown promise in phase II studies, a phase III study may be planned.

Phase III studies are designed *to measure the efficacy of treatments in prolonging life, in prolonging the time before disease recurrence ("disease-free survival"), or both, the effect on quality of life, and adverse effects. It is necessary to go beyond a phase II finding of antitumor properties because those properties do not always lead to life extension or improved quality. In the longer term, responses to these agents may be transient, conferring no survival benefit, and they may have serious toxic side-effects that could actually lead to premature death. Phase III clinical trials are typically randomized, and should be large, including at least hundreds of patients, preferably thousands. For agents that are moderately beneficial-e.g., producing a 10 percent increase in long-term survival--one randomized trial of typical size is generally considered insufficient proof, and the trial is replicated at least once before the results are considered sufficiently proven.*

ISSUES IN EVALUATING UNCONVENTIONAL CANCER TREATMENTS

The same principles of evidence apply to unconventional as to conventional treatments. The need ultimately for unbiased clinical trials, in all likelihood randomized clinical trials, is not obviated by any factor specific to unconventional treatments. In general, appropriate methods exist for evaluating all types of treatment, but the organization of clinical trials involving unconventional treatments may differ significantly from those in the mainstream, and the importance of various endpoints may differ as well. These issues are discussed below.

Endpoints

The aims of unconventional treatments and the claims made for them by practitioners or their supporters may include regression of tumors and improvements in survival, which correspond closely to the aims of mainstream cancer treatments. Another strong vein, however, relates to attempts to improve the quality of cancer patients' lives, e.g., general medical status, pain levels, activities of daily living, mood or emotional state, sleep patterns, medication use, rehabilitation status, stress management skills, self-esteem, abstract criteria (e.g., sense of purpose, meaning, belonging, inner strength), and nutritional status (7). While mainstream cancer researchers have begun incorporating quality of life assessments into clinical trials of conventional cancer treatments, few treatments in the mainstream are developed and tested specifically for their ability to enhance the quality of cancer patients' lives in the absence of direct antitumor effects. In most cases, a concern is that mainstream treatment, even if effective, may cause short-term or permanent changes leading to an impaired quality of life.

A variety of scales has been developed for assessing aspects of quality of life, both for cancer patients specifically and for general use (941). These have been applied in various types of psychological research, though not generally in clinical trials of interventions designed to enhance the quality of cancer patients lives. This is an area in which collaboration between researchers familiar with quality of life measurement and clinical trials experts is needed.

Organizational Issues

Regardless of the type of treatment or the context in which it is given, the aim of evaluation is to provide unbiased information about its effect on cancer patients. In this sense, the inferential basis for determining effectiveness will always be the same: is the patient better off with the treatment than without, all other things, on average, being equal. The way this comparison is achieved may need to be somewhat different for some unconventional treatments than is customary for mainstream treatments.

For treatments following the "medical model," those that consist of drugs or other regimens that can be specified according to a protocol, and for which the treatment setting is not thought to play an important part, clinical trials can be organized as for

other cancer treatments. Most of the pharmacologic and biologic treatments, whether used as primary treatments or adjunctive to mainstream treatment, would fall into this category. The clinical trials of laetrile, Vitamin C, and hydrazine sulfate (see ch. 5 and below), for example, were appropriately carried out in a conventional medical setting (the criticisms of the vitamin C trials did not have to do with setting).

Psychological, behavioral, and dietary treatments used adjunctively with mainstream treatments can also be studied using existing clinical trial designs, as long as they can be specified and isolated. Spiegel's randomized trial of a psychological intervention (824) serves as a good model. In that study, patients with breast cancer were randomly assigned to be offered a psychological intervention or not. Decisions about other types of medical treatment were left to the women and their physicians, and were not considered part of the clinical trial. The two groups were compared in the end by their survival. Dietary regimens and other behavioral and psychological approaches could be studied similarly.

It would also be possible for adjunctive treatments to be studied in the context of randomized clinical trials of primary treatments. In the simplest version of what is called a "factorial" design, patients would be assigned independently to two treatments, so four groups would result: 1) primary treatment plus adjunctive treatment, 2) primary treatment only, 3) adjunctive treatment only, 4) neither treatment. Comparing groups 1 and 2 combined with 3 and 4 combined would give an assessment of the primary treatment; and groups 1 and 3 combined versus 2 and 4 combined would give an assessment of the adjunctive treatment. These adjunctive treatments might also be tried in mainstream phase I and phase II clinical trials along with other experimental treatments to gather preliminary data for planning larger, more definitive trials. Studies of this type could be arranged in a medical setting, even if the adjunctive treatment were administered outside.

Treatments that would be difficult to isolate from their usual setting or to duplicate elsewhere, or treatments tied closely to an individual practitioner pose some greater challenges. (These would also generally pose the greatest difficulties in making them available widely to cancer patients.) These might *include, e.g., the Gerson treatment (though it is possible to isolate components of that treatment), IAT, treatment by Revici, and the macrobiotic regimen (although a particular diet could be isolated). If they desired to do so, practitioners (aided by experts in research design) could initiate studies of patients coming to them for treatment using conventional phase I and phase II designs. If preliminary evidence suggested an effective treatment, randomized clinical trials could, theoretically, be organized outside the treatment center, with patients randomized either to the center or to other treatment, but such studies entail greater practical and ethical problems. The discussion below, concerning 'best case reviews,' suggests a mechanism that might facilitate randomized clinical trials in such situations.*

Clinical Trials and INDs

Another issue to be dealt with is the desirability of conducting formal evaluations, such as clinical trials, under an IND. In most cases, this will be a legal requirement (for evaluations of new and unapproved drugs and devices).

The requirement that clinical trials be carried out under FDA-approved INDs may be seen as a formidable barrier by unconventional practitioners. Securing such approval is, indeed, a significant effort. But, as the case of Stanislaw Burzynski has demonstrated, it is possible, and it can be facilitated by help from FDA.

A big issue facing an unconventional practitioner contemplating applying for an IND is divulging proprietary aspects of how the treatment is made and administered. The FDA has been entrusted over the years with the trade secrets of large and competitive corporations, and has maintained their trust through vigilant protection of this information. Even the fact that an application has been filed is completely confidential, unless disclosed by the applicant. (During the course of this assessment, FDA would not inform OTA about the existence of IND applications.) The content of the IND application always remains confidential. While these safeguards will not convince some unconventional practitioners that the FDA can be trusted, the fact is that the practitioners cannot cite instances of unwarranted disclosure of this confidential information.

USING INFORMATION RETROSPECTIVELY FROM TREATED PATIENTS: EFFICACY

Before patients use new cancer treatments developed through conventional research and development, extensive testing in laboratory tests and in animals is conducted, and the specific progression of clinical studies described above is followed. Unconventional cancer treatments, by their very nature, do not follow this progression. There is no question that existing unconventional treatments could be treated like new treatments in the conventional pipeline, tested in the laboratory, in animals, and then in humans. But that is highly unlikely to happen, since most unconventional practitioners have not recognized the need for such testing, and the government would not undertake such an effort without a reason to believe the treatment might be effective. The operative question becomes, then, can the experience of patients taking these treatments be used in any way to determine whether they might be effective, and worth evaluating further, and also whether they pose particular dangers for patients?

A "best case review" approach is discussed in terms of gathering preliminary efficacy information, and a reporting system for adverse effects, to address the issue of safety. Some of the more commonly used approaches to assessing efficacy which are not valid are included as well, with explanations of why they don't work.

Efficacy: Some Techniques That Are Prone to Producing Invalid Information

Comparison With the Literature

It is tempting *to use the* records of patients already *taking unconventional treatments to try to derive some type of "response rate' or "survival rate' that could be compared with a' 'standard' rate, thus providing a quantitative estimate of the comparative "efficacy' of a particular treatment. While this approach has some intuitive appeal, it fails because there are no "standard" rates with which to make the comparison. The reason for this is that there is tremendous heterogeneity among cancer patients, even among those who have nominally the same type of cancer. While for most cancers it is possible to identify several important variables, "prognostic factors" (e.g., age, sex, stage of cancer), that are predictive of the likelihood of survival for a group of patients, the heterogeneity reaches beyond easily identifiable factors.*

Even more so than the particular patients who are treated at a given hospital, patients who opt for unconventional treatment are strongly self-selected, and as a group, may have very different characteristics from those of the total cancer patient population, some of which may be related to prognosis. In chapter 6, OTA's review of peritoneal mesothelioma patients treated with IAT is discussed. Clement and colleagues (202) compared survival of this group of patients with the average survival of peritoneal mesothelioma patients reported in series published in the literature. They concluded that IAT produced a two to three times longer survival time than conventional treatment. The authors did not note, however, that the ranges of survival times in IAT patients are similar *to the ranges* noted in reported series *of mesothelioma patients. A range of 7 to 80 months is reported for IAT-treated patients, while the literature reports they cite give survival statistics ranging from 1 to 60 months. One of the comparisons made in the paper by Clement, Burton, and Lampe is with a series of 45 patients whose mean survival was 6 months. For the 11 IAT-treated patients, the mean survival time was 9 months before they began treatment with IAT. This demonstrates some of the problems with comparing groups of patients outside of appropriately designed clinical trials.*

A recent study by Cassileth and colleagues (178) illustrates some of the differences in the distribution of known prognostic factors between a group of IAT patients and cancer patients in general. They reported:

> *The total of 79 subjects, all of whom were white, tended to be younger and of higher socioeconomic status than are cancer patients in general. The majority (82 percent) had received conventional cancer therapy prior to IAT, and 86 percent had completed their prescribed course of conventional treatment. Patients began IAT an average of 17 months following diagnosis. Prior to their first receipt of MT, 76 percent of patients were ambulatory.*

All of the characteristics noted by these investigators would have tended toward better outcomes in these patients than in cancer patients in general. Younger age, white race, higher socioeconomic status, and being ambulatory are all associated with

better prognosis. The fact that these patients began IAT on average about a year and a half after diagnosis means that they survived their period of highest risk (the portion of the survival curve with the steepest slope) of dying from their cancer. These patients already were 'survivors." None of this can be taken as evidence that IAT did or did not help them, but it does point out differences in the distribution of known prognostic factors. The authors recognized this, concluding:

> These characteristics make it impossible to draw valid inferences from this dataset concerning treatment efficacy and safety. . . The deficiencies of this dataset underscore the need for an unbiased, methodologically sound comparison of IAT and conventional cancer treatment modalities.

Cassileth and colleagues' study, however, was interpreted by the IAT Patients' Association (IATPA) as proving that IAT was effective. A "Dear Senator" form letter produced by the Patients' Association (for members to fill in their names and mail to the appropriate Senator) contains the following, which states that 'dramatic new evidence' emerged from Cassileth's study:

> The IAT patients studied were alive nearly twice as long as the average patient who is treated conventionally. Statistically, the odds against this being a chance occurrence are 100 million to one! (431)

This study and its interpretation by the IATPA illustrate the difficulty in presenting accurately and unequivocally the severe limitations of such data.

At the present time, it is not possible to compute rates of survival (or other response) that can be related meaningfully to particular treatments, using only the records of patients who have had those treatments, and attempting to compare them with some 'standard' survived (or other response) information. This statement can be qualified to except the unlikely case of an extraordinarily successful treatment, in which case no comparison might be necessary at all.

"Matching"—Another approach that is often tried is to "match" patients taking a particular treatment with patients who have similar personal and disease characteristics, and then track their survival. This approach fails on the same grounds as comparisons with overall statistics or with reports in the literature: the impossibility of identifying and matching on all the important prognostic factors, since important ones may be elusive.

A study of "ECaP" (Exceptional Cancer Patients) participants, by Morgenstern and colleagues (639), discussed in chapter 2, is a good example of a matched study. In that study, women with breast cancer who had participated in ECaP support groups were matched on age at diagnosis, stage of disease, whether they had had surgery, and "sequence of malignancy. On initial analysis, a significant benefit emerged for the ECaP group. But the matching factors did not take into account the very large effect of the "lag period" between diagnosis and entering the ECaP program. Some of the controls had actually died during the time corresponding to the lag period before the ECaP patient joined up. In addition, the matching factors did not cause the groups to be equivalent in their use of chemotherapy. This suggests that other personal and disease characteristics also differed, and some of these may have been related to prognosis. The final analysis showed no difference in survival once the known prognostic factors were accounted for. Studies such as this are bound to be inconclusive because of the virtual impossibility of successfully "matching' patients.

Efficacy: "Best Case Reviews"

One objective measure of the efficacy of a cancer treatment is its effect on the tumor itself. Not all treatments that shrink or slow the growth of tumors ultimately turn out to be of survival value to patients, but while antitumor effects are not "sufficient" to predict efficacy, they are, for treatments as we know them, "necessary." A first step toward determining the ultimate value of a treatment is to determine whether it has antitumor effects. (This is the main purpose of phase II studies of anticancer treatments.) Nearly all the unconventional treatments learned of in the course of this assessment do make claims for tumor shrinkage or disappearance, so it is not unreasonable to look for these effects in patients. The mechanism of claimed effects are relatively unimportant here, but the time scale for effects should be taken into account: some proponents claim that their treatments have direct cell-killing effects, which may happen rather quickly (e.g., laetrile, Hoxsey tonics), while for other treatments that claim to work by building and stimulating the patients' immune systems, the effects are described as more gradual (e.g., macrobiotics, IAT).

One way to determine whether a treatment has antitumor effects is to test it in a phase II trial. Given a treatment that has been used by hundreds or thousands of patients, however, is there another way of efficiently generating some, at least preliminary, information before a prospective trial is contemplated? NCI's laetrile case review (274), described in chapter 5, was an attempt at this. The results were disappointing because a relatively small number of evaluable cases were submitted, but still, valuable lessons were learned from it about laetrile and about the method itself. This "best case" approach, with modifications, could be used more prominently in determining which might deserve further investigation. One element that may be crucial to the success of a best case review is the active participation, or at least support, of the unconventional practitioner.

The objective of the best case review is to produce evidence of tumor shrinkage (or, in particular cancers, other accepted objective measures of lessening disease) in a group of selected patients (either current or former), with evidence documenting that the patients had the particular unconventional treatment under study and, as far as possible, that they did not have any other treatments during that time period.

The basic elements of each case in a best case review would be: 1) documented diagnosis by an appropriate licensed professional, including pathology reports and microscope slides of the tumor; 2) history of prior treatments; 3) length of time between the most recent treatment and the treatment under evaluation; 4) x-ray studies from before and after the treatment under evaluation was administered; and 5) a statement from the physician and the patient saying that no other treatments were administered at the same time as the particular treatment under evaluation.

These elements require a significant amount of documentation. Clearly, many patients who benefit from cancer treatment-mainstream or unconventional--could not be included in a best case review, because their records would not be sufficient to meet these demands. However, an adequate and convincing review could be based on as few as 10 or 20 successful cases. If a treatment is even moderately successful and has been used for many years, that number meeting the criteria should be available. Such a review will require time, patience, perseverance, resources, and the cooperation of professionals in the mainstream community, such as pathologists, oncologists, and specialists in nuclear medicine, which may seem a steep climb for an unconventional clinic to undertake. The Gerson Institute, one of the major unconventional clinics treating U.S. patients in Tijuana, has embarked on such a best case review, however. Results have not been reported, but it could prove to be the first successfully completed study of its type mounted by an unconventional treatment proponent.

It is important to note that a best case review is not the end of the evaluation line; some cautions must be kept in mind. This type of study cannot, except possibly in exceptional cases, provide definite proof of efficacy in terms of life extension, nor any estimate of rate of response to the treatment. In addition, the concerns expressed in the report of NCI's laetrile review are relevant: the possibility of falsified information being used, omission of information, either intentional or unintentional; other mainstream or unconventional treatment that may have been used by the patient without the unconventional practitioner's knowledge; the possibility of mistaking the natural variability of cancer for true regression; and the possibility of "spontaneous regression.' This last point is worth pursuing a little further.

So little data exist about the nature and rates of spontaneous regression that is almost impossible to discuss informatively. Spontaneous remissions are often invoked to explain otherwise unexplainable recoveries from cancer, yet such remissions are usually considered to be exceedingly rare phenomena. It is worth noting that two instances of "otherwise unexplainable regressions" have been described in chapter 5 of this report. One of the NCI-file patients in the laetrile review, who had had no treatment, was deemed to have had a partial remission (274); and the only long-term survivor in the first Mayo Clinic vitamin C study was a pancreatic cancer patient who had both subjective and objective evidence of lessening disease (though tumor status itself was not reported), and who was taking the placebo.

Overall, the best case review may be a powerful tool for supporters of unconventional cancer treatments who want to begin the evaluation process. It can be carried out relatively easily independent of major cancer research centers, although specialized expertise is needed for reviewing pathologic diagno-

ses and for interpreting scans and other medical testing information. It also is not free: patient followup and medical expertise can be expensive, and a large investment of time is required on the part of the unconventional practitioner or his or her representative. Nevertheless, it is doable, it poses no particular legal problems, and it does not involve securing an IND or the approval of an Institutional Review Board (IRB). OTA has recommended to Lawrence Burton and supporters of IAT a best case review of his selected, successfully treated patients as a prerequisite for carrying out a prospective clinical trial under Federal Government auspices. Importantly, NCI and independent researchers would look seriously at evidence from well-documented best case reviews of unconventionally treated cancer patients. The end result should be, if the evidence warrants, a somewhat eased entry into further evaluation through prospective clinical trials.

CAPITALIZING ON THE EXPERIENCE OF TREATED PATIENTS: SAFETY

Just as described above for assessing efficacy, there are some informative and some not very informative ways of using patient experience to assess the safety of treatments. Examples of both will be described in this section.

In cases where unconventional practitioners or clinics keep detailed patient records, it would theoretically be possible to examine them for adverse side-effects that might be related to the treatment. The practitioners themselves might also be good sources of this information, if they noted particular patterns of unintended effects. Such a means of detection is not unlike the way newly discovered adverse drug effects are reported to the FDA, at least for rarer effects that would not necessarily be detected in formal premarketing clinical trials. OTA found no reports of systematic records-based studies of adverse effects by unconventional practitioners, however, and it is probably not realistic to expect many, if any, to undertake these studies.

Another possible approach to gathering information on adverse effects in past (and possibly current) patients is by examining medical reports from physicians and hospitals who have seen patients after they leave unconventional treatment or who are seeing them concurrent with the unconventional treatment. Results of laboratory tests not generally carried out at unconventional clinics (e.g., liver function, kidney function, cardiac tests), descriptions of clinical symptoms, and autopsy reports for patients who have died are available in some cases. This type of investigation is most likely to be undertaken by mainstream groups concerned with unknown adverse consequences of unconventional treatments. Given that it is not the type of study in which the unconventional community is likely to participate, locating patients and confirming information about their unconventional treatment may be a difficult exercise. Several approaches are possible.

There may be cases in which the clinic or practitioner will cooperate by providing lists of current or former patients. Associations of patients (see ch. 7) have formed around particular clinics and treatments, and the associations may be willing to provide the names of members, or the names of members who have died. These associations are often autonomous and have somewhat different perspectives from the practitioners. Another approach, which has been tried, is to survey physicians and ask about their experiences. One such example, described in chapter 5, was the NCI/American Society for Clinical Oncology (ASCO) survey of ASCO members concerning patients they had seen who had been treated with IAT. After a significant effort, the authors found that the survey could not be viewed as a "definitive analysis of IAT efficacy or toxicity. No rates could be calculated, as the appropriate denominator for the sample could not be ascertained, and because the nature of the survey would have had the effect of eliciting responses from physicians who had particularly bad experiences. More to the point on the toxicity side, however, for the type of information collected to be valid, it would have to be "evaluated with a thorough chart review to determine whether other factors may have accounted for the findings. " Unfortunately, this survey approach has quite limited usefulness.

Another attempt to find information about adverse effects of IAT was made in 1981 by a physician who advertised in the Florida Association of Clinical Oncology Journal *(987). The advertisement asked physicians to send narrative reports of patients known to them who had been treated at the IAT clinic in the Bahamas, with the idea of starting a "registry" of such cases. Seven physicians responded reporting on a total of 21 patients (989).*

This, again, is probably not a particularly useful approach.

Aside from doing surveys, it is possible that useful information about adverse effects of unconventional treatments could be collected if physicians had an easy, open channel to report findings as they are noted, similar to their reporting of adverse effects of legal pharmaceuticals to FDA. There is currently no Federal agency with such a charnel. A' 'registry' could be opened to accept and keep on record documented cases of adverse effects resulting, with a high degree of probability, from unconventional cancer treatments. Currently, adverse treatment effects collected and reported by individuals or groups perceived as "quackbusters" often are not well-documented, though they may be accurate, and reach the public only through specialized newsletters, occasionally the popular press in a sensational way, and rarely, the medical literature. If reporting were perceived as a responsibility of any treating physician, and if available patient records were reevaluated by an office in a Federal agency, the registry of reported effects has the potential to be a useful reference for physicians and the public, for research, and possibly for legal actions.

TESTING TREATMENT MATERIALS FOR POTENTIAL ANTICANCER ACTIVITY AND STERILITY

Testing Treatment Materials for Potential Anticancer Activity

Currently, the Federal Government does not systematically seek out and screen substances in commonly used unconventional cancer treatments in the United States. NCI does test substances of plant and animal origin (including undersea organisms) collected from around the world by botanists, anthropologists, and oceanographers. Many herbal compounds popular in the United States, in some cases mixtures of more than one component, or individual components, are readily available in health food stores or by mail. The investment involved in acquiring and testing these materials in the current battery of preclinical screens, while not negligible, may be worthwhile.

If some of these materials were to demonstrate promising activity in preclinical tests, they could be considered for development in the rigorous system that has been devised for all conventional potential anticancer drugs. This would involve identification and isolation of active molecules, possible synthesis of the compound in the laboratory, and further biochemical and safety testing in animals. The other path open would be to try to study these products in clinical trials (after some preclinical safety testing) in the way that they are used by cancer patients in unconventional treatments.

Testing Treatment Materials for Composition and Sterility

Substances used in unconventional cancer treatments are often "proprietary," their composition deliberately kept secret, and they are often manufactured only at the treatment site, or by unregulated manufacturers. In these cases, there is often interest in the mainstream community in finding out whether the composition of these materials resembles descriptions by the proponents, and whether they may be contaminated by various types of organism. Treatment materials have been turned over to U.S. authorities by patients or the families of patients, and subsequently analyzed. The best known recent example of this was testing of IAT materials by NCI, which was reported in the Journal of the American Medical Association (246) in 1986. *In that case, significant contamination was reported, and the composition of the materials was reported to be mainly albumin. That testing, it is widely believed, led to the closure of the IAT clinic by the Bahamian Government.*

The claims of contamination are denied by Burton, who asserts that his preparation procedures precluded the possibility of contamination (114). There seems to be no way to ascertain the facts of this case, which has become celebrated in both the mainstream and unconventional communities.

Although the IAT example might suggest otherwise, it is possible that some practitioners might be willing to submit their materials for testing specifically for contamination, if procedures could be worked out to assure propriety on both sides.

CONCLUSIONS

Opportunities may exist to gather valid information about the efficacy and safety of unconventional cancer treatments; these are largely unexplored. The same types of study that are used to determine the safety and effectiveness of mainstream treatments—including ultimately randomized clinical trials—would be required to determine the value of unconventional treatments.

A potentially useful tool for beginning to evaluate unconventional treatments is the "best case review, which could be a first step toward prospective clinical trials. There may also be ways to gather some information about possible hazards of unconventional treatment, by opening a "registry" into which cases with appropriate documentation could be entered. Conventional physicians would probably be the main contributors to this.

OTA's experience with IAT was discouraging, but it may not be a good example of the way in which an unconventional treatment might enter the evaluation system. Burton did not seek the evaluation, and he never became fully engaged in seeing it move forward. Other practitioners or their supporters, such as Burzynski, and the Gerson Clinic personnel, have attempted to initiate some form of evaluation, with assistance from experts, and these efforts suggest that other practitioners might be interested in doing so as well.