

UNPROVEN REMEDIES:

LESSONS FOR IMPROVING TECHNIQUES OF

EVALUATING THERAPEUTIC EFFICACY

Emil J Freireich, M.D.

Professor of Medicine

Head, Department of Developmental Therapeutics

The University of Texas System Cancer Center

M.D. Anderson Hospital and Tumor Institute

Houston, Texas

GRANT SUPPORT: CA05230, CA05831, CA08859, CA10376, CA11520, CA14528

from the Public Health Service, National Cancer Institute, National Institutes of Health, and ACS IM 57 from the American Cancer Society.

UNPROVEN REMEDIES:  
LESSONS FOR IMPROVING TECHNIQUES OF  
EVALUATING THERAPEUTIC EFFICACY

Emil J Freireich, M.D.

When the treatment of any disease is not uniformly curative, there regularly occurs in the community, a number of unproven or "quack" remedies. The individuals who promote and distribute such remedies are almost uniformly firmly convinced of the efficacy of such treatments, yet the scientific evidence of effectiveness does not exist, and for many such remedies, exhaustive investigation by qualified clinical investigators have failed to provide any scientific basis for believing that these compounds are active. In this paper, I will attempt to analyze the technique which is almost regularly utilized by individuals who discover remedies of no value and become convinced that they are useful. By carefully understanding this technique, we can better appreciate the principles of scientific evaluation of therapy. Hopefully such improvement will lead not only to a more objective and more quantitative understanding of the role of treatment, but will at the same time, enhance the value of treatment for our patients.

HARMFUL EFFECTS OF UNPROVEN REMEDIES

Unproven remedies are an important social problem for our community because of the great harm that results from their use. There are three major harmful effects:

1) The interference with the treatment of the individual patient, for both palliative and curative treatment

The financial loss to the patient himself

The diversion of important and expensive resources of the community.

The harm to the individual patient is generally and most seriously in the form of interfering with proven treatment. Humans have become accustomed to using the psychological technique of denial in dealing with real problems. In caring for patients with cancer, we regularly find individuals who have sufficient information to know better, ignoring important signs and symptoms of disease such as blood in the stools, lumps, etc. Virtually every patient who develops a malignant disease has some degree of denial, which results in the delay in consulting his physician. The proponents of the unproven or quack remedies definitely contribute to this process of delaying treatment. They offer such things as prayer, vitamins and other relatively harmless medications, which the proponents claim can cure, or greatly palliate, cancer. Therefore, if individuals subject themselves to these treatments, they may relieve their anxieties, but their cancers (as is so regularly the case) will continue to progress. Thus, while receiving an ineffective or an unproven remedy for his cancer, the disease may progress from a condition where it could have been recognized and cured, to a circumstance where it is sufficiently advanced, so that the therapy will be at best, palliative, or in extreme circumstances, of no value.

As the treatment for cancer with our proven methods of treatment - surgery, radiation, and now chemotherapy, become effective for an increasing number of patients with this disease, this factor of delay becomes more significant. For each of the modalities of cancer treatment, the effectiveness is related directly to the extent of the disease; the probability of cure and of excellent palliation is best, the less extensive the disease at the time of treatment, and therefore, it is now certainly correct that any remedy, which either encourages or is directly responsible for a delay in the application of proven effective treatment is a serious and harmful matter.

The second major detriment of the unproven remedy is the draining off of community's and the individual's resources to activities which do not benefit anyone except the person who proposes such a remedy. This is a particularly cruel form of profiteering, since the one who accumulates the profit, that is the proponent of the unproven remedy, is deriving this profit directly from the suffering and illness of the unfortunate victims of the disease. Thus, the patient expends valuable personal financial and emotional resources and frequently returns to the legitimate medical community drained of the great majority of these resources.

Unfortunately, even more important than the personal loss is the loss to the community as a whole. We have read in the public press and the professional literature, of innumerable examples of people who are influential and eminent in our community, such as governmental leaders, senators, professors in major universities, basic scientists of esteemed reputation, who through their support of unproven remedies, divert fantastic efforts from legitimate scientific activities to the investigation of these unproven remedies. The commonest questions asked by a lay person inquiring about an unproven remedy is, "why doesn't some public or private institution such as a University or the National Cancer Institute, simply do a clinical study to determine if such a remedy is, once and for all, active or not?" Of course, they forget that there are innumerable proposed new treatments for these diseases which should be legitimately investigated if we had sufficient financial, professional and even patient resources to complete these investigations. By diverting activity into the investigation of remedies which have been proposed without any valid or scientific basis, significant interference with the processes of science and medicine results and

progress towards our legitimate goal of the cure or prevention of malignant disease is significantly impeded. Because of these harmful effects, the unproven remedies merit our careful consideration. We have to understand what the basis is for their continuing success in the community, and at the same time we must attempt to understand carefully the clinical research technique which the proponent or the cancer quack, regularly utilizes.

#### THE FREIREICH EXPERIMENTAL PLAN (FEP)

I have chosen to identify this technique with the use of my name, not to indicate that I either advocate, support or even discovered this important clinical research technique. I have used the eponym because I believe this to be the first formal formulation and publication of an experimental plan which assures that any remedy, whether it be a drug or a psychological treatment, a mystical therapy or a physical treatment, will always prove to be effective for virtually every patient with any serious disease. A careful understanding of the FEP will permit lay people, physicians, scientists and clinical investigators to readily identify publications which utilize this therapeutic plan, and thereby appreciate immediately its complete lack of value for selecting treatment for patients. Perhaps even more important, will be the ability to always use clinical research techniques which avoid the important pitfalls in the FEP.

#### REQUIREMENTS FOR THE FEP

There are two essential requirements for the successful application of the Freireich Experimental Plan (Figure 1). The first requirement is some form of treatment. Any type of therapeutic maneuver will do, provided it fulfills requirement number 2, which is that it is completely lacking in any harmful effects on a healthy or a sick person. The treatments which have been widely used in the past, are grouped in the figure into the four

categories. The first group are treatments involving alterations in psychological status of the patient, which have been among the most successful. Moreover, these types of treatment are frequently a component, and I would emphasize an important component, of the other forms of treatment. Drugs are very commonly used since they allow the proponent to actually deliver something physically to the patient. It is usually true that the drug has been poorly characterized, such as some type of an extract or a biological product, but even very well characterized chemical structures such as vitamin C have been advocated. A physical procedure has the added virtue of requiring that the individual receive his treatment by the proponent. Some type of a machine has been particularly effective. The final group which involves altering the patient's environment, has been widely practised, not only by the quack therapist, but by physicians. Again, it is important that the toxicity or the harmful effects of all these treatments be low.

If any treatment has either unpleasant or even dangerous side effects, then its usefulness in the FEP is severely limited. This essential requirement for a lack of harmful effects will be better understood when the technique is more clearly delineated. However, in addition to its essential requirement, it is usually the first thing that the proponent of the unproven remedy presents as one of the treatment's major virtues. The implication is that the lack of harmful side effects enhances the likelihood that such a treatment will be good for the patient. Of course, physicians recognize that harmful side effects occur for virtually every remedy of proven value. Such time honored remedies as narcotics for the relief of pain, digitalis for the treatment of congestive heart failure, to mention only two that are practised by every physician, clearly have steep dose toxicity response curves, and

require careful evaluation, not only of dosage, but of schedule of administration, for effectiveness. The presence of toxic side effects at inappropriate dosage, is of course, not a detriment to a highly effective treatment; virtually every treatment effective for cancer has its limiting side effects.

#### THE TECHNIQUE OF THE FEP

It is an important principle of the FEP, that all disease to which man is heir, has a natural variability. Man's survival as a species is attributable to a large number of physiological processes which are capable of correcting disturbances in our essential physiological functions. Thus, when any disease affects such a complex animal, there are immediately brought to bear, physiological processes which tend to correct or improve this disturbance. The result is that all diseases, regardless of the etiology, are associated with periods of remission and exacerbation. In Figure 2, we have diagrammed two different types of illness which both have the characteristic of being regularly, if not inevitably, fatal. The first (A) is a disease which is highly malignant and rapidly progressive, such as acute leukemia, choriocarcinoma in females, or other forms of malignant disease. For such malignant diseases, there are unambiguously well-established complete and very good partial remissions in the progression of these diseases which occur, but the frequency of this event is extremely low. In contrast, we have shown the progression of a disease which is much more chronic; examples include the chronic leukemias, human breast cancer, colon cancer, and other more slowly progressing, yet almost inevitably fatal forms of malignant disease. Here periods of progression and regression are more frequent and observed with greater regularity. While the overall progress is toward progressive worsening, it is important to emphasize that there is a high proportion of patients with slowly

progressive disease, who have important periods of remission. I would emphasize that these remissions are not, in my opinion, "spontaneous"; they are regularly observed and quite predictable and the remissions have identifiable physiological processes so that they can be understood. Yet it is clear that there is no disease that I know of, where inevitable and continuous progression is the universal characteristic. All disease is remittant, and it is this principle of illness which allows the serious scientific clinical investigator to best understand the FEP. The quack or the uneducated or inexperienced physician or biologist is generally woefully lacking in the knowledge or understanding of the disease process which he is treating. There are several recent examples of eminent scientists in other scientific disciplines including physics, biochemistry, and biology, who have been misled and become major proponents of unproven remedies, primarily because of their failure to appreciate this important characteristic of disease, widely appreciated by physicians.

#### INITIATING THERAPY AND EVALUATING THE RESULTS OF THE INITIAL TREATMENT.

(Figure 3). Treatment should be applied to a patient only after a period when his disease has clearly been getting progressively worse. This is indicated in the figure by the arrow progressing downward toward getting worse with time. If the patient's disease has recently become stable, or has begun a period of remission, it is best to withhold treatment, to determine whether a spontaneous recovery might occur. If treatment is applied during a period when disease is stable or improving, the treator and the patient may feel that the treatment was not crucial to success; thus, it is important to only apply treatment to patients where the objective and subjective evidence of the disease has been getting progressively worse in the period immediately preceding the treatment. At the point at which the treatment is applied there are only four conceivable outcomes



of the initial phase of treatment. The first is that the patient's disease becomes objectively, subjectively and unambiguously better. This possibility as indicated above, is always present, based on the natural variability of the disease, thus depending on the frequency of remission, a period of improvement is to be expected in some fraction of patients. Of course, for the FEP this immediately establishes that the treatment is effective when applied. The second possible outcome is that the disease remains stable; that is, neither significant improvement nor significant progression or worsening occurs. In this circumstance, the treator comes to the conclusion that the treatment is working, since at least its progression is arrested. What is needed, clearly, is either the application of the treatment at a higher dose, which will not, of course, result in any unpleasant side effects since the treatment is not toxic; or the treatment must be continued for a longer period of time in order to show its effectiveness. The third possibility is that the disease progresses. If the disease has progressed under treatment, the conclusion reached is that either the dosage administered was inadequate or the duration of treatment has not yet been sufficiently long. Therefore, it is terribly important to modify the treatment (vida infra). The fourth possibility is that the progression of the disease will lead to the death of the patient, in which case of course, the treatment had been delayed too long and was applied too late in the course of the disease for any hope of success. This negative outcome, however, must be ignored by design in the evaluation of the treatment, and these cases are generally considered either hopeless or otherwise removed from the denominator in evaluation of the results.

In summary, the evaluation of the initial treatment applied to patients whose disease has clearly been progressing results in the conclusion that some will clearly benefit by getting better, some will have stabilization

and simply need more treatment, some will progress and need a modification in their therapy, and those who die had delayed too long in coming to the therapist.

#### STAGE II OF TREATMENT

Having completed the first stage of treatment, we are left with a group of patients whose disease was either stable or progressed after the initial therapy. In all of these patients, the treatment is modified by increasing dose or prolonging duration of treatment; either one is acceptable, although the dosage change is generally the most effective and most widely used technique. The second stage of evaluation, then leaves only three possible outcomes again. Either the patient now becomes better, in which case it is now proven that the treatment is effective if given at a higher dose and for a longer duration. Again, the treatment may stabilize, and one simply uses the same conclusion that was used in Phase I; that is, prolongation or modification of dose as indicated. If the patient continues to progress, one can still resort to the initial conclusion used in Stage I or in stable disease patients. The result of Stage II of treatment, is that there will be another fraction of patients who will show benefit, while the remainder do not clearly benefit.

One then simply progresses through a series of steps identical to Stage II; that is, all patients who remain stable or progress simply have the dosage further escalated and the time prolonged. Ultimately, all patients will end up in one of two categories, either they have shown objective improvement, or they have died as a result of their disease (which, of course, was not the result of ineffective treatment, but simply because the patient had delayed too long in seeking help). Thus, the treator may safely conclude that the treatment approach is 100% effective, since virtually all patients will end up in

the category of having shown some improvement (Slide 4).

#### CONFIRMATION OF EFFECTIVENESS

Having established that the treatment is effective, the last important step is to confirm the treatment's effectiveness by modifying the treatment for all patients who show evidence of improvement. We appreciate that if the remedy is really worthless, that all of these periods of temporary improvement will of course be followed by recurrence of disease. Therefore once the patient shows clear-cut improvement it is important to modify the treatment by either lowering the dose or discontinuing the therapy. The basis generally given for this is that now that improvement has been established, the treatment is no longer necessary, either at its higher dose or at all. The consequences of lowering the dose or discontinuing therapy leave only three possible outcomes. The first is that the patient will continue to show improvement, which confirms for the therapist that it really was an effective treatment. However, the patient may either fail to continue to improve, that is become stable, or actually show progression again. These two outcomes confirm the effectiveness of the treatment, since once it was withdrawn, the disease again becomes active. This proves unambiguously that the treatment was responsible for the previous improvement, and therefore one simply has to reinstitute treatment, as one did at the very outset for Stage I of therapy, and proceed through the plan again, as one did at the very beginning. This confirming step serves the function of consolidating the initial impression that the treatment is uniformly effective, and perhaps most important, allows for the inevitable progression of the disease which would have occurred even if the treatment had been continued at the full dosage and schedule (Figure 5).

Thus, either informed (that is, deliberate and knowledgeable use) or uninformed (that is, inadvertent and accidental) use of the plan, both assure that the treatment will be effective and that the effectiveness can be demonstrated in virtually all patients with the disease.

#### BENEFICIAL EFFECTS OF UNPROVEN REMEDIES

The evident and continuing success of the medical quack should encourage inquiry into the basis for this success. It is clear that the medical quack does provide something that is highly desirable and highly effective, and accounts for his continuing success. I think that the essential commodity that the quack offers along with his treatment is "hope". The quack never tells the patient that his situation is hopeless and beyond treatment. He never uses terms like "inevitably fatal", or "terminal". He is generally full of confidence that the remedy will improve the outlook for such patients. He administers effective treatment for the feelings of hopelessness that accompany the poor prognoses for serious diseases such as cancer. This component of treatment is well-recognized by all practitioners of the healing arts. We struggle together in an atmosphere where the inevitability and certainty of death is widely appreciated. Yet our efforts are dedicated to the relief of suffering and to the prolongation of life. Those are essential ingredients of hopefulness. The quack, of course has the advantage of being thoroughly convinced that the situation is not without hope, and that his treatment will, in fact, benefit the patient. That is the secret of his success.

#### PHYSICIANS' CONTRIBUTION TO THE SUCCESS OF UNPROVEN REMEDIES

Physicians are constantly faced with the necessity of providing for the patient information which contains serious and often life-threatening prognoses.

There have been physicians who have withheld knowledge from the patient in the hope of averting the feelings of hopelessness and the inevitable depression which accompanies the patient being informed of a poor prognosis. This practice is no longer a tenable or a feasible approach. With improving quantitative, objective techniques for diagnosis and staging of disease, particularly malignant disease, the physician now has the capacity to make prognostic statements of fairly good precision. Therefore, it is morally, ethically, and legally necessary that the patient be informed of the physician's estimate of prognosis, as well as his statement about the best available treatment and its potential benefits and harmful side effects. The difficult problem is the problem of adequately informing patients of the implications of these grim prognoses. Such information requires extensive discussions, long investments of time, and physicians who are frequently busy and hurried are unable to make the commitment to the necessary discussions to completely inform the patients about all the knowledge relevant to their particular problem. In such a setting, patients may, through the technique of denial, run from the threat of either a disfiguring operation or a painful treatment, or an unpleasant therapy toward the medical quack who offers no toxicity and 100% success. It seems clear that the medical community must acquire the skills of the medical quack and combine these skills with his professional capabilities of effective diagnosis, prognosis and treatment.

One essential component is a well-trained, informed, up-to-date physician. If the physician is aware of the rapid progress in the palliation and even cure, of major illnesses such as cancer, he has the best opportunity to offer his patient the most promising proven treatment. However, even when the physician's knowledge indicates a serious and potentially hopeless situation, he should be

aware of the potential of clinical research as a therapeutic maneuver to assist the patient to avoid feelings of hopelessness. In the clinical research setting, treatments are selected for patients where the probability that the new treatment will be better than conventional is substantial. In such a setting, the clinical investigator can offer the patient the opportunity of being the beneficiary of any new discoveries which lead to improved management of these serious illnesses. Thus, clinical research can provide an effective form of therapy for hopelessness and a significant and positive alternative to medical quackery.

The major difficulty with clinical research is the risk attendant to clinical research. That is, the potential of harm. Allied with its potential for a less favorable outcome, is the vision of the clinical scientist as a heartless, objective, professional whose adherence to scientific principles supercedes his humane, physician, clinical, and personal characteristics, which we have come to recognize as an essential component of the patient-doctor relationship. This image of the clinical investigator as one who "experiments on people" has been aggravated in recent times by the use of clinical trial techniques which involve random allocation of patients to new and conventional treatments without the physician or the patient being able to affect the choice of treatment. The use of placebos in lieu of drugs for treating diseases, and the use of the blind, that is, where the patient is uninformed about which treatment he is receiving, or even more serious, the double blind, where both the physician and patient are uninformed about what drug or treatment is being given, or even the *reductio absurdum* triple blind circumstance, where the patient, the physician, and the person responsible administratively for interpreting the results of the trial are all uninformed about what treatment is being administered. This clinical

trial technique has proven to be extremely effective in the past. Not only has it helped in discovering minor differences between treatments, but it has also gained widespread acceptance in the biomedical clinical research community, as well as amongst physicians in the health care delivery segment of the community. There is a conviction that any knowledge generated by other techniques are somehow suspect and that information generated by the "randomized, double-blind, concurrent, controlled clinical trial" has an extraordinary degree of validity. There is no doubt about the reality of the effectiveness of such clinical trials, however, with widespread application of this technology, it has become clear that it is not regularly an effective technique and in some cases it can give misleading or false results. Perhaps more important, this technique does significantly interfere with the normal patient-doctor relationship. In recent years, it has been demonstrated that there are techniques for clinical research which are better suited for the discovery of new treatments, while at the same time offering for each patient and for each investigator the opportunity to fully utilize the clinical setting, that is, the patient-doctor relationship, toward the patient's benefit. It is clear that all techniques for research require quantitative, objective criteria for evaluation of therapeutic benefit. It requires a systematic experimental plan which is decided in advance and clearly avoids the pitfalls of the "Freireich Experimental Plan" described above. And finally, it is important that results in any group of treated patients be compared to an appropriate, properly selected, "control" group of patients.

#### EFFECTIVE TECHNIQUES FOR CLINICAL RESEARCH

1. Major dramatic alterations in therapeutic results. The observation of a dramatic change in outlook for patients as a result of treatment are easy to recognize and require only confirmation in larger series of patients.

Examples are innumerable, such as the effectiveness of antibiotics for the treatment of infections; the dramatic complete regression of choriocarcinoma following methotrexate therapy; the dramatic improvement in frequency of objective, complete remission in childhood leukemia, in Hodgkin's Disease, and in lymphocytic or histiocytic lymphoma, with multiple drug combination chemotherapy; the dramatic improvement in the survival of patients with pseudomonas septicemia following carbenicillin therapy, etc. In these circumstances, the primary ingredient of the experimental plan is to have a highly significant and important objective. If one has an objective of comparing treatment A and treatment B in a circumstance where the probability that treatment A will only be 1-5% better than treatment B, then the outcome is most likely to be either no difference or a slight difference. In contrast, if one enters a clinical study with a treatment which has a high probability of success in a circumstance where the success rate has been extremely low, then the potential for discovering major changes do exist. It is important to stimulate and encourage research aimed at what has commonly been called the "home run" mentality. Carbenicillin had dramatic activity against pseudomonas in vitro and the probability that a high degree of activity would be observed was high in the clinic. Since it was a penicillin, it was predicted that toxicity was low, and that was confirmed. Thus, to approach the study of such a drug by allocating patients to either penicillin known to be ineffective, or carbenicillin, with a high probability of effectiveness would have seriously compromised the potential for benefit to the patients who received the control treatment. Likewise, for the use of methotrexate in choriocarcinoma, a circumstance where the progression and mortality was extremely high. After observing dramatic regressions in the first few patients, it was only necessary to expand the number of individuals treated to demon-



strate unambiguously that fully 50% of the patients would have complete remission, in fact, cure of their disease with therapy. It would be a cruel type of human experimentation to have required that half of the patients receive treatment known to be ineffective in order to be certain that this 50% cure rate did occur. When new treatment is offered to a patient which has the prospect of a major change, the inherent risk of side effects will be infinitely more acceptable when the potential for dramatic change in the overall outcome is what is being sought by the investigator.

## 2. Dose Response

The power of the dose response in unambiguously demonstrating effectiveness of a treatment is frequently overlooked. For virtually every treatment, there will be a therapeutic toxic ratio, which is significantly affected by the dose, route and schedule of administration. If any treatment is twice as effective at a given dose than it is at another dose, then it is clear that the effectiveness can be ascribed to the treatment. If a series of doses is evaluated, then one can construct a dose response curve and make extrapolations to the expected result from either no treatment or from too high a dose. An example of this is the effectiveness of platelet and white cell transfusion for the management of bone marrow failure. In both of these circumstances, it was possible to demonstrate that the risk of hemorrhage and the response of infection was dose-related, that is, the higher the number of cells injected, the higher the circulating level in the blood, the higher the probability of control of hemorrhage and infection. Thus, the dose response study offers the clinical investigator the opportunity to discover the best way to administer the drug at the same time that it established the drug's unambiguous activity.

### 3. Staging of disease.

If a treatment is given to a group of patients and a percentage of patients less than half show objective and unambiguous benefit from the treatment, then a comparison of the treated group to a control group, only at the median, would reveal no or only a minor difference. Many treatments have been overlooked or declared ineffective in comparative trials because there failed to be a significant difference between the treatments at the median. This problem, which I have referred to as "median disease" relates to the fact that the technical aspects of the statistical methodologies are most developed around the average, or the median. One can avoid "median disease" by careful evaluation of clinical trials relevant to those factors associated with response. If a treatment is given to a group of patients with a disease, and 25% of the patients show complete remission, examination of the responding patients and those who failed to respond will frequently reveal characteristics present prior to treatment which identified the responsive patients. One important characteristic is the extent of disease, thus, treatments which are curative against early disease will have minor or only palliative effects against advanced disease. Choriocarcinoma referred to above is an example where after the 50% response rate was demonstrated, it was found that failure rate was accounted for by patients who had advanced disease, as evidenced by high titers of chorionic gonadotropin in the urine. Likewise, for Hodgkin's disease, the cures from radiation therapy were found to be related to the staging, that is, the extent of disease. Stage 1 patients being curable, whereas Stage 4 patients have virtually no cures. Careful selection of patients for treatment allows definition of effectiveness by defining the groups of patients where a high effectiveness occurs in contrast to those groups where effectiveness is low or where it does not exist.

#### 4. Matching

If a treatment is administered to a consecutive group of patients and the results are not dramatically, but only slightly better than has been observed in the historical data, then it can be effective to objectively match the patients treated with the new treatment with patients treated either concurrently or in the immediate past by other or more conventional treatment. Such matching techniques require matching for all of the variables known to effect the probability of response and assures comparability between the treated and the "control" group. The validity of the matching procedure can be checked by matching the "control group" patients receiving conventional treatment with another group of patients who also received the same conventional treatment, if the two groups prove to be comparable, then the prognostic factors which were selected do, in fact, identify a comparable group of patients. Then, differences between the new treatment and the conventionally treated matched control group can be interpreted as due to the new treatment.

5. Statistical procedures are available for quantitatively evaluating the importance of prognostic factors for predicting responsiveness. Using a stepwise multiple regression procedure permits selection of historical controls which are comparable to any group of patients treated with a new treatment. In such a way, it should be possible to objectively and quantitatively evaluate, in a series of sequential studies, whether each treatment differs significantly from the preceding one; and one can evaluate whether the prognosis in the overall results is improving with time and with change of treatment. Moreover, comparisons of treatments in different institutions and even different countries can be accomplished by careful analysis of objective and quantitative prognostic factors which assure selection of comparable groups of patients.

SUMMARY

The best clinical research maintains the clinical relationship between physician and patient such that the physician is in a position to offer each patient what, in his judgment is the best available therapy for his illness. The medical quack, or the purveyor of unproven remedies frequently, almost uniformly utilizes the "Freireich Experimental Plan". This plan assures that a treatment with little or no toxicity will be effective in virtually every patient with an illness, despite the fact that the treatment has no effect on the progress of the disease. The clinical investigator avoids the FEP by using quantitative, objective criteria and by using clinical research techniques which assure comparability between treated groups and appropriate controls. The medical quack offers the patient hope for recovery from his illness. The physician and the clinical investigator must strive to learn from the medical quack to incorporate this important ingredient of the therapeutic setting into his treatment plan. It should be possible to devise approaches to clinical research which offer the patient hope, which provide objective and quantitative data for the clinical investigator, and maximize the probability that each patient will receive the best available medical care for his illness.

I

THE FREIREICH EXPERIMENTAL PLAN

(Guaranteed to produce beneficial results)

REQUIREMENTS:

1. TREATMENT: Any form will do.
  - a. Psychic - meditation, prayer, biofeedback, psychoanalysis.
  - b. Drug - extracts, potion, pill, vitamin, chemical, sedative, biologic.
  - c. Procedure - rub, exercise, machine
  - d. Environment - temperature and humidity, sun.
2. LACK OF HARMFUL EFFECT.

Figure 1. The Freireich Experimental Plan - Part I

II  
THE FREIREICH EXPERIMENTAL PLAN  
(Guaranteed to produce beneficial results)

TECHNIQUE:

1. Proof of effectiveness
  - a. Natural variability of all disease.

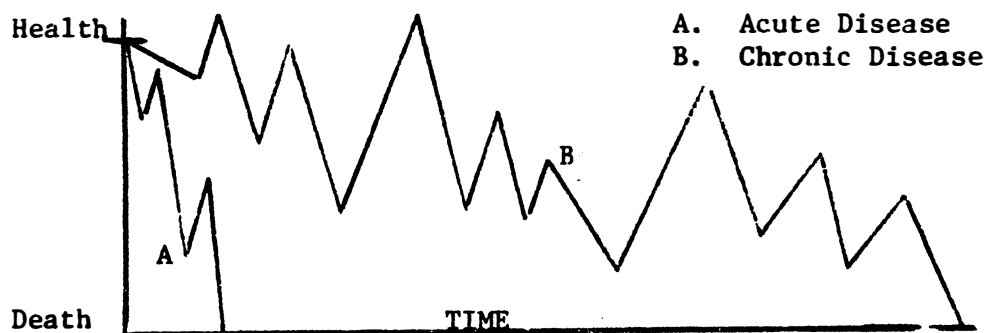


Figure 2. The Freireich Experimental Plan - Part II

III  
THE FREIREICH EXPERIMENTAL PLAN

TECHNIQUE:

1. Proof of Effectiveness
- b. Consequence of treatment (Stage 1)

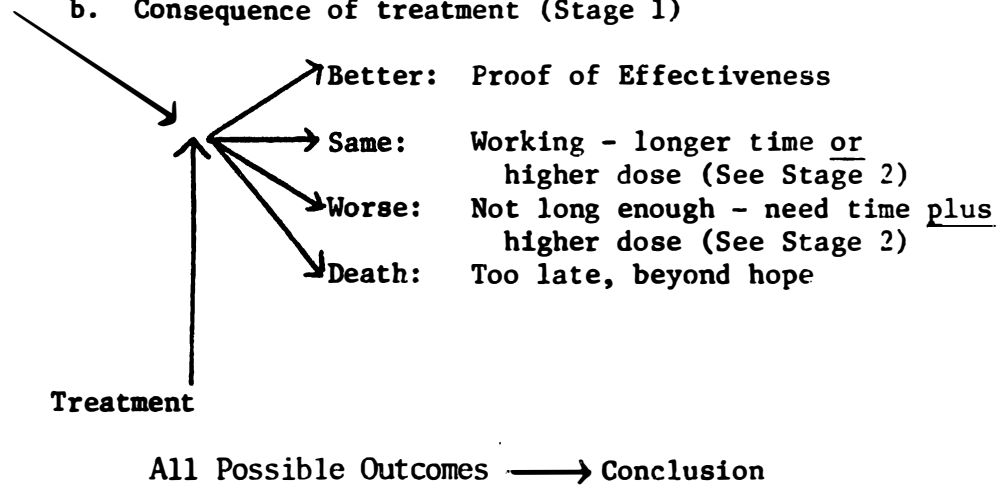
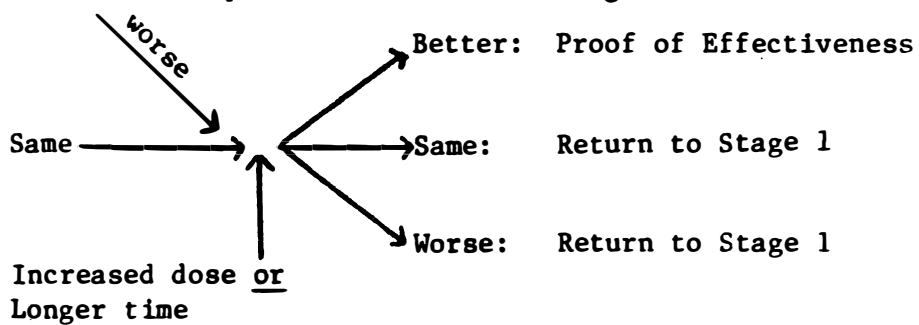


Figure 3. The Freireich Experimental Plan - Part III

IV  
THE FREIREICH EXPERIMENTAL PLAN

1. Proof of Effectiveness

c. Consequence of Treatment (Stage 2)



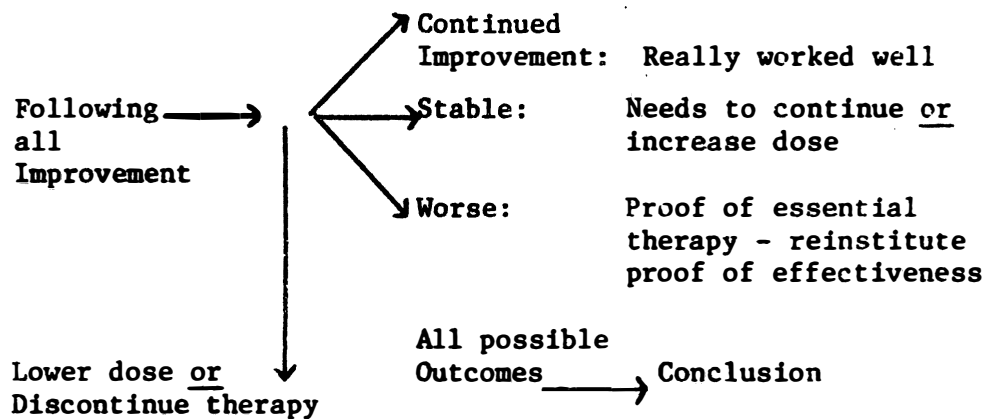
All Possible  
Outcomes → Conclusion  
Conclusion of Proof of effectiveness, Stage 1, 2, etc.:  
**CLEARLY 100% EFFECTIVE**  
(unless) too late, beyond any hope.

Figure 4. The Freireich Experimental Plan - Part IV



V  
THE FREIREICH EXPERIMENTAL PLAN

2. Confirmation of Effectiveness



CONCLUSION: Proof of essential nature of therapy

Figure 5. The Freireich Experimental Plan - Part V