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COMBINING PSYCHOSOCIAL AND DRUG THERAPY
Hypertension, Depression, and Diabetes

Health and Behavior: A Research Agenda
Interim Report No. 2

Summary of a Conference

Edited by Delores L. Parron, Fredric Solomon
and Robert J. Haggerty

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Psychosocial and Pharmacological Treatment Approaches:
Issues and Interrelationships

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PREFACE

A conference on "Psychosocial and Pharmacological Treatment Approaches: Issues and Interrelationships" was held May 28 and 29, 1980, at the National Academy of Sciences in Washington, D.C. The conference was organized by the Institute of Medicine, through its Division of Mental Health and Behavioral Medicine. Support was provided by the Alcohol, Drug Abuse, and Mental Health Administration and the National Institutes of Health. This meeting was the second in a series of six invitational conferences to be conducted over a two-year period as the principal data-gathering effort for a study of "Health and Behavior: A Research Agenda." The conferences will attempt to

- direct the behavioral sciences toward a wider range of health problems than the mental health issues with which they have traditionally been concerned
- link the biomedical and behavioral sciences
- stimulate interdisciplinary clinical and basic research.

The study is designed to assess the present and potential contribution of the behavioral sciences to our understanding of several serious and widespread public health problems, and find ways in which both the biomedical and behavioral sciences can be employed to reduce the burden of illness in this country. David A. Hamburg, M.D., director of the Division of Health Policy Research and Education at Harvard University and former president of the Institute of Medicine, is chairman of the committee for the study "Health and Behavior: A Research Agenda."

Under the chairmanship of Robert J. Haggerty, M.D., president of the W.T. Grant Foundation, New York, the conference on Psychosocial and Pharmacological Treatment Approaches brought together behavioral science investigators and biomedical scientists who have worked extensively on the biologic and behavioral aspects of hypertension, depression, and diabetes, along with scientists (both biomedical and behavioral) who have not worked directly in these areas. The participants from the biomedical and behavioral sciences who were outside the fields of hypertension, depression, and diabetes were selected because their concepts, methodology, or data would seem to have great potential for transfer to studies of each of these disorders. In general, the meeting was an opportunity to examine the contribution that scientific knowledge in "biobehavioral" areas has made and can make to the understanding of psychosocial and

pharmacological treatment modalities, and to explore the adaptation of this knowledge in behavioral intervention strategies. The discussions emphasized research approaches that could, in the future, be undertaken profitably in attempts to integrate relevant biobehavioral research into the health sciences that bear directly on medical care.

The opening presentation by Gerald L. Klerman, M.D., Professor of Psychiatry, Harvard Medical School (and formerly the Administrator of the Alcohol, Drug Abuse, and Mental Health Administration), outlined basic issues involved in the theoretical integration of biological, biomedical, social, and psychological conceptions of illness. Although the program agenda suggests that hypertension, diabetes, and depression have similarities in treatment (for example, requiring patients to make daily lifestyle adjustments, such as taking medication or following a diet), there also are considerations of distinct disease-specific problems. Thus, a separate panel considered each topic: hypertension, depression, and diabetes. Each panel began with an overview of the disease, emphasizing modern classification of the ailment and its natural history. Next, the current trends and controversies in pharmacological treatment were presented. Following this, the psychosocial interventions were described. The fourth presentation of each panel addressed concerns common to all three topics: Marshall Becker, Ph.D., discussed the Health Belief Model and issues related to adherence; Sol Levine, Ph.D., addressed social factors influencing the implementation of combined treatments; the importance of recognizing the needs of particular patients and modifying treatment approaches was highlighted in the presentation by Allan L. Drash, M.D. on psychosocial issues in diabetes, which included a special regard to child and adolescent diabetics and their families.

Following presentations by each panel, conferees participated in general discussions led by R. Brian Haynes, M.D., Ph.D. (hypertension); Myrna M. Weissman, Ph.D. (depression); and Ruth T. Gross, M.D. (diabetes). These plenary discussions elaborated key issues on biobehavioral research raised in the presentations. In summarizing the discussions, it is nearly impossible to attach a name to each significant idea represented. The transcript recorded virtually every listed participant as playing a useful role and so deserving partial credit for whatever value these proceedings may have. Appendix B lists the full conference agenda; Appendix C lists the participants invited to attend the conference.

OVERVIEW
PHARMACOLOGICAL AND PSYCHOSOCIAL TREATMENT APPROACHES

Robert J. Haggerty, M.D.

Medicine has relatively few types of therapy available: cutting, manipulating, dosing (drugs, nutrients, ionizing radiation) and talking (including advice to change a patient's lifestyle and environment). Dosing, especially pharmacological therapy, and talking have been mainstays of the physician's resources since Hippocrates, but pharmacotherapy has assumed greater dominance since the biochemical era has made it rational and efficacious. Talking or psychosocial therapy, including newer methods such as biofeedback, have created a good deal of interest in recent years, but researchers in this field largely have worked independently of researchers in pharmacology, even when they were studying the same disease. The world of medicine often is divided into broad groups, in part by the therapy used. Surgical, medical, and psychologic therapists have had few joint efforts in clinical care, and collaboration in studies of the efficacy of their respective treatments are rare.

The successes of biomedical research have contributed to the development of biological explanations of the etiology and pathophysiology of illness and its treatment. Much of modern medicine has been directed toward considering illness to be an outcome of specific agents or bodily malfunctions that usually are unrelated to a patient's environment and lifestyle. This model has had extraordinary utility but as the burden of illness has shifted to chronic disease and long-term care, limitations of this approach have become increasingly apparent. Moreover, advances in behavioral sciences and psychiatry have contributed to understanding of the behavioral factors in health and disease, and the paradigm of modern medicine has begun to include social and psychological factors in illness. Prominent in the integration of these concepts is the advent of behavioral medicine, a new interdisciplinary approach that incorporates into medical research and practice such disciplines as physiology, psychiatry, sociology, and psychology. Under the rubric of behavioral medicine, promising behavioral therapies based upon the notion of healthful interactions of mind and body have evolved. These studies demonstrate the need, in both psychiatric and general medical care, of greater understanding of the functions of psychosocial interventions (counseling, psychotherapy, or other behavioral techniques) in relation to biological (usually pharmacologic) treatment methods.

In the tradition of the Institute of Medicine, this conference was an attempt to create a setting for interdisciplinary communication. The conference this report summarizes was an effort to begin to bring together two branches of medicine--the dosers and the talkers--in the conviction that combined therapy will, for some illnesses, result in better patient care than any single therapy, and to explore research needs in the study of efficacy of therapies singly and combined.

Three prevelant illnesses--arterial hypertension, diabetes mellitus, and depression--were selected because each has been subject to dramatic pharmacological therapeutic advances in the past decade. There also has been substantial research on the effects of psychosocial therapy in each of these illnesses, but rarely have the factors contributing to the efficacy of these two types of therapy been evaluated simultaneously. Using the window provided by these three illnesses, we examined the state of our knowledge and where future collaborative work would be most fruitful.

There is little need to repeat the highlights of the introductory papers to each of our three topic diseases, or the papers outlining our knowledge of the effectiveness of pharmacology or psychotherapy. Each was prepared by a leading expert in the field. They described the causes, consequences, and therapy of arterial hypertension, diabetes mellitus, and depression.

There are common themes in the presentations of the clinical problems. In all three illnesses, control of the major presenting symptoms -- blood pressure, blood sugar, or depression -- improves outcome. This is not to say that there are not other consequences or other goals in therapy, but at least there are reasonably reliable, important, and easily determined measures by which to judge the efficacy of therapy. Thus, these three diseases are useful for determining the efficacy of combined therapies. In all three, genetic factors are known to play a role in etiology, although in each case the inheritance is polygenic and no specific gene-enzyme-biochemical link has yet been established. Nevertheless, there are clear biologic aspects. In hypertension, 50 percent of the variance in risk between individuals is due to genetic factors, but three other factors--weight, salt intake and stress-personality--in part related to behavior, account for a large part of the remaining variation.

Obesity also is a behavioral risk factor with etiological significance in diabetes and among some diabetics inactivity increases insulin need. Both obesity and inactivity have behavioral aspects. The complexity of this association, however, caused several conference participants to warn that knowledge of causal factors, even though they are behaviorally related, should not be interpreted to mean that successful treatment, once the disease occurs, can be achieved solely by control of these factors. There

may well be different behavioral approaches needed for prevention as compared with treatment.

In all three diseases, there has been a remarkable amount of pharmacologic research in the past decade. The specificity and efficacy of pharmacotherapy has been demonstrated for all three of our topic diseases. Analogous evidence concerning psychosocial therapies is at a much more primitive stage, but the volume and sophistication of research on psychosocial interventions described at this conference, especially for depression, was impressive. What was most lacking was study of the combination of pharmacologic with psychosocial therapy. In depression, a few preliminary studies have been reported of combined therapy, which indicate greater benefit from combined therapy than from either method alone. Control groups that received neither treatment showed the least effect.

There is some evidence of efficacy of combined pharmacologic and psychologic therapy in diabetics. Educational programs combined with modern pharmacologic control have resulted in fewer hospitalizations for ketoacidosis.

Behavioral factors in etiology have been most rigorously studied in hypertension. Animal research has demonstrated that confrontation between mice competing for food, or immobilization of rats, leads to arterial hypertension which is mediated by a rise in serum dopamine beta-hydroxylase. However, the complex interactions of kidney, brain, hormones, and enzymes, in initiating and maintaining hypertension, suggests different approaches for therapy at different stages of the disease process. Great interest has developed in biofeedback, relaxation response, aeorobic exercise, and diet control in the treatment of hypertension. These methods should prove especially useful for hypertensives who comply poorly with drug therapy, often because of unpleasant side-effects of the medications currently used. However, these behavioral treatments have been shown to have only a small effect on reducing the baseline or resting levels of blood pressure. They should be further assessed, especially for their ability to prevent severe pressure increases under conditions of stress. Research now needs to be directed at clinical studies of efficacy of behavioral methods of blood pressure control prior to or concurrent with the first step in the "stepped" drug therapy program.

An important point made in the conference was the need to specify the type of psychotherapy or psychosocial intervention being employed in clinical care. Psychological management extends to all patient care, even in the absence of specific mental disorders. Although humane patient care is not usually considered a specific treatment modality, there is wide agreement that therapeutic response can be enhanced by psychologically-informed intervention for chronically ill patients and their families. Psychological

management, counseling, or planned psychosocial interventions, are not specific psychotherapy, which may be used in the treatment of patients with concurrent mental disorders. Psychological management includes a proper explanation of the diagnosis; what the patient can expect in terms of prognosis and course; an explanation of the treatment, including side effects; and the availability of the physician for patient questions and regular visits. These visits may be brief; their frequency depends on the stage and nature of the disorders. Most patient visits are devoted mainly to review of the symptoms, efficacy of treatment, and side effects. For example, in the case of a depressive patient treated with medication in a general medical care setting, this would also include a review of depressive symptoms--lack of appetite, sleep disturbance, suicidal risk--and perhaps monitoring of plasma drug levels to determine drug effects. Psychological management does not ordinarily include discussion of specific interpersonal or intrapsychic issues, although these may be briefly explored. Usually the discussion of these issues occurs when they appear to interfere with adherence to the prescribed treatment.

In the general medical setting, counseling or psychological interventions typically are considered adjunctive to a therapeutic regimen in which medication is the primary treatment method: in the instances of hypertension and diabetes, medication and/or special diet may be reinforced by individual or group counseling. However, some psychobiological and psychosocial interventions may directly affect the symptomatology itself. For example, claims have been made for biofeedback and relaxation techniques in lowering blood pressure, and various measures to reduce stress (or its personal impact) have been regarded as directly helpful.

No universally accepted terminology exists for the many different kinds of specific psychotherapy. Although there are exceptions, one common denominator can be identified: in the specific psychotherapies there is verbal dialogue between the person administering the treatment and the person receiving it. This dialogue is specifically directed toward bringing about either desirable psychological or social change, or both, in the recipients. The goals of these verbal treatments can include reduction of symptoms, improved adaptation, better social functioning, increased self-esteem, greater assertiveness. Many specific therapies have been developed under a wide variety of rubrics and professional auspices. Some examples include counsel- ing, casework, psychoanalysis and all variants of individual psychotherapy, such as family and marital therapy, groups psychotherapy, and cognitive and behavioral therapy. There is no one standard psychotherapy.

The personal or host variables are even more important in psychosocial therapy than in pharmacotherapy. Variations in results

may be due to the type of person treated, as well as the type of treatment. Studies are needed to predict which person is most likely to show severe psychologic disturbance as a result of illness, or to be a non-compliant patient, as well as which will vary in response to drugs. Compliance with pharmacotherapy for many diseases, is in large part a behavioral issue and deserves increased research. We know a good deal about attitudinal and other correlates of noncompliance. We now need carefully controlled trials, based upon this research, of ways to overcome noncompliance. One of the most promising approaches to improving compliance among patients has been to make changes in the education of physicians.[1/] Noncompliance with psychosocial as well as pharmacologic therapy has rarely been studied and may be a factor in who accepts therapy as well as who complies once therapy has begun.

The specific quality of the psychosocial intervention is obviously an important issue. Some of the differences in results obtained in studies of behaviorally-oriented therapies for our three topic diseases probably are due to variations in the quality of treatment. Studies in the future must record and quantify the input (behavioral therapy) variable as well as the outcome with more precision. Even in studies of depression, only some of the many possible psychosocial interventions have been evaluated. The "purity" of the treatment, a major problem in research on the efficacy of psychotherapy, is rarely a problem in well-designed pharmacologic research. In future studies of combined pharmacologic and psychosocial therapy it will be important to define which is primary, which is adjunctive, and whether they are interactive in a synergistic or negative way.

An important aspect of all illnesses and their therapy is the socio-cultural context in which they occur: the value or attitude of society towards different ills, and the degree to which the social network can be mobilized for help. For instance, people are reluctant to identify themselves as friends of the mentally ill, but not as friends of diabetics or hypertensives. There are delays in seeking care that differ by illness and culture. Behavioral research could be especially helpful in understanding the influences of these factors and in proposing strategies for eliminating them.

We were reminded that the professional culture as well as lay culture dictates aspects of therapy. If we want to encourage more psychosocial therapy, we may have to change education, reimbursement, and prestige within the health professions. Studies of the broader

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1/ T.S. Inui; E.L. Yourtee; and J.W. Williamson. "Improved Outcomes in Hypertension after Physician Tutorials: A Controlled Trial." Annals of Internal Medicine 84 (1976): 646-651.

cultural influence will require researchers with skills to study these socio-cultural variables.

In today's climate of cost-consciousness, research on the behavioral aspects of any illness must examine the trade-offs between cost and effectiveness. One discussant noted that the cost in the hospital of treating 184 diabetic patients who required limb amputations was seven million dollars. Psychosocial interventions, combined with pharmacotherapy, could reduce this complication, but such an effect might appear in cost-saving terms only after several years. Therefore, there is a need for long-term as well as short-term studies of behaviorally oriented therapy. The market or competitive strategy now being advanced for financing of health services may not be responsive to such long-term feedback loops. Research in combined behavioral-pharmacologic treatments must be sensitive to measure the cost effectiveness of this approach.

A major theme of this conference was the need for "action" or "implementation" research. Once efficacy studies, of single or combined therapy, have been completed, and shown to be positive, there remains a need to demonstrate how these can be translated into practice, to find resources to pay for them, and to gain acceptance by society and all patients who have need.

Behavioral science has a powerful role to play in conjunction with traditional biologic research at the levels both of the individual patient and of society if we are to improve the nation's health. This conference began such collaboration between researchers to achieve that goal.

DISCUSSION SUMMARY: COMBINED THERAPIES IN CLINICAL PRACTICE AND IN RESEARCH

Interdisciplinary biomedical and behavioral research on hypertension, diabetes, and depression should broaden the perspective of investigators and lead to more effective treatments. However, conducting such studies presents formidable challenges in collaborative design, execution, analysis, and interpretation.

Hypertension

Clinical research on hypertension amenable to collaborative inquiry includes analysis of patient characteristics and behaviors, the longitudinal course of the disease, and new approaches toward ensuring improvements in the quality of patient's life. Other multidisciplinary studies are evaluation of the efficacy of various therapies, clinical consequences of patient noncompliance with prescribed regimens, and obstacles to monitoring blood pressure changes of the individual patient or in the population at large.

Few Experimental Data on Combined Treatments

Lester Luborsky presented results of his current research comparing pharmacologic and behavioral treatments of hypertension. Although there are studies comparing the efficacy of different pharmacologic treatments or of different behavioral treatments, his work represents an attempt to compare, in a single experiment, both types of therapies.

Dr. Luborsky's study focused on patients with borderline to mild hypertension: 140/90 mm Hg to 160/103 as measured by a standard sphygmomanometer during a two-week, eight-session baseline evaluation period. Ten to 15 patients were randomly assigned to each of four groups: (1) pharmacologic treatment, (2) metronome-conditioned relaxation 1,2/, (3) biofeedback, and (4) metronome-conditioned mild exercise. The pharmacologic treatment group received antihypertensive medications, the second and third groups participated in behavioral therapies, and individuals in the last group served as a control. Of special significance were the difficulties encountered in the early stages of the research: first, it was difficult to find hypertensive patients who had not

already received medication therapy and, second, 40 percent of the research subjects were lost from the study during the baseline period because their blood pressures had returned to normal--the so-called "baseline effect."

Dr. Luborsky reported that the medication group improved significantly compared with the psychosocial and control groups, which did not significantly differ from each other. These results confirmed the findings of an earlier pilot study. 4/ However, given previous demonstrations of the efficacy of behavioral treatments for hypertension, Dr. Luborsky questioned the wisdom of relying solely on a statistical analysis comparing group means. Consequently, he analyzed the data within each of the four groups to determine the percentage of patients actually benefiting from their treatment. An important finding emerged from this analysis: approximately 50 percent of patients in both biofeedback and medication groups showed a drop in blood pressure to 140/90 or below. The 50 percent improvement rate is similar to that reported by the Hypertension Detection and Follow-up Program (HDFP) Cooperative Group for the patients in "stepped care."* (Dr. Luborsky's medication group had received "stepped care," which involves systematic stepwise administration of complementary antihypertensive medications to achieve or maintain reductions in blood pressure.)

Additional research may be able to determine which types of patients seem to respond better to behavioral treatments. The importance of this research is underscored by the fact that many patients report negative side effects from antihypertensive medication, a problem that could be eliminated or delayed if

*The HDFP refers to a community-based, randomized, controlled trial study comparing the effects of two antihypertensive treatment programs on five-year mortality rates. 3/ The protocol included screening 158,906 individuals from 14 communities in the United States. From this group, 10,940 persons with high blood pressure were referred to special centers and were randomly assigned to one of two treatment groups. One group was treated using the "stepped-care" program. In the other treatment program, "referred-care" patients received standard referrals to their usual sources of medical care, special referral efforts being made only if the individual evidenced severe hypertension or organ system damage. The stepped care group clearly benefited from the systematic management of treatment. Their control of blood pressure was consistently better over a five-year period, and although two-thirds of them continued to receive medication, 50 percent attained blood pressures in the normotensive range. Compared with the referred care group, mortality rates from a variety of diseases were lower for the stepped-care group.

proved effective. Dr. Luborsky suggested that, in certain cases, physicians consider initiating treatment of hypertension using a behavioral rather than pharmacological method.[5] Such an approach could constitute a "step zero" in the stepped care program. Redford Williams reported that he also reached this conclusion from a different set of research results.[6] Both investigators thought that the low-risk hypertensive patient was a suitable candidate for behavioral therapy as a "step zero" in hypertension treatment.

Although the avoiding of unnecessary medication of hypertensive patients seems to be a desirable goal in clinical care, the appropriate length of a delay before instituting pharmacological treatment is a question for study. Dr. Luborsky indicated that the two-week, eight-session baseline period he employed appeared to be long compared with other hypertension research designs. Dr. Luborsky interpreted as a therapeutic success rate the observed "baseline effect" that produced a research subject drop-out rate of 40 percent. From a clinical perspective, conferees thought that it might be appropriate to delay drug treatment of borderline hypertensive patients, especially given the existence of the "baseline effect" and the evidence that behavioral treatments may be as efficacious as drug therapy in some cases. Doing this also would increase opportunities to assess the efficacy of other behavioral treatments because patients would not immediately be placed on drug therapy.

Issues in Diagnosis and Treatment

The diagnosis of hypertension remains relatively undifferentiated. Ethan Sims observed that diabetologists were in a similar circumstance some years ago; their solution was to distinguish between adult-onset diabetes and the juvenile type. An analogous situation may exist with hypertension. According to Dr. Sims, many physicians acknowledge treating at least two types of hypertensive patient, the "lean, hungry hypertensive" and the "overweight hypertensive." Dichotomies such as these may prove clinically useful by directing attention to salient patient characteristics or by calling attention to modifiable aspects of the patient's environment. Perhaps adding behavioral components would assist decision-making about the need for and type of treatment. The patient so evaluated may benefit from more individualized interventions, for example, being offered information about regulation of salt or calorie intake, or being informed about some basic relaxation techniques.

Conferees thought that additional empirical studies about psychosocial correlates of hypertension could help in refining diagnosis, improving understanding of the disease course, and

informing those who must medically manage the disorder. Three examples of psychological and social confounding variables were cited: the "white coat" or reverse placebo effect of having elevated blood pressure only in the health care provider's presence, the time of day at which blood pressure is read, and varying blood pressure readings found in patients who routinely monitor their own blood pressure. Such factors are problems not only in clinical care, but also in experiments.

A recurring clinical and research challenge centers on patient adherence to prescribed therapeutic regimens, such as taking medicine, following a particular diet, or regularly engaging in a program of exercise. However, an emphasis on the patient's conscious or unconscious failure may be misplaced; other factors may be implicated as well. Conferees suggested that physicians' behavior--communication of authority, credibility, enthusiasm, empathy, or sympathy--may affect patient adherence to prescribed therapies as much as the patient's attitudes or beliefs. When health care personnel recognize the importance of these factors, patient compliance may be altered.

Many conferees acknowledged that behavioral factors affect adherence to antihypertensive regimens. Some patients may have underlying conflicts that contribute to resisting treatment; for example, some patients believe that monitoring and regulating one's blood pressure constitutes a self-nurturing process that may cause subconscious guilt to be harbored and thus preclude therapeutic success. Clinicians should be aware of such impediments to effective treatment and realize that improving physician-patient rapport may not be sufficient to ensure compliance. Psychotherapy and even psychoanalysis may also be necessary. A multi-modal approach of behavior therapy, drug therapy, and psychotherapy may result in better patient adjustment and recovery.

An important area for research on adherence are the potentially adverse coping patterns related to the alterations in lifestyle dictated by the demands of the treatment regimen. For example, unpleasant drug side effects in otherwise asymptomatic individuals may well override the possibility of increased risk of long-term complications as a consequence of sustained hypertension. Many conferees thought that behavioral treatment of hypertension could be worth wider application, because unlike many drugs it is not associated with negative side effects.

At the Menninger Clinic, Elmer Green has successfully treated 60 hypertensive patients with a program of intensive psychosocial intervention emphasizing biofeedback self-regulation. Forty-eight of these patients (80 percent) were on drug therapy but had become dissatisfied with the medication. Within five to six months of beginning the biofeedback training program, these patients were able

to discontinue their medication and remain normotensive by the criteria of their cardiologists. Dr. Green noted that the success of his program rested on several factors: (1) effective teaching of the technique by competent trainers; (2) an intensive and comprehensive plan for behavioral change, including psychotherapy for personal problems, autogenic training, progressive relaxation, and various types of meditation; (3) using machines and visualization techniques to monitor and reinforce responses; (4) extending the treatment over several months. Controlled clinical trials are needed to assess the efficacy of this treatment approach. Dr. Green emphasized that assessments of the therapist's ability to teach the technique must be included among the variables in any research on biofeedback. This variable rarely receives attention in the early stages of experimental design. Too often the investigator and clinician are unaware that ineffective teaching is the weak link in the program.

Dr. Green emphasized certain aspects of biofeedback training that the trainer must be aware of to be effective. One is the clinical implications of the conceptual distinction between learning and performance. Biofeedback therapists frequently do not require the patients to demonstrate that they not only can reach, but also maintain some criterion level of performance. Important questions for investigation are the appropriate duration and intensity of relaxation training to effectively learn and perform heart-rate regulation, and the effectiveness of biofeedback treatment in the home setting. Only after researchers routinely define "success" in achieving a training effect can attention properly be turned to comparing the adequacy and efficiency of different biofeedback techniques.

Implicit in the orientation of the behavioral therapist is attention to the therapeutic encounter and its contribution to successful therapy. The behaviorist's conceptualization of the therapist-patient relationship may circumvent some of the difficulties usually associated with traditional notions about this interaction, in which patients assume it is necessary to relinquish control to the therapist. If a patient is informed at the outset of treatment that the therapist is only a facilitator and that the patient is the one who controls behavior and decision-making, then he or she may feel free to ask questions, express doubts, determine realistic expectations about success, and, when necessary, to ask for aid in coping with changed or still unresolved problems. Because motivation to continue in treatment frequently improves, adherence problems become less salient.

Monitoring Blood Pressure

For the patient, self-monitoring of blood pressure has implications for therapy, especially when combined treatments are employed. But techniques of monitoring the degree of elevation of blood pressure remain under-researched despite their clinical significance in long-term health maintenance. Careful monitoring of blood pressure accompanied by assessment of other events in the patient's life, such as environmental stressors or dietary changes, may provide important clues about specific factors responsible for raising or lowering blood pressure. Two questions that have yet to be fully explored emerged from discussion of self-monitoring blood pressure: how can the patient best learn blood pressure lowering techniques? how can the instructor best teach such techniques?

From an epidemiological perspective, determining various subgroup prevalence rates of high blood pressure may result in more appropriate interventions. Biological and psychosocial factors may differentially influence hypertension prevalence; for example, baseline data on normal blood pressures are unknown for many racial and ethnic groups. Consequently, diagnoses and treatment made on the basis of a large population average may be inappropriate and costly to patient and society. It is important that researchers be aware that definitions of "normal" blood pressure may vary as a function of the group under study.

The dramatic decline over the last decade in the incidence of stroke and stroke mortality can only be accounted for in part by pharmacologic advances. Greater awareness of hypertension and early entry into treatment account for a substantial amount of the decreased incidence. Community-based hypertension programs have identified specific groups at high risk for hypertension. The assistance of recognized community leaders, such as members of the clergy, is then enlisted in delivering health care messages and encouraging individuals to continue monitoring of blood pressure and adherence to the prescribed treatment. It has been noted that the health care provider's influence on certain patients may be secondary to that of community leaders. This kind of public health outreach program is being tried in many cities.[7]

Some Suggestions for Research

Although clinical evidence suggests that behavioral therapies may offer an adjunctive or possibly alternative treatment approach for certain patients already receiving antihypertensive medication, the clinical usefulness of these new therapies must be firmly established. Attention must also be directed toward consideration of potentially negative consequences of "failing" on a behavioral therapy program. Some conferees suggested that patients might feel

guilty for this failure, and even feel punished when they subsequently had to take medications. On the other hand, a number of conferees suggested that, as adjuncts to medication regimens, behavioral and psychotherapeutic approaches could facilitate adherence. A hindrance to progress in developing treatments is the lack of financial support for studies evaluating the efficacy of these techniques. Thus, many questions remain unanswered and newer techniques remain underdeveloped or untested.

In addition, many nonpharmacologic interventions await development because of lack of understanding of the basic biology of hypertension: what mechanisms or conditions are responsible for lowering blood pressure? what percentage of lowered blood pressure is due to weight loss? and what percentage is due to salt decrease?

In making suggestions about research topics, conferees urged that explicit requirements be made for interdisciplinary collaboration and multivariate research design and analysis. Interdisciplinary studies could call attention to previously unrecognized factors posing risks for subgroups in the population. Multivariate assessment of the population at large or subgroup analysis might disclose the additive or the interactive effects of two or more risk factors. More complex analyses would contribute to understanding the possible multiple etiology of hypertension. Examples of potentially relevant factors included genetic vulnerability, poverty, residence in a high-crime or an urban setting, and access to medical treatment. Failure to assess important characteristics associated with particular subgroups, such as idiosyncratic health beliefs regarding the importance of medication, can result in inappropriate conclusions. In summary, the participants asserted that a collaboration of biomedical and behavioral scientists would greatly enhance the understanding, diagnosis, and treatment of hypertension and its long-term complications.

Depression

The treatment of depression frequently employs both psychosocial and pharmacological approaches, but studies assessing the efficacy of such combinations are rare. Presentations at this conference of preliminary findings of research on the long-term efficacy of single and combined treatments* for depression provided an empirical basis

*See presentation by Gerald Klerman, p. 35 and presentation by Myrna Weissman, p. 95.

for conferees to identify components of psychotherapeutic, pharmacogical, and combined treatments of depression. Although the effects of drugs and psychotherapy only for treatment of depression were discussed, similar considerations will arise in combined treatments for other psychiatric disorders.

Current Concepts of Depression and Implications for Treatment

Until recently, depression was characterized as a single disease. Conferees suggested that using the term "the depressions" might serve to remind scientists and to inform the public of the heterogeneity of the disorder and to suggest more complex conceptuals and encouraged further research and treatment options. Viewpoints among the conferees appeared to vary as a function of the model they believed best characterized depression. Three perspectives were evident: (1) a biological concept of depressive disorders, said to result from disturbances in a metabolic, endocrine, or biochemical system; (2) a psychodynamic concept, the disorder viewed as a reflection of defects in psychosexual or interpersonal psychological development; (3) the biopsychosocial model, which suggests that it may be advantageous to classify depressions according to certain distinguishing psychological and social difficulties that interact to produce different symptom patterns, for example, depressed individuals frequently have difficulty coping with a variety of problems, such as death of a loved one, unrealistic expectations, work-related stress, or lack of social supports in their lives. The manner in which these difficulties evolve and interact can promote depressive symptoms that are accentuated by the ensuing biological dysfunction. These biological and psychosocial factors may form a type of feedback loop from which escape may be difficult unless the treatment combines psychosocial and pharmacological approaches.

Barry Blackwell said that the therapist's perspective or preferred model for conceptualizing depression extends to and influences clinical practice. For example, the biopsychosocial model suggests that there are different levels of organization, different symptom patterns, and different outcomes associated with drug treatments. Using a biopsychosocial model of illness, drug therapy could be seen as having positive effects in two groups of patients: (1) in a major depressive syndrome, high levels of tricyclic antidepressants seem to work to the patient's advantage by altering catecholamine levels; and (2) in minor effective disorders, low doses of tricyclics, particularly the more sedative types, are prescribed, usually by primary care physicians. These mildly symptomatic patients appear to experience a sedative drug effect. Dr. Blackwell said that the benefit to these patients may derive largely from the fact that they are sleeping better and consequently their ability to cope may be enhanced.

From a clinical perspective, depression represents a challenge to differential diagnosis because the symptoms and severity of illness are so variable. When the development of a significant depression is insidious and not associated with external causes, patients may not realize how deeply depressed they are. When they do bring themselves to complain, the depressive mood is presented indirectly, for example, patients may wonder if they need vitamins for their lack of pep or loss of appetite. More often, patients are already privately aware of their depression while they present their somatic complaints, but the mood disorder itself is not elicited unless they are asked specifically if they feel depressed. Compounding the problem is the likelihood that a depressed individual may not seek care by a psychiatrist but instead by a primary care physician, who may not discern whether the vaguely perceived physical complaints for which a patient requests help are actually the problem or if these are manifestations of problems that are psychological, but for which the patient cannot find adequate descriptors. This is particularly true in the case of those who regard feelings of grief, disappointment, and hopelessness as private feelings, which they are not inclined to share unless the discomfort they experience becomes quite severe. When the physician confronts a patient with the suggestion that depression may be causing certain difficulties, the patient, after some reflection, may agree. However, the depressed person may resist entry into the mental health system even when that referral might be highly appropriate; many patients fear not only the social stigma often associated with such treatment, but also the generally high cost of psychiatric care (and limited private insurance coverage). In addition, some primary care physicians are reluctant to refer patients for psychiatric treatment because they do not wish to risk offending or frightening patients and possibly prompting them to abandon seeking help.

Pharmacological Treatments of Depression

Most psychiatrists choose to prescribe drugs, psychotherapy, or a combination of the two on the basis of their assessments of the needs of depressed patients, rather than solely utilizing therapeutic tools derived from one particular ideological or theoretical base. Careful evaluation of clinical features can help identify those patients with drug responsive depressions as distinguished from those for whom drugs may be contraindicated; the time and care invested in pre-treatment evaluation is vital to the success of the therapeutic effort.

In many cases, the practice of combining pharmacotherapy and psychotherapy reflects the therapist's dissatisfaction with either treatment administered alone, as well as the hope that the combination will yield greater benefit for the patient. A commonly

held view underlying the use of combined therapies in the treatment of depression is that the psychotherapeutic process will be facilitated by the introduction of drugs which relieve some symptoms and enable the patient to engage in and benefit from the psychotherapy. It is relatively uncommon to find a severely depressed patient whose treatment consists only of psychotherapy without medication to relieve prominent and persistent symptoms, such as insomnia, anxiety, and disturbed physiological function. It is also uncommon for these patients to receive drug therapy without participating in some form of psychotherapy as well, even if it is only "supportive" in nature. However, considering the whole spectrum of depression, combining pharmacological and psychosocial treatments may not be appropriate or necessary in all cases.

Although there is apparently widespread acceptance of the pharmacological approach to treatment, controversy exists about combining drugs and psychotherapy. Further study is needed, preferably in controlled clinical trials, to answer such questions as: Are there antagonisms between drugs and psychotherapy? Is psychotherapeutic communication really facilitated by the medication? Is the patient's motivation for insight into his problem impaired rather than enhanced by improvement of mood and reduction of other symptoms as a result of drug treatment?

Because the interactions between psychotherapy and pharmacotherapy are so often discussed in the abstract, important patient variables, such as the symbolic importance of the medication-taking process and the need of some patients to define themselves as "medically ill," are often minimized or overlooked. Philip Berger observed that the act of giving a prescription legitimizes the illness in the eyes of some patients. With the initiation of drug therapy, many patients no longer attribute responsibility for illness to themselves. They may become more amenable to psychotherapy because they feel that the "illness" is responsible for the negative interpersonal events they have experienced. Conversely, a patient may have a negative reaction when drug therapy is prescribed because he may have expected psychotherapy to have been offered as the primary treatment. The patient may feel that the prescription of medication defines him as "less interesting" as a candidate for insight therapy. Thus, the use of drugs may result in loss of self-esteem on the part of the patient.

Martin Seligman thought it was important to question what meaning the patient gives to illness, especially about who or what caused the illness and who is responsible for it. He also thought there could be an antagonism between pharmacotherapy and psychotherapy if drugs are not given in such a way as to maximize the patient's role in the recovery process. Although drug therapy usually produces better verbal facility and general well-being, it

can sometimes become easy for the patient to "let the drug do it all." If responsibility for healing is allowed to shift away from the patient and onto the physician, the patient may avoid the changes necessary to improve his or her quality and experience of life. Both physician and patient must remain vigilant to the existence or development of attitudes that would deter recovery or promote relapse.

Issues of adherence to medical regimens take on special significance in the use of combined pharmacological and psychotherapeutic treatments. The giving and taking of the medication can have symbolic significance for both the patient and the physician and can have an influence on the efficacy of both the pharmacotherapy and psychotherapy processes. For example, some physicians may overemphasize medication as a way of avoiding psychological issues that are troubling to them as well as their patients. Some patients may focus most of the discussion during the visit to the physician's office on the medication in order to avoid the discomfort of self-scrutiny. Others may attach a "magical" significance to the prescription as the solution to their anxiety and psychological distress. Even when the physician appropriately prescribes a drug treatment, the patient may resist using the medication as directed for a number of reasons. Two of the most common reasons are unpleasant side effects of the drug, or the patient expects that relief can be achieved through psychotherapy alone and does not recognize the value of the medication in the process.

Assessments of the Efficacy of Treatment

There are two central issues involved in assessing the outcome of treatment. One is the efficacy of various treatments in producing remission of certain symptoms. The other is the prevention of relapse, particularly in major depressions.

Myrna Weissman presented findings from evaluations conducted on patients one year after they stopped receiving treatment.[8,9] These individuals had received psychotherapy, drug therapy, or both. At the initiation of the study the patients had no differences in symptoms. Initial indications suggested that patients who had been given psychotherapy, with or without drugs, performed better one year later on measures of social functioning than did those who had received drugs alone.

Maria Kovacs [10,11] reported her work comparing cognitive therapy and pharmacotherapy. Although both cognitive therapy and pharmacotherapy were associated with significant reductions in levels of depression, the cognitive-therapy patients showed greater symptomatic improvement and higher treatment-completion rates. A

one year naturalistic* follow-up of subjects who completed the protocol found that both original treatment groups generally were well. At one year, depressed patients who had received cognitive therapy still were less symptomatic on a self-rated depression scale than patients who had received pharmacotherapy. Although the study revealed several interesting trends in favor of cognitive therapy, none of the between-group differences was significant. Dr. Kovacs said that the follow-up suggests that for a distinct portion of patients, cognitive therapy or pharmacotherapy on a short-term basis may offer temporary symptomatic relief but not prevent relapse or recurrence of the depression.

Studies of tricyclic antidepressants in the prevention of relapse of major depression indicate that patients maintained on medication for one year after the depressive episode generally functioned well socially and showed the least recurrence of symptoms. Patients treated with medication only during the acute phase of depression were more likely to have relapse and poor social functioning during the following year.

While supporting the value of pharmacotherapy in improving mood and reducing symptoms, these studies also suggest that psychotherapy aimed at helping patients to solve interpersonal problems is of value. The studies of both Dr. Kovacs and Dr. Weissman imply the need for more research to demonstrate the differential effects of various kinds of psychotherapy and various kinds of drugs used alone or in combination on remission of symptoms and in preventing relapse. A confounding issue in follow-up studies is the lack of clarity in determining whether patients who become depressed subsequent to treatment are experiencing relapse or, because of the phasic nature of some depressive illnesses, are experiencing a new episode of the disorder.

Suggestions for Research

Conferees suggested that improvements in the diagnosis and treatment of depression have accompanied the development of more accurate and valid instruments to assess symptoms. These developments, which build on much recent progress in refining conceptualizations of depression to reflect the heterogeneity of the disorder, offer the potential of assisting rapid diagnosis and initiation of the appropriate therapeutic intervention. An

*In a naturalistic follow-up, the contact with the patients is not designed to provide therapy. The patients are free to seek or enter any treatment at any time with any service provider.

anticipated benefit of these advances is that treatment would be more specifically tailored to the patient's needs. Research is needed on the efficacy of various therapies and characteristics of patient-therapy matching that could influence the therapeutic outcome.

Most of those suffering from various types of depressive disorders are seen only in the general health (primary care) sector and never receive specialized mental health care.[12] Some research on the identification and management of mental health problems in primary care settings is currently underway, but relatively little is known about the kind, extent, and effectiveness of treatment being provided. Controlled, randomized trials are needed to determine what types of patients are best treated by primary care psychotherapy and what types of patients should be referred to psychiatrists. Carefully designed outcome studies are also needed to find what type of psychotherapeutic techniques are appropriate in the primary care setting. Is it cost effective to provide psychotherapy in the primary care setting?

Diabetes

As a chronic disease, diabetes requires attention to medical, psychological and social aspects of patient care. The complexity and range of potential problems in long-term care led the conferees to urge a shift from traditional models of treatment in which physicians have been expected to bear nearly all responsibility. A team approach to care of the diabetic should have responsibility shared among the patient and other team members, so as to ensure appropriate support for the patient's development of self-care and an adoption of behavior that reduces health risks and maximizes functional health status. The team would consist of the patient, physician, nurse, and dietician or nutritionist, all of whom have designated responsibilities. Other members--psychiatrist, social worker, physical therapist, psychologist, podiatrist, and pharmacist--would be available as needed. Some conferees thought that this approach was not cost effective, but others contended it offered specific advantages. Some physicians indicated that, despite the fact that education in self-care is an essential part of treatment, they often lacked time to educate the diabetic at his or her level of understanding and emotional need. Thus the team approach appeared to be important in providing continuity of care for these patients.

Leona Miller highlighted the importance of behavior that reduces health risks associated with diabetes. Results of cost-offset analyses she conducted in California, where there are approximately 400,000 diabetics, showed that in one hospital alone the cost of treating 184 diabetic patients requiring amputations was seven

million dollars. Dr. Miller thought that perhaps all but seven or eight of these amputations could have been prevented.

Exercise was mentioned as an important adjunct of good medical care in preventing some of the long-term negative consequences of diabetes. Juanita Archer said that the benefits of exercise for diabetics included that it increases peripheral sensitivity to insulin. Although the general relationship between exercise and increased peripheral insulin sensitivity has long been known, Dr. Archer thought that there has been insufficient appreciation of the potential of vigorous exercise as part of the treatment of diabetics.

Conferees thought that emphasizing the reduction of health risks for the diabetic would require changes in professional education and in priorities of clinical care. Not only must the physician be better trained in daily care of the diabetic, but also medical education must communicate the importance of reducing health risks and maximizing functional health status. One suggestion was to incorporate into medical education the contributions of behavioral science research in areas such as patient motivation, and patient compliance--the proper adherence to medical regimens and programs.[13,14] A better understanding of the determinants of patient adherence to medical regimens would greatly improve success of medical interventions. Conferees suggested devising and testing different methods for achieving patient adherence and conducting cross-cultural and developmental studies of variations in patient compliance.

For the adult diabetic, the most important aspect of patient management is preventing and treating obesity. Conferees suggested that research be conducted on two of the chief causes of obesity: overnutrition and lack of exercise. Some specific topics for research include (1) the social, biological, and psychological mechanisms contributing to overeating; (2) methods of controlling overeating; (3) making dieting a more effective treatment by using a team approach to ensure continuity of medical care; (4) the developmental aspects of overeating, namely, the different patterns of eating in children and adults; (5) the role of exercise in the overweight patient's therapy; and (6) techniques of maintaining non-eating behavior by the patient at home. Conferees observed that research could profitably be conducted across the life span and urged that studies be conducted on the interaction of obesity and aging. They noted that, although the association between obesity and adult-onset diabetes is known, the extent to which childhood obesity is a determinant of adult obesity is not known.

Advances in Treatments

As many of the longstanding problems in treating diabetes are overcome, new challenges seem to emerge almost simultaneously. As

purer forms of insulin become available, certain benefits can be expected, especially fewer cases of insulin resistance requiring costly insulin desensitization procedures. The actual costs of these newer insulins will be reduced, not only because of the lower costs of mass production, but also because the patient will require smaller doses. However, only part of the treatment problem is solved by the development of purer insulin. Clinical researchers increasingly are directing attention to finding a way of administering insulin in a manner more closely like the normal body functions. The problem involves more than simply developing the necessary technology. For example, insulin pumps, currently about the size of a small transistor radio, mimic the insulin-producing mechanisms of beta cells. Several conferees thought that these pumps should appear far more attractive to the patient than twice-daily insulin injections and ensure adherence to the prescribed regimen. Medically, the pump appears advantageous in reducing the long-term complications of diabetes. However, one investigator reported some resistance among adolescent female patients to wearing the insulin pump. One interpretation of this resistance was that these patients feel their self-image to be more seriously affected than their future physical health status. Given its potential utility as an adjunct to the development of better insulin, research to understand patient attitudes toward using these devices must be undertaken.

Behavioral approaches to the treatment of diabetes have received little attention, although they may be useful adjuncts to insulin therapy.[15/] There was a suggestion that biofeedback may be used to lower blood glucose levels, but research is at a very preliminary stage. Patient counseling and psychotherapy were proposed as important adjuncts to the care of the diabetic. These interventions were seen as especially useful in helping patients cope with the knowledge of having a chronic and potentially life-threatening disease.

Opportunities for Clinical Research

Understanding of the pathophysiology of diabetes remains far from complete. For example, the processes of aging of the beta cells is an important area for research. Conferees said that, because the mechanisms responsible for insulin resistance have not been studied adequately, the treatment interventions to eliminate or reduce this problem have lagged behind. Research also was suggested on the long-term physiological effects of oral agents used in diabetes treatment.

Clinical advances in both pharmacological and non-pharmacological treatments for diabetes appear to be dependent upon improvements in measuring blood glucose; specifically, the development of more

sophisticated, accurate, and painless means for patients to monitor levels of blood glucose could provide the foundation for better medical and behavioral treatment approaches by enhancing motivation for self-care. A related area for research involves the positive or negative effects that new medical technologies, such as the insulin pump, will have on patient adherence. Techniques allowing patients to receive immediate feedback about changes in blood glucose improve opportunities to move immediately toward correcting the situation. Many participants agreed that if patients had more support in monitoring daily changes in their blood glucose, the long-term medical benefit would be fewer complications typically associated with this disease. Conferees also noted that it may be helpful to conceptualize "biofeedback" in a broader, more inclusive way: any time the individual receives or perceives information about events happening within the body, such as changes in blood glucose levels, that information should be considered biofeedback.

Several physicians noted that diabetics frequently appear to misinterpret the symptoms of hypoglycemia. Studies of patients' reports of hypoglycemia symptoms followed immediately by blood glucose measurements indicate that blood sugar often tends to be abnormally high, not low. This kind of misinterpretation suggests the need for research on the interaction of physiology and individual perceptions and beliefs. It also suggests that basic research be conducted to answer questions about health attitudes and behaviors. In experimental studies with humans beings as subjects, the patient's awareness of or assumptions about the intent of the research can influence the results. Therefore, researchers must give special attention and care to the study design and selection of appropriate control groups.

Physicians in the group provided a list of research questions for behavioral scientists: (1) What is the nature of information processing in children? What level of sophistication does the child possess, and how does it vary with age? (2) How do patients respond when presented with new information? For example, what is the response of a diabetic woman when she first is informed that she is pregnant? How does she adjust to the dual medical requirements of pregnancy and diabetes? (3) What concepts do patients have about the causes of illness and their control of its course and its consequences? Do these change with age? (4) What is the impact of disease on the patient's self-image? How does the illness affect the patient's network of social support? (5) How can knowledge about cognitive developmental differences between children and adults be applied in transmitting to patients information that will be meaningful, useful, and effective? Several physicians urged behavioral scientists to conduct research to help physicians determine the best ways to give information. Behavioral research has uncovered many useful techniques for accomplishing this task, but there is a lag in communicating them to the medical community.

An Example of Interdisciplinary Research

Maria Kovacs described her longitudinal, interdisciplinary research on diabetes as an example of the type of inquiry made possible by biomedical and behavioral science collaboration. The study focuses on two key areas: assessing the level of psychopathology in diabetic children, and determining children's level of understanding of diabetes. It uses a repeated-measures design, incorporating assessment not only of the diabetic child, but also of the child's family. Physicians and psychologists evaluate the diabetic children and their families four times during the first year they participate in the study and at least three times a year during following years. Detailed medical, psychological, and intellectual observations of each child are made during regular medical check-ups. These baseline data allow calculation of intercorrelations at various points in time in order to predict adaptation to the illness.

To explore the prevalence and nature of psychopathology among diabetic children, Dr. Kovacs posed four research questions. First, does any psychopathology, specifically depression, exist in diabetic children? Second, might a depressive episode be indicative of an adaptive, rather than a maladaptive, coping response? Third, if there are adaptive and maladaptive depressions, might these differ developmentally? That is, might the older child be more equipped intellectually to evaluate the meaning of this illness experience? Fourth, might the fact of having a depressive episode be a predictor of subsequent adjustment of diabetic children?

Dr. Kovacs said that the answers to these questions cannot be obtained without a design that allows for longitudinal study and coordinated medical and psychological assessments. Many of her research leads had derived simply from asking the children to tell about the problems associated with having a chronic illness. One particularly useful set of issues, namely coping strategies, were discovered using this open-ended technique. It uses a repeated-measures design, incorporating assessment not only of the diabetic child, but also of the child's family. Physicians and psychologists evaluate the diabetic children and their families four times during the first year they participate.

Diabetic children seem to report very similar behaviors after leaving the hospital. Dr. Kovacs believes these may constitute a coping function. It is not uncommon for a diabetic child, upon release from the hospital, to invite friends over to view the syringes and reduction kits. A particularly adaptive child may even use the "Tom Sawyer" routine of "allowing" some of the nondiabetic children to do the reduction for them.

Dr. Kovacs' presentation stimulated a discussion of barriers to conducting clinical research, and especially the complications posed by the absence of a common language among clinicians and researchers. For example, the meaning of the term "depression" is often not specified operationally by clinicians. This variability can result in confusion and frustrate attempts to generalize results or replicate research. Several participants asserted that depression represents a failure to cope rather than an adaptive response and suggested that true depression should always be treated. One participant thought that perhaps such "depressions" did serve as a protective period of withdrawal from the constant demands of a chronic, potentially debilitating disease. It was noted that Cassem and Hackett studied depressive reactions to myocardial infarction,[16] and found that the occurrence of depression often depends upon complex interactions among combinations of factors, such as the phase of the illness, degree of denial, and amount of anxiety. This type of research has not been conducted for diabetes.

It was suggested that a special dilemma often posed for the individual who is both a researcher and a clinician that arises from the attitudes and value system of the scientist as contrasted with those of the clinician. One physician, for example, said that he believes a depressive episode should always be treated with the best available therapy. However, if he is in the midst of an experiment testing a depression treatment versus a placebo, should he finish the experiment if his "clinical impression" convinces him of the efficacy of the depression treatment? Examination of these and other ethical dilemmas faced by scientist/clinicians in treatment research should be encouraged.

Comparisons of Hypertension, Depression, and Diabetes

Conferees compared hypertension, depression, and diabetes in two ways. First, they focused on symptoms and disease patterns. Second, they noted themes in research and treatment that appear common to the three disorders. Hypertension, depression, and diabetes evoked observations all appear to be relatively chronic and to have negative side effects associated with pharmacological treatment. Hypertension and diabetes are similar in that the patient is often unaware of the existence of the disease; however, the length of time needed for the unchecked disease consequences to manifest themselves is usually shorter for diabetes than for hypertension. Once diagnosed, there seem to be few socially disruptive effects of disease in persons with hypertension or adult-onset diabetes. But depression and juvenile-onset diabetes are similar in that both illnesses tend to have negative

psychological and social effects, not only on the patient, but also on the patient's network of family and friends.

In their second comparison, conferees thought that hypertension, depression, and diabetes had many similarities in the types of approaches needed in research and treatment. For example, weight control, diet, and exercise are under-researched but common links in prevention, etiology, and treatment of diabetes and hypertension. Also, several themes already discussed throughout the conference (in connection with depression or hypertension) were mentioned as relevant to diabetes treatment, these included (1) adherence to medical regimen, (2) the role of the patient in the treatment process, (3) the role of patient expectations and concepts, (4) the importance of self-regulation and self-monitoring processes as part of daily health routine, (5) the need for better education of physicians and other health care providers about teaching patients self-care techniques, and (6) the need for more research on the efficacy of psychosocial, treatment interventions.

Collaboration of Biomedical and Behavioral Sciences

The conferees were asked to consider how the collaboration between biomedical and behavioral sciences could be stimulated to enhance knowledge for clinical care. Four areas were selected for emphasis: (1) prospects for new research and treatment initiatives; (2) availability of new research approaches and critiques of current methods; (3) composition of interdisciplinary research teams and desired training experiences for team members, and (4) identification of academic, funding, and disciplinary barriers to the conduct of research in hypertension, depression, and diabetes.

Several specific areas for new or added research were suggested by conferees, including (1) multimodal treatment approaches, both psychodynamic and behavioral, in illnesses other than mental disorders; (2) the effects of anxiolytics such as diazepam on blood pressure; (3) blood flow training for diabetics, where clinical evidence suggests its utilization in healing foot ulcers; (4) the relationship between the amount of overt symptomatology in an illness and ensuing patient compliance with prescribed regimens; and (5) long-term effects of unsupervised self-regulation programs as a means of reducing costly follow-up care.

The use of drugs as facilitators of behavioral change techniques was suggested by Richard Surwit, who noted that shaping behavior and reinforcing infrequently occurring behaviors could be enhanced through judicious prescription of drugs that would increase the likelihood of producing the desired behavior. For example, a peripheral vasodilator can be prescribed for patients attempting to learn a vasodilation technique. The vasodilation would become a

more frequently occurring response, and would be more easily reinforced and learned more quickly. The combination of anxiolytics with behavioral techniques also was suggested to be researched in the treatment of anxiety.

An area of research suggested by Martin Seligman was on the interaction of drugs with human cognition. He thought that the question of drug/psychotherapy interaction was too global and perhaps too premature for study. Rather, he said that there are three areas of human cognition that may influence the activity of drugs: (1) control--what effects result from systematically varying the amount of control individuals have or perceive they have in a situation; (2) information--to what extent does the amount of information an individual has interact with the activity of the drug and compliance in taking the drug? and (3) attributions--to what extent does a person's perception of an illness and its cause affect compliance and drug activity?

Conference participants also deemed greatly under researched the matters of social supports and coping skills.[17,18] The absence of social supports is an important environmental predictor of depression; it is associated with increased suicide, mental illness in all age groups, and mortality from various diseases. How to begin incorporating social supports into treatment regimens is not understood. It was suggested that if used as a variable in research, "support systems" must be described fully and not reported simply as being present or absent. For example, one can describe the intensiveness of the support system, or the amount of interconnectedness between members. Some participants viewed as equivocal the early evidence for the efficacy of social supports in long-term maintenance of treatments especially where compliance is a major issue for a person staying in the treatment program.

Gary Schwartz suggested studying the selectivity in patterns of actions and effects of behavioral compared with biomedical treatments. For example, a diuretic affects specific components of the cardiovascular system, but a generalized relaxation response to a biofeedback technique may enhance the patient's well-being at a number of different levels. Cost-benefit analysis should include assessing the total set of effects caused, for example, by the diuretic as against those from relaxation training (some examples of additional effects might be a greater sense of control and fewer health care visits). A second suggestion was to study combinations of health problems in the same individual. The practice of assessing interactive effects should be a routine consideration in planning studies of health problems. For example, it is possible to get combinations of effects across several levels of human functioning. Cognitive aspects of behavior--such as, expectancy effects--are not sufficiently studied in a systematic way. Several conferees also emphasized the need for support of research into

factors that contribute to the maintenance of health in routinely healthy individuals.

Some of the broader policy issues identified by participants were closely tied to the encouragement of certain research initiatives. For example, policymakers should be aware that although prevention is a valuable pursuit, it is almost always more difficult to achieve because it involves treating a larger number of individuals in the population than will actually contract the disorder. Therefore, questions always will be raised about cost-effectiveness, and it is important that attempts to answer them not be too simplistic. It was also suggested that small interdisciplinary groups be convened to develop the research priorities within various areas amenable to combined treatments and to determine what evidence should be required before specific actions are proposed. There also should be an awareness that few procedures--survey, clinical, or experimental--are without possible negative effects. This should be a routine question in the evaluation of research.

Conference participants currently engaged in interdisciplinary or multidisciplinary research identified some of the difficulties inherent not only in working on these kinds of research projects but also in obtaining funding for them. Many thought that the chief problems in carrying out multidisciplinary research arise from the highly disciplinary, fragmented and parochial organization of science and of the professions which are reflected in the organization of universities and of other institutions that carry out research. These problems impinge on the research in two areas particularly:

1) Interdisciplinary efforts are often viewed as either not contributing to or at cross purposes with disciplinary, department-based programs. In medical settings, clinical departments have often found it difficult to apppoint, and especially to promote, faculty outside of their own discipline to do this kind of research. On the other hand, investigators in the behavioral sciences rarely have access to clinical populations, or even to ask questions in this area. A perhaps more serious problem is posed for the investigation themselves. If they engage in a multidisciplinary effort that lasts for any time, they tend to become dislocated from the main career tracks in their own disciplines, to the detriment of their career advantage. They tend to find themselves out of the main stream of the activities of their departments, and often viewed as being engaged in something that is not really geared to their own disciplines. Working with colleagues from a different field is also difficult from the perspective that, more often than not, the representatives of one field is simply performing a service function for the representative of another. It was

pointed out that interdisciplinary research is easier to implement when both parties openly acknowledge what they have to offer the other and what they hope to gain. Sentiment rarely sustains interdisciplinary work, but pragmatism can. Sound scientific leadership, the existence of a well defined research goal and an environment conducive to collaborative research are essential parts of a successful approach to interdisciplinary research. The absence of any of these elements will militate against attaining programmatic objectives. Another aspect to be considered in dealing with interdisciplinary research is that investigators participating in this research effort must have both a basic understanding and respect for each of the disciplines making a contribution to the study.

2) The multidisciplinary approach to research is not presently well understood or appreciated. Often the group that is asked to review a multidisciplinary proposal is usually made up of people who do not have multidisciplinary interests and who approach the review from a purely parochial point of view. Many reviewers appear to be boggled at the complexity of multidisciplinary research and hence, assume that the researchers are equally overwhelmed. A common suggestion from the scientific review panel is that certain parts of the project being reviewed be submitted as separate proposals even though it may be important that these data be collected at the same time that the main data base is assembled or not collected at all.

In spite of the problems noted above, many participants believed that if researchers can identify a meaningful scientific question and propose a reasonable method for attacking it, a granting agency usually can be found that is interested in the answer to this question and will fund the research. This has been found to be true with governmental and private agencies, boards, and foundations. It was pointed out that investigators must have realistic expectations of granting agencies and not become overly pessimistic about their chances of obtaining financial support for their work. There was agreement that granting agencies are not likely to fund interdisciplinary research simply because it is interdisciplinary, and seems a desirable thing to do. The point was reiterated that if an interdisciplinary research proposal is built around a meaningful scientific question, it can probably find a sponsor, and the fact that the proposed investigation is multidisciplinary may make it more attractive to a sponsor, rather than less.

The crossing of disciplinary barriers received attention in two areas, the training of health professionals, and the health care delivery system. Robert Haggerty said that at present there are only a few programs designed to teach behavioral aspects of

pediatrics, for example, teaching pediatricians how to deal with chronic diseases that have behavioral consequences. He saw as major obstacles the absence of relevant research findings to transmit to pediatricians, and the lack of specific training programs in the field. A related problem is the inadequate funding of residencies to train pediatricians in behavioral issues of pediatrics. Encouraging the "team approach" to patient care might be one way of achieving interdisciplinary communication. The point was emphasized that the "team approach" had been quite common in the past, before the advent of so many medical specialty areas and complicated reimbursement policies of most third party payers--the primary financing agents for most people's health care.

It was noted that the patient-physician relationship exerts major therapeutic influence. The health professionals' perceptions of etiologies and their styles of presenting treatment affect patients strongly. Research was called for to discover how current health care training and delivery systems can influence health professionals behaviors particularly those behaviors that minimize the descriptive effects of patient confusion, fear, and anger, and utilize appropriate reassurance to change patients' attitudes toward illness and treatment.

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CONCEPTUAL ISSUES IN COMBINED PSYCHOSOCIAL AND PHARMACOLOGICAL TREATMENTS

Gerald L. Klerman, M.D.

The topic of this conference represents an interplay of my current and long-term identities. As a government official, I am here representing one of the two Public Health Service agencies which have contributed to the initiation, funding, and planning of this series of conferences on behavior and health. I am also here as an investigator with a special interest in the evaluation of psychotherapy alone and in combination with drugs. I hope this conference will extend these approaches beyond psychiatric illness to include other conditions having a psychological (or mental) component, such as hypertension and diabetes.

Increased Sophistication in Therapeutics Research

Dr. Hamburg has identified the growing interest in the interface between behavioral science and health. To that I would add a second consideration: the growing sophistication of research on therapeutics.

The crucial event occurred in 1962, when the Kefauver-Harris Amendments to the Food and Drug Act mandated, for the first time, that evidence for efficacy would be required for the approval of a new drug. Today we take the criteria of safety and efficacy for granted in the health field. However, its mandating was a hard fought congressional battle. Many may not be aware that prior to 1962, evidence for efficacy was not required for the marketing of new pharmaceutical products. Until that time, only evidence of purity, provided for in the 1908 legislation, was required. Interestingly enough, safety and efficacy criteria are not included at present in the federal statutes for any other medical procedures. For example, they are not required for Medicare or Medicaid reimbursement, which stipulates that they be only "necessary and reasonable." There is currently a vigorous debate in Washington over proposals which would extend the criteria of efficacy to psychiatric treatment, such as psychotherapy. The Senate Finance Committee is considering legislation embodying that principle.

New advances in therapeutics involve the adaptation of new computer technologies. Computers have made possible the application of advanced statistical techniques, such as multivariate analysis, to the handling of bodies of data from large and diverse patient populations. This capacity is particularly necessary for the large scale trials required in hypertension and in other health disorders.

The randomized clinical trial is accepted as the best and most rigorous procedure for establishing the efficacy of any form of intervention--therapeutic, preventive, or diagnostic. Although the randomized trial was initially developed for the evaluation of drug treatment, it has now been extended to almost all interventions, including surgery, radiation, and various forms of psychotherapy. Another advance is reflected in the use of this technology to study combinations of therapies.

I shall use "psychotherapy" very broadly, to include behavior modification and counseling. There has been a dramatic expansion of a number of techniques with increasing specificity.

Along with greater specification of the conditions for which the treatment is hypothesized to be effective and greater specification of techniques or component techniques, there also has been parallel development of technologies to assure the "purity" of psychotherapy.

One of the more serious problems in evaluation methodology of psychotherapy is "purity" or uniformity. If one performs a drug trial of a diuretic, one can be reasonably sure the 100 milligrams of Diuril in New York is the same as 100 milligrams in Moscow or Philadelphia. That cannot be said for 100 hours of psychoanalysis in Boston or Frankfurt. This problem with uniformity is not insurmountable, however. There are a number of innovative techniques, some of which we may learn about today from the Philadelphia and New Haven groups, to "purify" psychotherapy for research by using TV techniques, manuals, and training of technicians or therapists.

Interest in this field goes beyond methodology or the practical need for more effective treatment of such widespread disorders as diabetes, hypertension, or depression. Intertwined with the practical concern for improving therapeutics is an explicit conceptual interest of the participants to develop a broader concept of health, a concept of health that would involve the integration of biomedical, behavioral, and even psychosocial factors. In contrast to a previous generation, in which most of the emphasis on such integration was at a theoretical or even polemic level, the field of combined treatments allows a greater specification and testing of the concepts and hypotheses in real life situations distinct from polemic debate.

The Outcomes of Combined Treatment Research

With this introduction as to the growth of the field of therapeutics, I shall now shift to my identity as investigator and share with you some conceptual and methodologic considerations in the conduct of research on combined treatments.

What would be the requirements of evidence sufficient enough to establish the efficacy of drug-psychotherapy interventions?

It is generally agreed that the controlled clinical trial is the most rigorous test for efficacy and safety. Where two or more treatments are involved, as in drug-psychological treatment interactions, the optimal design criteria would be a four-cell design as shown in Table 1. This design allows for testing of a number of hypotheses concerning both the main effects of the treatments and their interactions.1/

TABLE 1. STUDY DESIGN FOR EVALUATION OF DRUG AND PSYCHOLOGICAL TREATMENTS

	Drug treatment	
Psychological treatment	Experimental	Control
Experimental	1	2
Control	3	4

This design requires random assignment of patients, selected by predetermined, explicit criteria. to four groups: a group that receives the drug alone, a group that receives the psychotherapy alone, a group that receives the combination, and a group that receives some sort of control.

Many studies use only components of this four-cell design. For example, the typical drug study is a two-cell design which compares the drug versus the control, with the conventional control, a placebo.

I have depicted a set of hypothetical outcomes in which some improvement measure is shown by bar graphs (Figure 1) for two or more comparison groups. The bar graphs assume that minimal methodologic criteria are met: predetermined criteria for selection, a randomized or some other form of systematic assignment to the experimental and control groups, predetermined quantitative measures of outcome, and some degree of blindness on the part of the observers as to which treatment the subjects or patients are receiving.

The assumption in almost all drug studies is that the drug-treated group will show a greater degree of improvement over the control group (usually a placebo group). Applied to behavioral or psychotherapy interventions, even the achievement of this level of design has been a source of controversy regarding both its

appropriateness and difficulty in execution. Numerous debates have arisen over the appropriate outcome measures, the nature of the placebo, or appropriate control group in psychotherapy research.

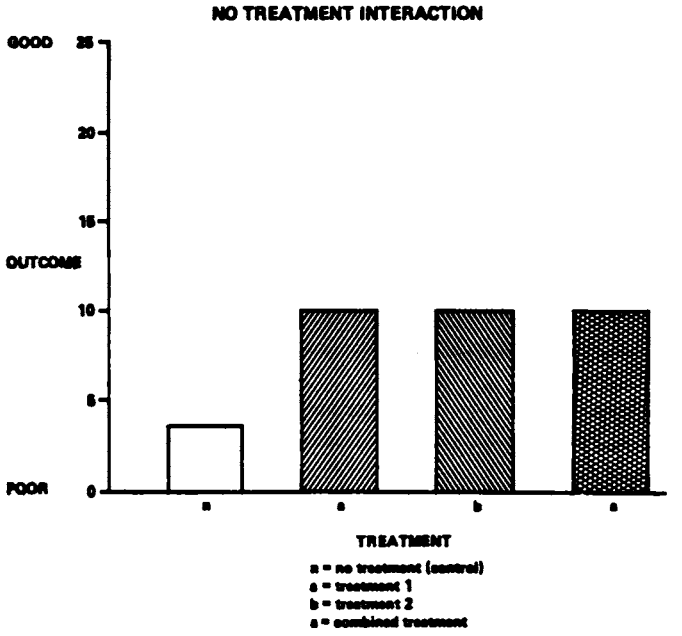

Figure 1

To make matters more complicated, in the Boston-New Haven Collaborative Study of Depression, we used a six-cell design in which we had two non-drug controls, a placebo group, and a no-pill group. This was an attempt to test whether or not there was a placebo variable or increment over and above the nonspecific conditions of numerous rating scales, and the illness itself. There seems to be an implicit notion in much of the placebo literature that the placebo is uniform in all conditions and in all circumstances.2/

This design was first suggested to me by Peter Dews. Most of the literature on placebo groups deals with the specific expectations around pill taking--its so-called "magical" and dependency expectation--and a whole host of other nonspecific factors, such as use of rating scales and the special attention of being in a research project. In the Boston-New Haven study, we did not find any placebo effect over and above the "no-pill" condition in a long-term (eight month) treatment study of depressives. We did find a drug:"no-pill" or drug:placebo difference, but we could not detect any placebo effect over and above the "no-pill" condition in that study.

The assumption in most combined treatment research is that there will have been independent evidence of the efficacy of the individual drug and the individual psychotherapy before the combined design study is initiated.

Again, I use the term "psychotherapy" in a very broad sense to include counseling, various forms of behavior modification, reassurance, and as other regimens. There is no uniform psychotherapy, just as there is no one drug. But for the purposes of methodological analysis, the assumption of combining treatments is that there will have been shown, by independent studies, separate efficacy for the drug and for the psychotherapy over a control group.

Ideally, before combined treatments are employed, four types of evidence should be available:

1. Evidence of the efficacy of each treatment modality.

2. Understanding of the mechanism of actions of the two treatment types.

3. Verified concepts that bridge the two treatments and provide a reasonable basis for combination.

4. Evidence for the efficacy of the combination.

In Figures 2-4, the height of the bars representing treatment outcome is equal for both the psychotherapy and the drug groups. This reflects an attempt to be even-handed and fair. It is conceivable that one could, whether hypothetically or by actually measuring specific parameters, find various heights or treatment outcomes.

For example, in studies of depression, Beck and his associates 3/ have published evidence from a two-cell design that cognitive therapy is equal in efficacy to treatment with a tricyclic. Their finding has challenged the conventional wisdom of the depresson field which had assumed that drugs would have more impact than any behavioral or psychotherapeutic intervention.

Assuming one has the minimal four-cell design, what are the possible outcomes (Figures 2-4)? I have attempted to catalog the possible outcomes, the relationship of the combined cell to the two individual treatments. In these figures, bar "a" refers to the psychotherapy, and bar "b" to the pharmacotherapy. Bar "c" refers to the combined treatment. At least five categories of outcomes are discussed in the literature.

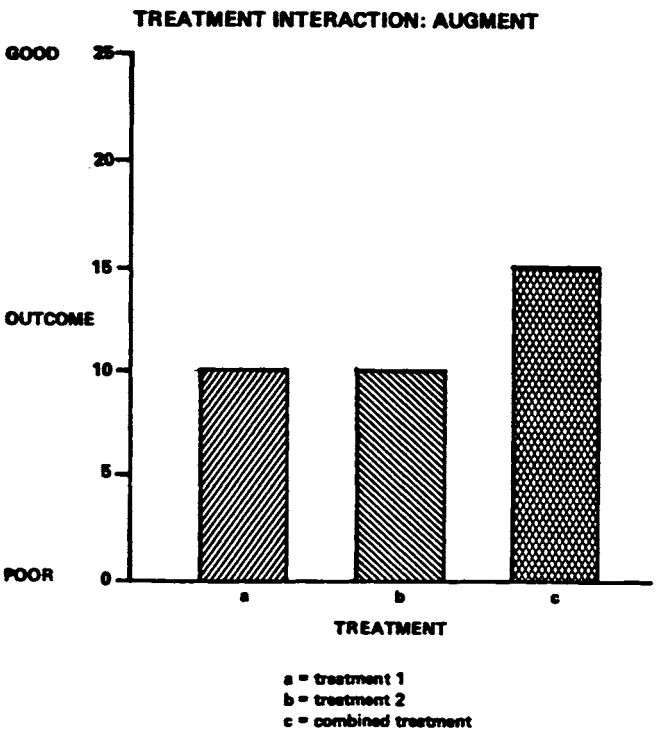

Figure 2

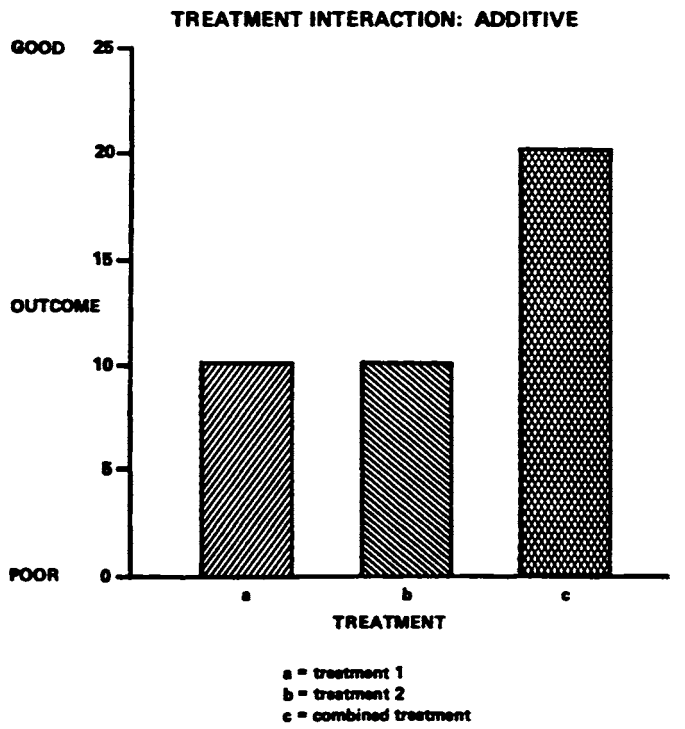

Figure 3

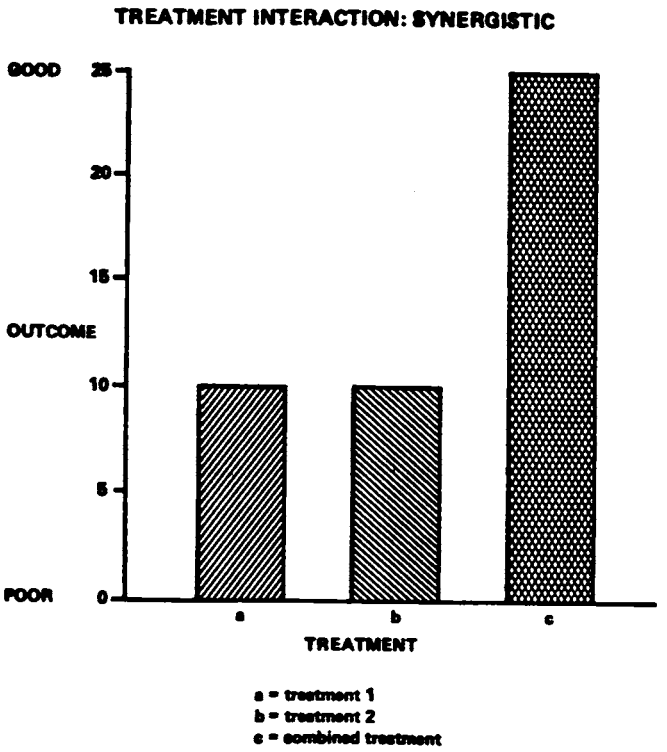

Figure 4

Based upon the optimum experimental design, a number of interactions can occur between the drug and psychological treatments:

1. No Interaction (See Figure 1): Combined treatment has the same effect as individual treatments.

2. Augmented Interaction (See Figure 2): Combined treatment enhances the effect of either treatment alone.

3. Additive Interaction (See Figure 3): Combined treatment has the effect of both treatments added together.

4. Synergistic Interaction (See Figure 4): Combined treatment effect is equal to more than the effects of the two individual treatments added together.

5. Inhibitory Interaction (See Figure 5): Combined treatment compromises the effect of either treatment alone.

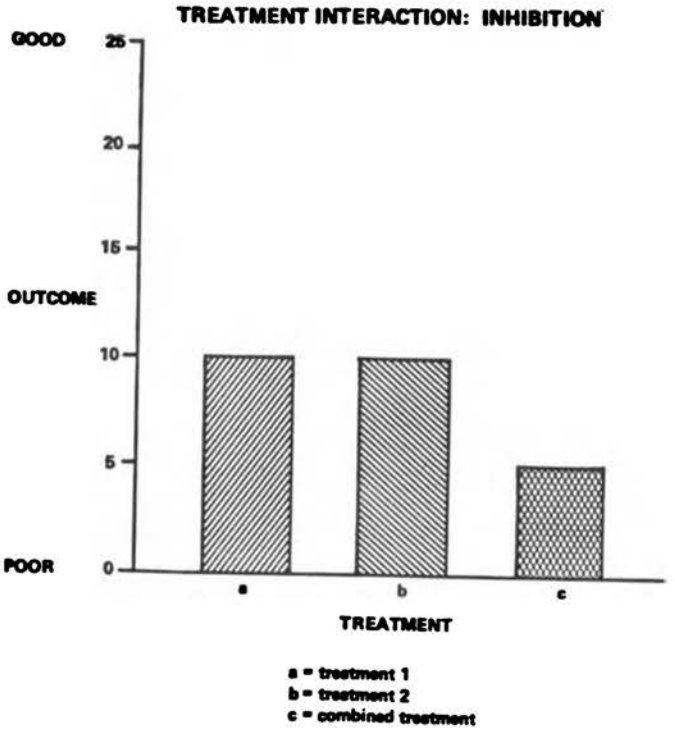

Figure 5

One outcome could be no effect of a combination (Figure 1). This is "no interaction outcome," in which the effect of combined treatment (bar "c") is no greater than either treatment 1 (bar "a") or treatment 2 (bar "b") alone. If it reaches the sum of bars "a" and "b," we have another implicit model, the additive model (Figure 3), in which one plus one equals two. The augmentation model (Figure 2) represents, for example, that one plus one equals a sum greater than one, but less than two.

Ideally and optimistically, we hope for synergism (Figure 4) in which the sum is greater than its parts, that the combined treatment will produce a magnitude of effect greater than the sum of the two individual treatments.

I have attempted in the past few years to find examples of each type of outcome. The most common is one in which there is some degree of augmentation, namely, the combined treatment offers something better than either treatment alone. Relatively few studies have used ordinal scales or quantitative measures and actually looked for the algebraic sum.

The assumption of additive effects states that the combined treatment is the algebraic sum of the two component treatments. This has actually occurred in at least one instance--our research in the Boston-New Haven Project on the treatment of acute outpatient depressives. It is described in a paper by DiMascio, Weissman, Klerman, and others in the Archives of General Psychiatry.4/

In this study, the outcome measure utilized was the Hamilton score (Figure 6). The Hamilton score is not, however, a specific measure of improvement. Rather, it is the level of psychopathology at the end of the 12-week study. The mean score at the end of the study was covaried for the initial level. The data illustrate a perfect additive model. The control group, which was a non-scheduled treatment--"here is our phone number, you call us, we won't call you"--had a mean Hamilton score of 14 at the end of the treatment.

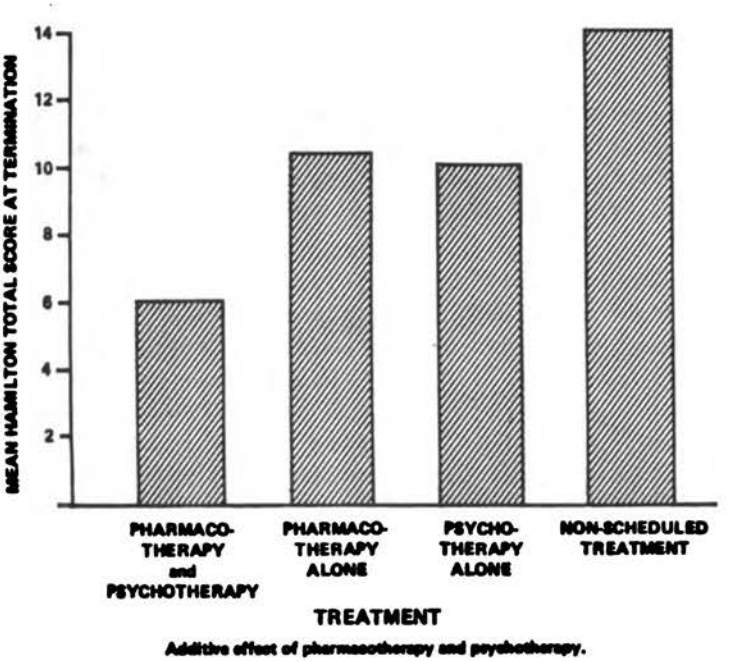

Figure 6

At the same time, our study demonstrated that the two individual treatments for depression were equal in efficacy. This finding corroborated the study by Rush, Beck and Kovacs,3/ in that the psychotherapy was equal in efficacy to imipramine treatment, as in their case, or to amitriptyline in our case, and that the mean Hamilton score for the two groups was 10. The difference between

the mean score of each of the two treatment groups and that of the control group was four. Adding these differences, the change in mean Hamilton score for both groups is observed to be equal to the level of change in psychopathology achieved between the combined treatment group and the control group.

There is one reported case of a synergistic model in which the combined treatment effect was algebraically greater than the two. A paper by Paykel et al, 5/ reported that the effect on social adjustment for the drug and psychotherapy combined treatment group was greater than the effect of either treatment alone.

The last example is that of inhibition, in which the combined treatment does less well than either of the two component treatments. There is a suggestion of this in some of Dr. Stunkard's research. Figure 7 is taken from the Stunkard study of weight reduction 6/, using medication alone and in combination with behavior therapy. During the first six months of weight loss, there was a benefit with combined treatment over either medication alone or behavior therapy alone, with some suggestion that the effects were additive. However, in the second six months after the experimental phase, when there is an expected regaining of the lost weight, the combined treatment group regains more weight than does the behavior treatment group. It may well be that some of the learning effects of behavior therapy alone are offset by the

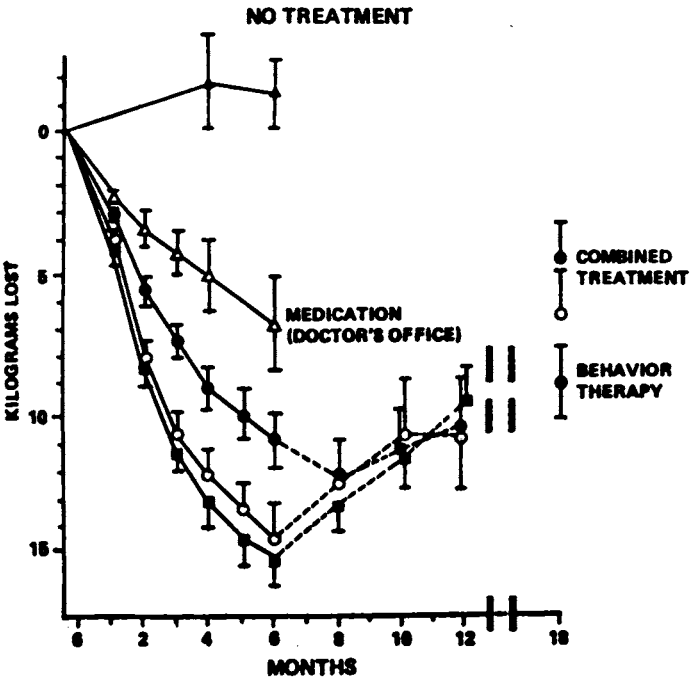

Figure 7

combination of medication plus the behavior therapy. This study is of interest not only for its practical value in the long-term management of obesity, but for two issues.

First, some interactions may be temporal or phasic. In this study, during the experimental phase, there was one set of effects of combination and they reversed themselves over time. That may occur in other disorders. Depending on the pathophysiology or the natural history of the disorder, the nature of the interactions may be different during the acute phase for an illness such as depression or an acute episode of diabetes, compared with the rehabilitative or long-term maintenance phase. Second, as this graph illustrates, the result of combination may not always be additive, augmenting, or synergistic. Although such positive interactions are hoped for, we must also be aware of negative interactions. These are well-known in drug combinations, but they have not been adequately discussed with respect to the combination of drugs and psychotherapy.

Summary

To summarize. I have attempted to bring two perspectives to this important conference: first, the policy view as seen by a government official, in which there is a blurring of the artificial distinctions between behavioral and biomedical research. Second, I have discussed, from an investigator's view, the dramatic and widespread advances in therapeutics over the past 20 years, many of which should not be taken for granted. We see a variety of therapeutic technologies, both hardware, such as computers, and soft technologies, such as randomized designs. They were initially developed in the evaluation of drug treatments but now are increasingly being applied to surgery, radiation, preventive interventions, and psychotherapeutic and behavioral interventions.

Twenty years ago, when I entered the field, there was a lively debate as to whether one could do systematic, quantitative research on psychotherapy or behavioral techniques. That debate is no longer meaningful. There are enough studies demonstrating that one can quantify the behavioral and psychological outcomes that concern us. There are enough studies indicating that techniques such as randomization and systematic blindness can be applied to behavioral and psychotherapy techniques. There are some difficult problems in defining the purity of the behavioral and psychotherapy measure. Although they are difficult, they are not insurmountable. I am optimistic, both from a policy point of view and from my past identity as an investigator.

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A CLINICAL REVIEW OF HYPERTENSION

Stevo Julius, M.D., Sc.D.

The blood pressure is the pressure needed to keep the blood flowing through the blood vessels. It is developed by the heart. The peak pressure achieved within one cardiac cycle is the systolic blood pressure, and the lowest point to which the pressure falls in that cycle is called diastolic blood pressure. This blood pressure is very tightly regulated unless there are exceptional circumstances that call for a change of blood pressure.

An illustration of how closely the blood pressure is regulated can be found in comparative physiology. The blood pressure of rats, dogs, and humans is the same. The giraffe is the obvious exception, since in order to maintain adequate circulation within a brain at such a distance from the heart, the pressure must, consequently, be higher.

The mechanisms that control the blood pressure are related to factors that determine the volume of the blood and the caliber of blood vessels. These are the two major components that determine the blood pressure. It is sufficient to say that three major systems are involved in the regulation of both the volume and of the caliber of the blood vessels: the nervous system, the kidneys, and a whole host of hormones.

Hypertension is a state of abnormally high blood pressure, and this is where we immediately have a problem: how to define what is "abnormal" and what is "normal." Blood pressure levels are distributed in a Gausian fashion in the general population.1/ It is, therefore, hard to find a point at which to define "abnormal." Traditionally, when there is a continuous distribution, "abnormal" is defined as being two standard deviations outside the normal mean, and this definition has also been applied to hypertension. Since hypertension leads to excess mortality and morbidity rates, another way of defining what is normal and abnormal is to find the point at which the blood pressure-related mortality and morbidity exceeds that of the general population.

Combining both approaches, it is best to define hypertension as blood pressure sustained repeatedly over a level of 150/90 mm Hg. Normotension can be defined as blood pressure around 120/80 mm Hg. Values lying in between normotension and hypertension should be called borderline hypertension, as these levels carry some increased, but not overwhelming, morbidity. There is a need for a buffer between what is termed normal and that termed abnormal.2/

What causes the blood pressure to increase, and what are the causes of hypertension?

Regulation of blood pressure is so complex that elevated levels can stem from abnormalities in a number of systems. There are a large number of specific conditions called secondary hypertension. These are easily identifiable clinical syndromes, probably 20 or more in number.3/ They will not, however, be elaborated upon in this presentation. In spite of a large number of causes, this secondary hypertension accounts for only five percent of all observed hypertension. Ninety-five percent of the situations in which there is elevation of blood pressure above normal, are cases of so-called "primary" or "essential" hypertension. These terms are other ways of saying that we are dealing with a condition of unknown origin. It is this condition, primary hypertension, that we ought to talk about this morning.

I would first like to talk about the consequences of high blood pressure and then about the causes, for obvious reasons: we do not know that much about the causes, but we do know a lot about the consequences. There are two types of consequences of high blood pressure. One set of consequences is directly related to the increased pressure within the blood vessels. Since the heart must work excessively to raise the blood pressure, it eventually fails. Congestive heart failure is one of the prime consequences of untreated hypertension. Another consequence of increased blood pressure levels is that of hemorrhagic stroke due to the rupture of a cerebral blood vessel.

The other set of consequences of high blood pressure is related to the wear and tear on the blood vessels. Excessive pressure levels cause premature aging of the blood vessels and lead to an accelerated development of arteriosclerosis. Consequently, a patient with hypertension at age 50 may have blood vessels which are similar to those of a 70 year old. Among the consequences of this premature atherosclerosis are: heart attacks due to narrowed coronary blood vessels; kidney failure due to arterionephrosclerosis; and another type of cerebral stroke, cerebral infarction, in which there is no bleeding within the brain but the blood supply to an area of the brain is decreased due to obstruction of cerebral blood vessels. Since these consequences are very similar to the process of aging, they involve a number of organs. Therefore, it is not hard to visualize what is the impact of hypertension on the general population.

Cardiovascular diseases are the leading cause of adult death in the United States, and it is estimated that hypertension accounts for about 50 percent of this mortality. There are about 20 million people with hypertension in the United States and probably an additional 20 million with borderline hypertension. Thus, the tremendous impact hypertension has on public health can easily be seen.4/

Before becoming too pessimistic, there is something good to be said about hypertension. There are two points to remember. First, regardless of the cause of the increased blood pressure, the consequences are always the same. That is to say, if hypertension is caused by the kidney or if it is hypertension of unknown cause, the consequences are always related to the degree of the blood pressure elevation. The second point follows from the first. Even if the cause of the disease is not known, lowering the blood pressure per se has a salutary effect. If the cause is not known, but one is able to lower the blood pressure, it is possible to prevent the consequences of the increased pressure.5/ These facts have some implication for the topic under discussion: how to modify the behavior to improve blood pressure control.

Among the causes of essential hypertension, a strong genetic component has been identified. Two lines of evidence substantiate this. The first comes from animal experimentation. Inbred colonies of rats have been developed that will, in 100 percent of cases, develop hypertension, proving that hypertension can be genetically transmittable. Another aspect of these models is also interesting: what is being inherited? It is now obvious, however, that there are many different types of inherited hypertensions, each seeming to have different organ systems involved. The Japanese hypertensive rat is very different from the Milano strain of rat in Italy and the Brookhaven strain of rat in the United States. Consequently, although there is a genetic basis for hypertension, it is not likely that the same abnormality is inherited in all types of hypertension. A second line of evidence comes from human studies. It has been demonstrated that there is a congruence of blood pressure between siblings, twins, parents and offspring. This occurs in an expected fashion, so that in monozygotic twins about 50 percent of the variance of blood pressure is explained by the genetic component.4/ Upon this genetic background, however, something has to fall to elicit hypertension. I wish to talk about three possible areas where behavioral factors may influence the development of hypertension.

One well-recognized factor in hypertension is overweight. Human studies indicate that overweight at the outset or gain of weight over a period of time tends to contribute to the development of hypertension.6/ There is also evidence that reduction of blood pressure can be achieved by weight reduction. Weight is not a large component, however, and probably accounts for only ten percent of the variance of the blood pressure seen in epidemiological studies.

Another factor is the influence of salt intake on the development of hypertension. We know that the blood pressure can be lowered by decreasing sodium intake, proving that salt is also a

contributory factor in hypertension. Evidence is coming from population studies, which are fraught with methodological problems. In my own mind, there is very little doubt that populations that eat very little sodium do not have a high prevalence of hypertension, while populations eating large amounts of sodium tend to have the highest prevalence of hypertension.7/

A third factor that may be contributory to both hypertension and behavior is the role of the nervous system. It is well known that temporary arousal, fear, or psychological stress cause a temporary elevation of the blood pressure. This response is very reproducible. It is more complicated, however, when one wants to translate that information into an etiological component of chronic high blood pressure. Experiments which used repeated pressor episodes to cause hypertension have not succeeded in creating permanent severe hypertension.8,9/ The other line of evidence that the nervous system may influence the development of hypertension comes from personality testing in patients with hypertension, particularly those with mild borderline hypertension. Patients exhibiting borderline hypertension show a conflict-prone personality profile, allowing for speculation that personality may play a role in the etiology of the disease.10/ There is evidence that about 20 percent of the patients with hypertension, predominantly those with mild hypertension, have increased biochemical markers of sympathetic activity.11,12/ This again indicates that the sympathetic nervous system is somehow involved in the development of hypertension.

Finally, there is pharmacological evidence for the involvement of the autonomic nervous system in hypertension. That evidence has been obtained by blocking various components of the sympathetic and parasympathetic nervous systems which have demonstrated differences in sympathetic and parasympathetic tone between patients with hypertension and normotensive control subjects.13/

In summary, at least three major factors contributing to the development of hypertension in genetically prone individuals are related to behavior and may be influenced by behavioral changes. Therefore, they may deserve further discussion during this conference. Adding another behavioral factor to this, the frequent lack of compliance with pharmacological treatment, there is sufficient research evidence linking hypertension and behavior to propose attempting a unified clinical approach. I would like to stress one very important point as we progress through discussions during these two days. We should not make the mistake of confusing behavioral factors that may lower the blood pressure with factors that may cause hypertension. If we engage in discussion of how to lower the blood pressure through behavioral maneuvers, we should not misconstrue this to mean that behavioral factors are the cause of blood pressure elevation.

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PHARMACOTHERAPY OF HYPERTENSION

Adrian O. Hosten, M.D.

Everyone who has treated hypertension will recall patients who have demonstrated that the hospital environment is often enough to lower their blood pressure. In the clinic they are given a number of drugs which they swear they have been taking faithfully. Yet they come back time after time with marked elevations in blood pressure. They are hospitalized, and without any change in therapy it is noted that the blood pressure is under significantly better control. It seems that separation from their usual stressful environment ameliorates their hypertension. This suggests that the recent awakening of interest in non-pharmacologic management of this disease is well-founded.

In any event, drug therapy of hypertension has come a long way in recent years. Excellent drugs for the control of high blood pressure, regardless of the cause, are available. As a result, the well-known ravages of hypertension are on the decline. Premature death from stroke and cardiovascular complications is decreasing.1/ The black population, which seemed to share disproportionately in the scourge, is happily sharing in the improvement. As patient compliance with the drug regimen increases, blood pressure control is achieved, and the incidence and severity of end organ damage declines.

In order to appreciate the rationale for drug therapy, let us review briefly some basic points in the pathophysiology of hypertension.

The blood pressure is the resultant of the cardiac output and the total peripheral resistance. The interplay between these two factors is influenced by a number of important reflex regulatory mechanisms that involve the arterioles or resistance vessels, the veins or capacitance vessels, the kidneys and the heart. These mechanisms include: (1) the control of sympathetic outflow, (2) the renin-angiotensin system, and (3) the regulation of extracellular fluid volume.

Sympathetic outflow may be triggered when baroreceptors in the carotid sinus, aorta, and left ventricle sense changes in blood pressure and relay impulses to the brain stem for processing. The result is the release of catecholamines, both in the central nervous system and at nerve endings in the heart and blood vessels. It is possible that sustained hypertension develops as a result of excessive stimulation of adrenergic nerves.

The kidneys are central to the regulation of systemic blood pressure. They are the source of the hormone renin, which changes renin substrate from the liver to angiotensin I. The latter is

changed by a converting enzyme to angiotensin II, one of the most potent vasoconstrictors in the body. Angiotensin II causes the blood vessels to constrict and thereby increases the peripheral resistance. Furthermore, the kidneys are the guardians of the extracellular fluid volume, using its concentrating and diluting capacity to conserve or unload fluid as the needs of the body dictate.

The object of pharmacologic therapy is to lower the blood pressure by interfering with these various regulatory mechanisms. Such therapy may be aimed at lowering the peripheral resistance on one hand, or at decreasing the cardiac output on the other. Historically, most of the drugs used in the therapy of hypertension have been directed at sympathetic function in one way or the other. There are drugs which act centrally to influence the outflow of sympathetic impulses from the central nervous system. There are drugs which act on the sympathetic ganglia, drugs which act beyond the ganglia at the postganglionic level, or directly on the blood vessels. Usually, all of these drugs have been used in conjunction with diuretics whose major influence is on extracellular fluid volume.

Some drugs have multiple sites of action. Alpha methyldopa, for example, probably exerts its major antihypertensive effect by stimulating alpha adrenergic receptors of the nucleus tractus solitarius in the brain stem, but it may also interfere with postganglionic adrenergic action by serving as a false neurotransmitter. Furthermore, it is known to inhibit renin release. Rauwolfia alkaloids, such as reserpine, act centrally in the hypothalamus and in the vasomotor center, as well as peripherally at the postganglionic sympathetic nerve endings, depleting catecholamines and thereby lowering blood pressure.

Drugs which act at the sympathetic ganglia, represented by trimethaphan (Arfonad) are not widely used now. Their use, in any case, was limited to the hypertensive crisis, especially when associated with dissecting aortic aneurism, encephalopathy, subarachnoid bleeding, and pulmonary edema. However, because of the many side effects and the availability of drugs which are easier to use, ganglionic blockade for control of blood pressure is largely history.

Drugs which act on the postganglionic sympathetic nerve fibers--reserpine, the rauwolfia alkaloids, guanethidine, and bethanidine--deplete the storage granules of catecholamines and thereby produce vasodilation. Indeed, guanethidine used to be the most potent orally administered drug available for the ambulatory care of the severe hypertensive. Its many side effects, including severe postural hypotension, impotence, ejaculatory dysfunction,

diarrhea, neuromuscular and other troublesome side effects, were tolerated only because there was little alternative. Its use is already fading now that we have minoxidil.

Monoamine oxidase (MAO) inhibitors, like pargyline, act much like the catecholamine depletors because they increase the amine stores filling them, what might be called false neurotransmitters. Octopamine, for example, accumulates. When stimulated, the nerves released octopamine plus the regular catecholamines, whose effect is thereby significantly diluted. These MAO inhibitors, though potent antihypertensives, are not popular because of their side effects and their potential for precipitating a paradoxical hypertensive crisis if the patient is exposed to tyramine and other amines in cheddar cheese, bananas, and other foods.

The next level of drug action is at the receptor sites. The alpha-adrenergic blocking drugs phenoxybenzamine and phentolamine have not found much use in hypertensive therapy, largely because of their many adverse side effects. Phentolamine was used in the diagnosis of pheochromocytoma, but even this regitine test has been replaced by the more diagnostic and risk-free biochemical tests. The beta-receptor blocking agents represented by propranolol (Inderal) and metoprolol (Lopressor) enjoy wide use. The latter was introduced as a cardioselective beta-blocker without the side effects of bronchoconstriction, which is the main adverse effect of propranolol. The mechanisms of action of the beta-receptor blockers in reducing blood pressure is still not fully understood. The earlier explanation that they lowered pressure by decreasing cardiac output, although still a factor, does not seem to be the major one. Their blockade of renin release, as well as of peripheral beta receptors, are additional factors. Their possible role in central beta blockade may well be a significant mode of action.

Some of the most popular antihypertensive drugs in current use act directly on the blood vessels. They include hydralazine, sodium nitroprusside, diazoxide, and minoxidil. Prazosin was initially thought to belong in this group. However, as pointed out above, it is now known to act by selective post-synaptic alpha-adrenergic blockade. Hydralazine, sodium nitroprusside, minoxidil, and diazoxide directly dilate the resistance or capacitance blood vessels, or in the case of nitroprusside, both groups of vessels. The net effect is a decrease in the peripheral resistance and a dramatic fall in blood pressure. Minoxidil is the newest of these drugs, having only very recently been released by the FDA. It is proving itself to be a very valuable drug in the control of severe hypertension. Indeed, since its introduction, bilateral nephrectomy for the control of malignant hypertension is seldom necessary.

The next category of drugs, the diuretics, act largely by decreasing blood volume. Some of them, thiazides, for example, have been ascribed the additional effect of decreasing the concentration

of sodium in the blood vessel wall, and thereby decreasing the reactivity of the blood vessels.

There is no question that control of moderate to severe hypertension using the above drugs in various combinations significantly reduces the risks of end organ damage. Since the National High Blood Pressure Education Program went into full gear during the period 1972-1977, age-adjusted death rates for hypertension and hypertension-related diseases declined by as much as 20 percent. There was no good evidence until recently that people with mild hypertension benefitted from such drug therapy, especially when the side effects of the drugs were considered. The evidence is now available from the report of the Hypertension Detection and Follow-up Program (HDFP).2/

The HDFP was a community-based study involving over 10,000 persons, 71 percent of whom had mild or borderline hypertension (diastolic blood pressures between 90 and 104). It compared the mortality of patients who were treated by a so-called "stepped" care approach and patients who were treated by what was called "referred" care. Under the latter, patients were referred to their private physicians or their clinic for routine care. It was found that during the five-year period of the study, the death rate among those patients on the stepped care program was nearly 17 percent less than that of the referred group. This information suggests that, whatever the side effects of drug therapy, even in patients with mild hypertension, the risk:benefit ratio is favorable.3/

The question of whom to treat is easily answered. Individuals with diastolic blood pressures in excess of 90 deserve some sort of treatment. The object is to control high blood pressure and reduce the risks to victims of this serious public health problem. The necessity for treatment is even more critical for those patients with some risk factors. The heavy salt user, the patient who is young and black, the patient who already has evidence of end organ damage, such as cardiomegaly or renal insufficiency, should be treated vigorously to control the hypertension. Even if they must risk the side effects of antihypertensive drugs, the price is well worth it. The elderly should also be treated to control hypertension but with particular caution with regard to the kinds of drugs prescribed.

The stepped care plan to the treatment of hypertension is a reasonable approach. The first step drug is a diuretic designed to help control blood volume. At the same time, the patient might be instructed in adjusting his or her lifestyle, at least as far as the intake of salt is concerned. Indeed, one might use salt restriction alone before starting drug therapy.

If the diuretic alone is ineffective, one of the drugs in Step Two--clonidine, methyldopa, prazosin, propranolol, or one of the

rauwolfia alkaloids--should be added. Whichever drug is selected, the dose is increased as indicated to control the pressure or until the maximum dose is reached. If one Step Two drug (e.g., methyldopa) fails, a second or even a third in that group of drugs may be tried before going to Step Three.

When all drugs in Step Two in combination with a diretic prove inadequate, the Step Three drug hydralazine is added. It should be noted that this drug is often used quite successfully as a Step Two drug. Its tendency to cause tachycardia limits its usefulness in patients with angina, except when a beta-receptor blocker is part of the regimen. Furthermore, it is finding wider use now in reducing afterload in patients who have one of the complications of hypertension, namely congestive heart failure.

Should triple drug therapy (for example, with a diuretic, a beta-receptor blocker, and a peripheral vasodilator) fail to control the blood pressure, then a Step Four drug is added. Until recently, this meant the addition of guanethidine. Now, however, there is minoxidil, a potent orally-administered peripheral vasodilator. This drug, only recently released by the FDA, holds strong promise for the severe hypertensive.

There is another drug, still undergoing clinical trials, which lowers blood pressure, probably by modulating the renin angiotensin system. That drug is known as Captopril, a converting enzyme inhibitor. It blocks the production of the potent vasoconstrictor angiotensin II from angiotensin I. Its place in the antihypertensive armamentarium is not yet established.

In summary, there is no question that hypertension should be treated, whether it be mild or severe. For mild hypertension, behavior modification, at least in terms of reducing salt intake, may be all that is necessary. When drugs are indicated, there should be no hesitation to use them, for despite their side effects, antihypertensive drugs have a positive risk/benefit ratio, even for the patient with borderline or mild hypertension. The benefit is even more striking for patients with severe hypertension. The mild sedation and drowsiness produced, especially by the centrally acting drugs; the sexual dysfunction induced by many of the drugs; the postural hypotension; and the risk of hemolytic anemia--these are risks worth taking because the stakes are high. Patients should be educated regarding the seriousness of hypertension and encouraged to comply with the therapeutic regimen. The cost is well worth it, since the evidence shows that the complications of hypertension can be significantly decreased with adequate control of the blood pressure. The mortality rate, even among those with mild hypertension, can be reduced by lowering the blood pressure whether by drugs, by non-pharmacologic therapy, or by both.

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BEHAVIORAL APPROACHES IN THE PREVENTION AND TREATMENT OF HYPERTENSION

Redford B. Williams, Jr., M.D.

Any consideration of behavioral approaches in the prevention and treatment of hypertension must address two key issues. First, what is the role of behavior in the etiology and pathogenesis of hypertension? Second, what is the currently available evidence that behavioral approaches might be useful in the prevention and treatment of hypertension?

The Role of Behavior in the Etiology and Pathogenesis of Hypertension

The case for a role of behavioral factors in the etiology and pathogenesis of hypertension can be summarized as follows: the brain transduces experience into physiological change and, since the brain is integrally related to behavioral expression the means whereby behavior might participate in the pathophysiological events leading to hypertension are at least potentially present.

The distinguished English physiologist Sidney Hilton has made the point that the brain is not set up to organize single or isolated physiological responses, but rather to integrate a wide variety of behavioral, somatomotor, neuroendocrine, and physiological responses which serve some adaptive function for the organism in coping with the demands of the environment.1/ This concept has important implications for any consideration of the role of behavior in the etiology and pathogenesis of cardiovascular disease -- particularly hypertension. It suggests that behavioral responses to environmental demands are inexorably linked with physiological and neuroendocrine responses which, if elicited frequently and intensively enough, could play a role in the mosaic of factors contributing to the pathogenesis of hypertension.

The best example of such an integrated behavioral/physiological/neuroendocrine response pattern is the defense reaction, which is elicited in circumstances where emergency motor activity is required, as well as during the performance of mental work tasks. The anatomical location of the brain system mediating expression of the defense reaction has been extensively demonstrated.2/ Jan Brod demonstrated that performance of mental arithmetic problems with harassment elicited essentially the fullblown defense reaction in humans.3/ This consists of an increase in somatomotor activity, an increase in cardiac output, vasoconstriction in skin and viscera, and vasodilation in skeletal muscles. We have recently been able to demonstrate in our laboratory that, in addition to the muscle vasodilation during mental arithmetic problem solving, there is also a significant increase in plasma levels of norepinephrine, epinephrine, and cortisol in young adult male subjects.4/ In a

classical study which needs to be replicated, Folkow and Rubinstein were able to show that rats subjected to chronic low levels of stimulation in the defense area of the hypothalamus over a period of weeks developed sustained hypertension.

In addition to the defense reaction, which is elicited by mental work tasks in humans with its characteristic muscle vasodilation and cardiac output response, there is extensive animal and human experimentation suggesting the existence of another integrated behavioral/physiological/neuroendocrine response pattern. During careful observation of environmental sensory stimuli, it has been shown that there is an active vasoconstriction in skeletal muscles in humans.5/ We have recently been able to show that only plasma norephinephrine shows a substantial increase during sensory intake behavior, while plasma epinephrine and cortisol are relatively unchanged.4/ Anderson and Brady have also shown in dogs that during pre-avoidance periods (during which dogs are generally closely attentive to a manipulandum placed before them), an increase in peripheral resistance and fall in cardiac output is observed as blood pressure rises.6/

The conclusion I wish to draw from the foregoing is that there are known mechanisms whereby environmental events can be shown to influence not only the somatomotor behavior of the organism, but also the cardiovascular and neuroendocrine responses in an integrated, linked fashion, such that blood pressure elevations can be induced by environmental events utilizing both cardiac output and peripheral resistance mechanisms.

Given these potential mechanisms, has it been shown that psychosocial stimulation is indeed capable of inducing sustained hypertension? Obviously, this case is much harder to make in humans than in animals, and the evidence before us is limited to the animal research area. The most convincing evidence for the induction of sustained hypertension in animals comes from the studies of Henry and colleagues, in which a particular housing arrangement leading to frequent confrontational episodes between male mice competing for food is shown to result not only in sustained hypertension, but also in characteristic anatomic changes in the heart, blood vessels, and kidneys.7/ In a study employing rats, Lamprecht et al showed that over four weeks of daily immobilization stress, blood pressure gradually increased into the hypertensive range.8/ Concomitant with this blood pressure increase, a measure of sympathetic nervous system activity -- serum levels of dopamine beta hydroxylase (DBH) -- also showed a gradual increase, suggesting that the chronic daily stress episodes increased blood pressure via an effect to increase sympathetic nervous system discharge. At the end of the four week period of daily immobilization stress, if the animals were simply followed over an additional four weeks, it was found that DBH levels fell rapidly, reaching control levels within one to two

weeks. In contrast, blood pressure required nearly four weeks to return to control, normotensive levels. This suggested that while the sympathetic nervous system may have been playing some role in the initiation of the hypertension during chronic immobilization stress, other mechanisms may have come into play in the continued maintenance of the elevated blood pressure levels.

This phenomenon is illustrated even more convincingly in a recent study of the desoxycorticosterone (DOCA)-salt hypertension model in rats.9/ Pretreatment with intraventricular, but not intracisternal, 6-hydroxy-dopamine (a neurotoxin specific for catecholaminergic neurons) was found to block the subsequent development of hypertension in rats treated with DOCA and salt. At about four weeks after being started in the DOCA-salt regimen, if animals that had previously received intracisternal vehicle alone or intracisternal 6-hydroxy-dopamine were given intraventricular 6-hydroxy-dopamine, the hypertension was reversed. However, if the intraventricular 6-hydroxy-dopamine was delayed until about six to seven weeks after institution of the DOCA-salt regimen, the hypertension was no longer reversed by the intraventricular 6-hydroxy-dopamine. This suggests that even in a model of hypertension which is generally considered to involve renal mechanisms, the central nervous system catecholamine mechanisms are necessary for the development of hypertension. Moreover, these findings suggest that this involvement of CNS catecholamine mechanisms, while crucial for the initiation of hypertension, is not so intimately involved in the maintenance of hypertension once established beyond a certain length of time.

This study suggests that there is something crucially different about the involvement of brain mechanisms in the initiation phase of hypertension as compared to the maintenance phase. Therefore, this kind of information needs to be considered as we attempt to identify behavioral interventions which might be undertaken at different phases in the hypertensive process. In particular, it suggests that the initiation phase might be an especially important period in which behavioral approaches to reduce sympathetic nervous system activity might be efficacious.

Potentially Useful Behavioral Approaches in the Prevention and Treatment of Hypertension

The recently published results of the hypertension detection and follow-up program (HDFP) make the case that treatment even of mild levels of hypertension can be effective in reducing morbidity and mortality due to hypertension. Patients with mild hypertension, however, are likely to be particularly difficult to treat with antihypertensive medication, due to the unpleasant side effects of these agents as well as to the fact that patients with mild hypertension typically are quite asymptomatic. It is in this group

of patients in whom treatment has now been shown to be useful that compliance with pharmacologic measures might be most difficult to obtain. Therefore, this group would be the most likely target for behavioral approaches to the prevention and treatment of hypertension. An additional rationale for this conclusion is that such patients are more likely to be in the initiation phase of their disease process--a phase which, as I noted above, may be one in which behavioral attempts to reduce sympathetic nervous system activity could well be most effective.

There are numerous recent reviews detailing the various attempts which have been made to reduce blood pressure using biofeedback and other behavioral techniques. Rather than describe these studies in any detail, I would simply refer the reader to the excellent review by Seer.10/ In general, these studies have shown that it is much easier to train people to raise their blood pressure above resting level than it is to train them to decrease it. This apparent lack of clinical effect may be due to the fact that studies in this area typically have patients sit quietly at rest and then attempt to have them reduce their blood pressure levels through either biofeedback or other behavioral techniques. Thus, there may be a floor effect preventing further significant falls in blood pressure. Many investigators in this area now feel that, rather than attempting to train patients to reduce blood pressure from baseline resting levels, it would be more effective to train patients to maintain a lower blood pressure level under conditions of physical or emotional stress--conditions which in ordinary circumstances would be expected to result in increased blood pressure. Whether such an approach will have a clinically significant blood pressure lowering effect remains to be seen in further studies.

Another problem in evaluating behavioral approaches to blood pressure control involves the question of how control is assessed. Most evaluations of pharmacologic means of treating hypertension have simply relied upon blood pressure levels in the clinic situation. An important issue in evaluating behavioral approaches to blood pressure control in particular concerns whether the treatment is effective in helping the patient to maintain lower blood pressure during everyday life as well as when blood pressure is being measured in the clinic situation. Future studies evaluating various behavioral approaches will need to incorporate some means of assessing the effect of the intervention on blood pressure during more naturalistic conditions.

With regard to the clinical efficacy of a behavioral approach employing stress management training along with relaxation skills training for the control of blood pressure, Richard Surwit has noted (unpublished observation) that such an approach results in a decrease over days in both blood pressure lability and mean blood

pressure level. This pattern of gradual decrease in both blood pressure lability and mean blood pressure level over time with practice of relaxation and stress management techniques has now been duplicated in several patients in our clinic. Whether such anecdotal findings can be demonstrated in controlled outcome studies remains to be seen, but the available evidence is certainly encouraging.

Another behavioral approach which can be highly effective in reducing blood pressure is regular aerobic exercise. Blumenthal et al recently reported statistically significant falls in resting blood pressure over the course of a ten-week exercise program even among normotensive subjects.11/ Another lifestyle change which has long been known to result in reduced blood pressure levels is reduction of sodium intake below the current high levels typical of the average American diet.

In conclusion, it is clear that the case remains to be made that behavioral approaches will be efficacious in the treatment of any form of hypertension, sustained or mild. As noted in the foregoing, however, there is a sound scientific case to be made for a rationale using behavioral approaches, and there is some promising preliminary, anecdotal evidence suggesting that behavioral approaches may well eventually be shown to have a place in the prevention and treatment of hypertension.

As a stimulus to discussion and future research efforts in this area, I would propose that rather than employing a mild diuretic as the first step in the "stepped care" approach to treatment of hypertension, we substitute a behavioral treatment package for that first step in the approach to the patient with mild hypertension. This behavioral treatment package would consist of the following, either alone or in combination: (1) stress management training employing relaxation skills training and other behavioral techniques designed to help people cope better with life stresses, (2) a program of exercise--jogging for 45 minutes about three times per week, (3) a behaviorally oriented weight reduction program for those patients who are more than ten percent above ideal body weight, and (4) a program utilizing behavioral modification principles to help patients reduce sodium intake--the level should not be too extreme, perhaps in the range of two to four grams of sodium per day.

It is my prediction that such a behavioral treatment program employed as the first step in the approach to the patient with mild hypertension would have the following results: (1) the proportion of patients who remain hypertensive upon further follow-up would be diminished by such a program, (2) the number and dosage level of medications that would have to be utilized in the second step would be diminished, and (3) compliance with both the behavioral and pharmacologic regimens where needed would be improved. All of these

predictions are research questions which can be answered with available approaches and technology, and I hope that many of the readers of this paper will be stimulated to make an attempt to implement such a behavioral treatment program.

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ROLE OF PATIENT ATTITUDES AND BELIEFS IN PATIENT COMPLIANCE

Marshall H. Becker, Ph.D.

My assigned task for this presentation is to briefly review findings from research on the influences of individuals' health-related attitudes and beliefs on adherence to recommended and prescribed medical regimens. Obviously, a great many other factors (e.g., characteristics of the patient, condition, regimen, treatment setting, and provider-patient relationship) are known to play important roles in the noncompliance phenomena; however, I would argue that (1) a large body of empirically-based literature is now available which suggests that patients' attitudes make a substantial contribution to their decisions about cooperation with treatment plans, but this information is frequently ignored or overlooked by both compliance researchers and health care practitioners; (2) important compliance-related attitudes and beliefs can be readily and easily assessed; (3) these subjective perceptions are often more likely to be amenable to modification than are other factors affecting compliance; and (4) attempts to ameliorate patient compliance which deliberately bypass attitudes and focus directly upon the activities to be performed (e.g., "behavioral therapies") have met with little success with regard to long-term maintenance of the desired behaviors.1/

It may be best to begin by noting that, from an attitudinal perspective, the patient's decision not to accept medical advice may be quite reasonable, particularly in light of past compliance incidents that he or she has personally experienced, witnessed, or heard about. Some of the possible outcomes of patient compliance and noncompliance are shown in Figure 1.

In our thinking about patient compliance, we usually imagine cases which fall in cells "A" and "D"; that is, achievement of the preventive or treatment goal is simply dependent upon whether or not the individual follows our advice sufficiently. In this manner, we tend to forget that a great many therapeutic incidents occur which fall in the "deviant case" cells of the figure. For example, one commonly encounters (and experiences) circumstances wherein faithful adherence to regimen does not yield the desired outcome (i.e., cell "B"). The diagnosis may have been incorrect, the prescribed therapy may have been incorrect (or inadequate, or inefficacious), the patient may not respond to a particular treatment; the preventive measure may not have been sufficient, and so forth. The "lesson" learned (or attitude developed) by the individual is, "Sometimes, even if you do everything the health professionals tell you to do, you still get sick/don't get well." One encounters similar

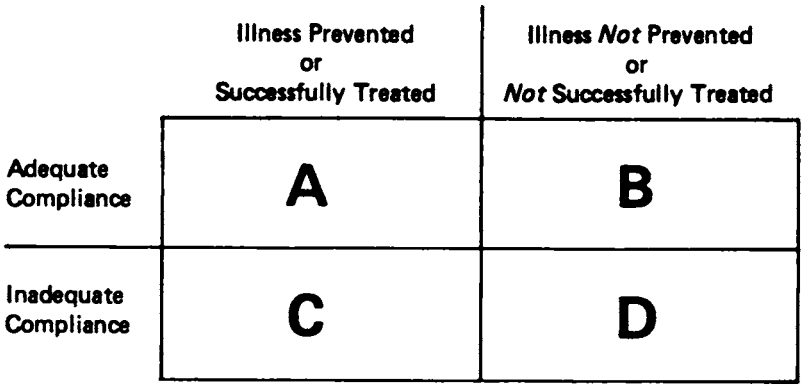

Figure 1. Some possible relationships between degree of patient compliance and health outcomes

learning experiences in cell "C." Here, despite poor compliance, the patient nonetheless recovers (or does not become ill). Again, the wrong diagnosis may have been made and the symptoms may abate naturally. Much acute illness disappears without treatment, and risk-factor behaviors (e.g., cigarette smoking, overeating, diets high in saturated fats and cholesterol) do not usually result in readily-observable illness in the short run (nor does every risk taker become ill even in the long run). Here, the "lesson" learned (and concomitant attitude developed) is, "Sometimes, even if you don't do everything the health professionals tell you to do, you still get well/don't get sick."

Furthermore, many persons have experienced (or heard about) the potential iatrogenic consequences of different medications and therapies. Individuals are continually exposed by the mass media to controversies, contradictions, and often reversals with regard to public health and medical care recommendations (e.g., the recent debates about the merits and/or dangers of obtaining Swine Flu immunizations, sharply altering dietary patterns, achieving "normal" body weight, and others). One is reminded of the contemporary relevance of Chapin's comment, made in 1915, that "[t]he opprobrium of our art is that preventive medicine, like its other branches, has

taught much that has had to be unlearned. We ought not to be surprised that people do not believe all we say, and often fail to take us seriously. If their memories were better, they would trust us even less."2/ Thus, in light of the information and experiences just described, it is indeed not surprising that patients have developed a variety of health-related attitudes and beliefs affecting their decisions about both the necessity and the desirability of following professional advice. We must add to these an additional concern: the multiplicity of health beliefs, learned from parents and peers, through personal experience.

Over the past two decades, a variety of models have been constructed which aid us in our attempts to focus on a particular set of attitudes that can help to explain patient compliance decisions, and through the modification of which we might hope to increase compliance levels. Although these formulations offer a number of different orientations and variables, they all contain one or more elements of a particular model initially developed to predict compliance with such preventive health recommendations as obtaining immunizations, screening tests, and annual checkups. This "Health Belief Model" contains the following elements (Figure 2): (1) the individual's subjective state of readiness to take action, which is determined by both the person's perceived likelihood of susceptibility to the particular illness and by his or her perceptions of the probable severity of the consequences (organic and social) of contracting the disease; (2) the individual's

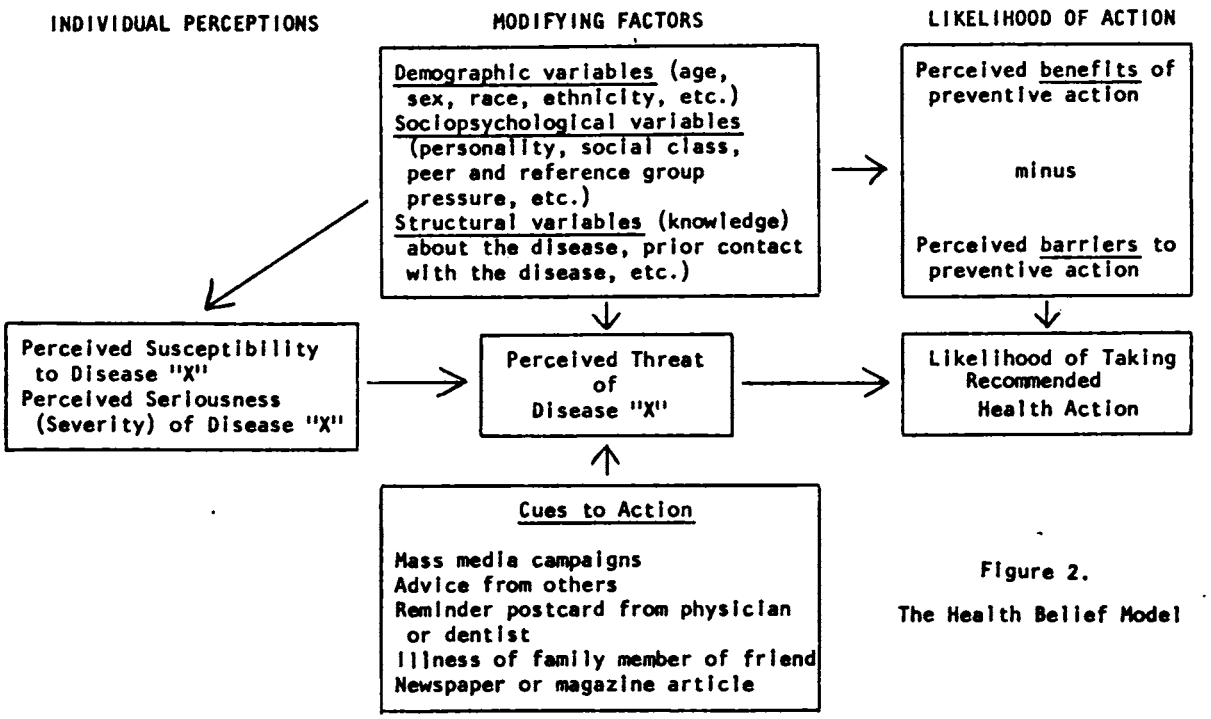

Figure 2.

The Health Belief Model

evaluation of the advocated health behavior in terms of its feasibility and efficaciousness (i.e., an estimate of the action's potential benefits in reducing susceptibility and/or severity), weighed against his or her perceptions of physical, psychological, financial, and other costs or barriers, such as possible side effects, involved in the proposed action; and (3) a cue to action must occur to trigger the appropriate health behavior; this stimulus can be either internal (e.g., the perception of symptoms) or external (e.g., interpersonal interactions, mass media communications). Although it is assumed that diverse demographic, personal, structural, and social factors can, in any given instance, influence an individual's health-related perceptions, these variables are not considered as direct causes of health action.

The Health Belief Model has now been applied successfully in a large number of research efforts to explain and predict individuals' health-related behaviors in both preventive and curative situations. For example, many studies have obtained positive correlations between an individual's subjective estimate of personal susceptibility and adherence to preventive recommendations. These include screening for cervical, breast, or other cancers; for tuberculosis, heart disease, Tay-Sachs disease, and for dental problems; immunizations against various illnesses; adoption of an accident-preventive device; risk-reduction actions to prevent coronary heart disease; a postpartum program of contraception; and well-child (preventive) clinic visits.

In examining the relationship between perceived susceptibility and taking prescribed medication, researchers have employed the concepts of "resusceptibility" and "belief in diagnosis," as some diagnosis of illness has already been made. For example, one investigator reported that compliance with a regimen of long-term penicillin prophylaxis by college students with a history of rheumatic fever was greater for those with higher subjective estimates of the likelihood of having another attack. Similarly, other researchers have found significant positive associations between a mother's belief in the possibility of her child's contracting rheumatic fever again and compliance both in administering the penicillin and in clinic attendance. One study obtained substantial correlations between a mother's compliance with a regimen (penicillin and clinic appointment-keeping) prescribed for the child's acute illness (otitis media) and her feeling that the child was resusceptible to the present illness, her belief in the accuracy of the diagnosis, and her perception that her child was "easily susceptible to disease." Similar measures of the susceptibility constructs have been shown to be related to compliance with antihypertensive regimens; a diet regimen for obese children, a drug regimen to prevent or control asthma attacks in children, dietary intake restrictions, and medications (to control serum phosphorus and potassium levels, and fluid weight gain between treatments) for

patients with end-stage renal disease who are receiving regular hemodialysis.

Although medical estimates of the severity of an illness are not usually predictive of patient cooperation, studies of preventive health behavior have obtained correlations between relatively higher degrees of belief that incurring the condition would be serious and compliance with health recommendations involving dental care, preventing an accident, seeking care in response to symptoms, initiating actions to prevent coronary heart disease or postpartum conception, and bringing the child to the clinic for prevention-oriented care.

No significant associations were found, however, between perceptions of seriousness and participation in several types of screening programs or for accepting immunizations. Recent interpretations of these findings suggest that for asymptomatic individuals, very low levels of perceived severity are not sufficiently motivating, and very high levels are inhibiting or immobilizing. Thus, both extremes are associated with low likelihood of taking preventive health action. Parallels may be found in the literature on individuals' delay in seeking diagnosis for cancer symptoms.

In the case of compliance with prescribed medications, the results are positive and consistent: the level of perceived severity of the condition (either for one's self or one's child) regularly predicts adherence to the regimen. Unlike the situation applying to preventive health actions, a prescribed regimen suggests that a diagnosis of illness has been made, and the patient is either experiencing symptoms or, as in the case of rheumatic fever prophylaxis, has experienced them before. It may therefore be that the presence of physical symptoms produces an elevating or "realistic" effect on perceived severity, motivating the patient to follow the physician's instructions as long as indications of illness persist (or to avoid their recurrence). Indeed, patients often state that they stop taking their medicine as soon as they feel better.

A field experiment to identify factors associated with participation in a cervical cancer screening program demonstrated that women who were compliant were more likely to believe that such a test could detect cervical cancer, such a test or examination could reveal illness before the appearance of clinical symptoms, and early detection would lead to a more favorable prognosis. Other studies of preventive health behaviors have yielded positive (usually statistically significant) correlations between perceived efficacy and subsequent compliance with recommendations to obtain immunizations; be screened for tuberculosis, cancer, and Tay-Sachs disease; make prophylactic dental visits; and take action to avoid unplanned pregnancy, coronary heart disease and other problems.

Perception of benefits is also shown to be related to patient compliance with medication and other therapies. Several investigators have found belief in the ability of penicillin to prevent recurrence of rheumatic fever to be predictive of adherence to the regimen. In one study, "belief in the efficacy of clinic medications" predicted regular administration of the prescribed penicillin; others have shown that subjects with stronger positive beliefs about the value of adherence to their doctor's instructions (in terms of feeling healthier and reducing the chance of future strokes, heart attacks, and kidney problems) were more likely to report medication compliance and to have filled and refilled their prescriptions. Finally, one study obtained significant associations between the patient's faith in the benefits of medical intervention and degree of cooperation with diet and medication therapies.

Although perceived costs have been measured in a variety of ways, several variables have been dependable predictors of noncompliance. For example, regardless of the level of the individual's concern about poliomyelitis, he or she will not obtain the recommended vaccination if there is some questions as to the vaccine's safety. Concerns about pain, discomfort, or monetary costs related to obtaining preventive dental care are also negatively associated with compliance, and other regimen-specific barriers have been discovered.

Certain perceptions of characteristics of the regimen are fairly consistent predictors of adherence for prescribed therapies. Cost and side effects are usually associated with compliance, and the greater the duration of the therapy, the more compliance decreases over time. The degree of behavioral change required is also negatively correlated with patient cooperation, and the general rule is that prescribed actions are easier to obtain than proscribed behaviors.

Finally, while all of the studies mentioned have assessed (and sometimes tried to alter) the attitudes and beliefs of health care consumers, quite encouraging results are available from research which employed Health Belief Model concepts in an attempt to modify the attitudes and behaviors of physicians in order to achieve ultimate improvements in the compliance levels of their patients. In a controlled clinical trial, Inui and associates 3/ assigned one of two groups of physicians to receive special tutorials (about one to two hours in length) whose content emphasized both compliance difficulties experienced by patients with hypertension and possible strategies for altering patient beliefs and behaviors based on the Health Belief Model. After only a single session, physicians in the experimental group were observed to spend a greater proportion of clinic visit time on patient teaching, and their patients later exhibited higher levels of knowledge and appropriate beliefs about hypertension and its treatment. Moreover, the patients of tutored

physicians were subsequently more compliant with the treatment regimen and demonstrated better blood pressure control.

There are, of course, a great many other studies showing relationships between various kinds of personal-level attitudes/beliefs and different health-related behaviors, and we do not have time for a detailed discussion of these projects. However, I hope that in this brief presentation I have succeeded in "raising your collective consciousness" about the roles played by attitudes and beliefs in the phenomenon of patient noncompliance. This is really a plea to a behaviorally-oriented audience for an "additive model," along the lines of Dr. Klerman's earlier remarks. We have a wonderful behavior modification and behavior therapy repertoire; by adding a concern with the patient's attitude and belief system, I believe we would obtain at least an additive, and perhaps a synergistic, effect on compliance.

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A CLINICAL REVIEW OF DEPRESSION

Robert Spitzer, M.D.

The term "depression" can be viewed as a symptom, a syndrome, a disorder, and possibly a disease. As a symptom, depression is something that every human being knows about because depressed mood seems to be a built-in capacity that we all have, and there is probably a very good evolutionary reason why we have the capacity for depression. All of us regard depression, if it is within certain bounds (and sometimes those bounds are not so easy to define), as a normal mood and not in any way pathological.

One can also speak of depression as a syndrome, and here we are describing the pathological. The notion of a syndrome is a clustering of behaviors and symptoms that generally come together. This definition avoids the issue of whether there is a single etiology.

When certain syndromes take certain forms, we classify them as disorders. The term "disorder" as used to describe depression is less specific than the term "disease," which in medicine generally implies a much greater understanding of a particular etiology or pathophysiological process. So, using the term "disorder" holds that issue in abeyance.

How does a depressive syndrome manifest itself? Typically the patient will complain of a depressed mood. If the mood is more severely depressed, the patient may be able to recognize that it is very different from the kinds of sadness that he or she may have experienced on having lost someone to whom they were close. Some patients may not complain of a depressed mood, but instead may only complain of a loss of interest or pleasure, that things just don't have the same excitement and vitality that they have had before. A depressed mood can be expressed in many different ways, but sadness, discouragement, hopelessness, pessimism, or some loss of interest or pleasure is an absolute requirement for the depressive syndromes. (We are avoiding here the issue of whether there are masked depressions, that is, depressions which do not have any of these central features of disturbed mood.) Loss in interest or pleasure may be rather profound, particularly in the more severe depressions in which the patient will report that there is no part of life from which he or she derives pleasure.

There are additional features of the syndrome in addition to this loss of interest or pleasure. For example, appetite is frequently disturbed, usually decreased, and there may be considerable loss of weight. More rarely, appetite may be increased, with a gaining in weight. Depressed persons commonly

suffer from sleep disturbances. They especially report difficulty falling asleep, as well as middle insomnia, in which the patient wakes up in the middle of the night, and is unable to get back to sleep for some time. In more severe depressions, terminal insomnia is fairly common, in which the patient awakens after four or five hours of sleep (when they customarily had slept for eight hours a night) and is unable to return to sleep.

Psychomotor disturbance is also common in depressive syndromes. It may be experienced as agitation, in the form of inability to sit still, or pacing. It may also take the form of psychomotor retardation where all movements are slow, including speech with long pauses and slowed body movements.

Rather regularly the patients will complain that they do not have the energy that they used to have. There will be complaints of sustained fatigue in the absence of physical exertion; accomplishing the slightest task seems difficult or impossible. Patients will frequently complain of difficulty in concentrating, slowed thinking, difficulty making decisions. They may have trouble with memory.

Self-esteem is frequently disturbed and some would argue that it is invariably disturbed in a significant depression. The individual may have very exaggerated notions of having failed himself or his family. There may be efforts to search the environment to justify this bad feeling. This may lead to pathological guilt where very minor deviations in conduct in the past are regarded as terribly sinful; sometimes this reaches delusional proportions.

Most individuals with a full depressive syndrome have a significant decrement in their ability to function occupationally and socially. This can vary from mild impairment to complete incapacitation. Commonly there are fears of dying, wishes to die, or suicidal plans or attempts. Suicide is obviously the most serious complication of depression.

There are other features frequently present that are not as central to the depressive syndrome. These include anxiety, hypochondriasis, concern about physical health, panic attacks, various phobias, and avoidance of situations that cause anxiety.

As I mentioned earlier, guilt can sometimes be of delusional proportion. There may be other forms of delusions that are generally consistent with the depressed mood. Patients may feel that they have a disease. They may feel that other people are persecuting them for things that they have done, and that they deserve to be persecuted in some way.

Classification and Differential Diagnosis of Affective Disorder

It is important to recognize that a depressed mood or a depressive syndrome is frequently associated with a variety of medical disorders. Some substances, such as antihypertensive medications, can cause a depressive syndrome. We would refer to that as an organic affective syndrome.

There are psychotic disorders whose relationship to affective disorders proper is still one of controversy and uncertainty. Schizoaffective disorder is an example of that. This diagnosis can be made for individuals who show both the typical depressive features, but also show features that are very suggestive of schizophrenia. Whether this is a third disorder or represents some point on a continuum between the two disorders is really unclear.

Adjustment disorder is an important category, for individuals who, in response to a specific psychosocial stressor, develop a moderate degree of depression, but not the full syndrome that was described earlier. Depressive symptoms which often appear after the loss of a loved one are not considered a mental disorder if they are not unduly severe or prolonged.

Within the classification of affective disorders there are two major categories, the first being major affective disoders. The term "major" can be justified in the sense that it is equivalent to the concept of a full depressive syndrome. The major affective disorders include major depression in which there are only episodes of depression and bipolar disorders in which there are one or more episodes of mania (with or without a history of a major depressive episode). Major depressions are further subclassified either as a single episode or as recurrent.

The chronic mild affective disorders are a separate group. Here there are two which are somewhat parallel to the major affective disorders. These are cyclothymic, which includes mild episodes of depression and hypomania (that are not full manic episodes), and dysthymic disorder. In the recent (third) edition of the Diagnostic and Satistical Manual of Mental Disorders (DSM-III), "dysthymic disorder" is a new term which refers to what has been called depressive personality or depressive character (See Table 1). Included in this group are individuals who, for at least two years, have had a relatively sustained degree of mild depression. This is an important cateogry because both community surveys and the clinical field trials of DSM-III found this to be a frequently used category. In fact, many ambulatory psychiatric patients appear to be suffering from this disorder.

TABLE 1*

Dysthymic Disorder or Depressive Neurosis

Differential diagnosis. Major depression; normal fluctuations of mood; chronic mental disorders, such as obsessive-compulsive disorder or alcohol dependence, when associated with depressive symptoms.

Diagnostic criteria.

A. During the past two years (or one year for children and adolescents) the individual has been bothered most or all of the time by symptoms characteristic of the depressive syndrome that are not of sufficient severity and duration to meet the criteria for a major depressive episode.

B. The manifestations of the depressive syndrome may be relatively persistent or separated by periods of normal mood lasting a few days to a few weeks, but no more than a few months at a time.

C. During the depressive periods there is either prominent depressed mood (e.g., sad, blue, down in the dumps, low) or marked loss of interest or pleasure in all, or almost all, usual activities and pastimes.

D. During the depressive periods at least three of the following symptoms are present:

(1) insomnia or hypersomnia
(2) low energy level or chronic tiredness
(3) feeling of inadequacy, loss of self-esteem, or self-deprecation
(4) decreased effectiveness or productivity at school, work, or home
(5) decreased attention, concentration, or ability to think clearly
(6) social withdrawal
(7) loss of interest in or enjoyment of pleasurable activities
(8) irritability or excessive anger (in children, expressed toward parents or caretakers)
(9) inability to respond with apparent pleasure to praise or rewards
(10) less active or talkative than usual, or feels slowed down or restless
(11) pessimistic attitude toward the future, brooding about past events, or feeling sorry for self
(12) tearfulness or crying
(13) recurrent thoughts of death or suicide

E. There are no psychotic features, such as delusions, hallucinations, or incoherence.

F. If the disturbance is superimposed on another mental disorder or a preexisting mental disorder, such as obsessive-compulsive disorder or alcohol dependence, the depressed mood, by virtue of its intensity or effect on functioning, can be clearly distinguished from the individual's usual mood.

*Tables 1 and 2 adapted from: American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (Third Edition). Washington: American Psychiatric Association, 1980.

The criteria for a major depression have been specified as follows: a dysphoric mood or loss of interest or pleasure, and at least four of the eight associated symptoms mentioned before have been present for at least two weeks. (Table 2) There is some degree of arbitrariness in requiring four symptoms, which are experienced for at least two weeks, but I think one of the methodological advances that we have had in our field is the ability to more clearly define the boundaries of some of these disorders.

Exclusionary symptoms include the absence of a known specific organic factor, such as the presence of an antihypertensive drug, which may be causing the syndrome.

It is well known that individuals with schizophrenia may become quite depressed, but it seems best to regard that as an atypical depression and not as a major depressive episode so that schizophrenia is another exclusionary criterion, as is uncomplicated bereavement. Individuals with bereavement do not generally go to psychiatrists, and if they do go to their general practitioner, it is generally for symptomatic help in sleeping. It seems wise, nevertheless, to put uncomplicated bereavement as an exclusionary criterion, since on a cross sectional basis, individuals experiencing bereavement actually show this full syndrome.

Within the major depressive episodes, we also subclassify by criteria determining whether there are psychotic features. This subdivision clearly has management implications. There is more likely a need for inpatient care when there are psychotic features--gross impairment in reality testing, delusions or hallucinations, or depressive stupor. There is some evidence that when there are psychotic features (usually delusions) the response to antidepressant agents is not as good as when they are absent.

The syndrome called "melancholia" is another important distinction in the DSM-III. We find this term preferable to the term "endogenous" depression, which has been used in the past and which implied that clinical features of a more severe depression were not brought on in reaction to a stress. There is now considerable evidence that these endogenous or melancholic features can be precipitated by stress, and therefore it seemed best in the DSM-III to use a term from the Greeks, melancholia, which is more neutral with regard to etiology.

In the melancholic or endogenous syndrome, loss of pleasure and lack of responsivity (that is, the patient does not feel any better, even if something good happens to him or her) is a required feature. Three of the symptoms of melancholia overlap with the basic features of a depression, but there are some that are rather different. The distinct quality of depressed mood refers to the

TABLE 2

Major Depressive Episode

Differential diagnosis. Organic affective syndrome, primary degenerative dementia, multi-infarct dementia, psycholological reaction to functional impairment associated with a physical illness, schizophrenia, schizoaffective disorder, dysthymic disorder, cyclothymic disorder, other chronic mental disorders associated with depressive symptoms, separation anxiety disorder, uncomplicated bereavement.

Diagnostic criteria.

A. Dysphoric mood or loss of interest or pleasure in all or almost all usual activities and pastimes. The dysphoric mood is characterized by symptoms such as the following: depressed, sad, blue, hopeless, low, down in the dumps, irritable. The mood disturbance must be prominent and relatively persistent, but not necessarily the most dominant symptom, and does not include momentary shifts from one dysphoric mood to another dysphoric mood, e.g., anxiety to depression to anger, such as are seen in states of acute psychotic turmoil. (For children under six, dysphoric mood may have to be inferred from persistently sad facial expression.)

B. At least four of the following symptoms have each been present nearly every day for a period of at least two weeks (in children under six, at least three of the first four):

(1) poor appetite or significant weight loss (when not dieting) or increased appetite or significant weight gain (in children under six consider failure to make expected weight gains)
(2) insomnia or hypersomnia
(3) psychomotor agitation or retardation (but not merely subjective feelings of restlessness or being slowed down) (in children under six, hypoactivity)
(4) loss of interest or pleasure in usual activities, or decrease in sexual drive not limited to a period when delusional or hallucinating (in children under six, signs of apathy)
(5) loss of energy; fatigue
(6) feelings of worthlessness, self-reproach, or excessive or inappropriate guilt (either may be delusional)
(7) complaints or evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness not associated with marked loosening of associations or incoherence
(8) recurrent thoughts of death, suicidal ideation, wishes to be dead, or suicide attempt

C. Neither of the following dominate the clinical picture when an affective syndrome (i.e., criteria A and B above) is not present, that is, before it developed or after it has remitted:

(1) preoccupation with a mood-incongruent delusion or hallucination
(2) bizarre behavior

D. Not superimposed on either schizophrenia, schizophreniform disorder, or a paranoid disorder.

E. Not due to any organic mental disorder or uncomplicated bereavement.

patient acknowledging in some way that this depressive feeling or mood has a very different quality than prior feelings of sadness or depression.

Diurnal mood variation refers to the depression being worse in intensity in the early morning and gradually getting better. Early morning awakening, as mentioned before, is more characteristic of a severe depression. Marked psychomotor retardation or agitation is quite characteristic, as is significant anorexia, weight loss, and excessive guilt. Finally, of course, the patient can be between episodes or in a state of remission, and it is possible to code that as well.

In regard to the clinical features of depression, there is evidence that major depressions can occur throughout the age spectrum, including in infancy. Although there is controversy as to whether the features of depression in childhood are different from those in adulthood, it seems as if the basic syndrome that I presented here applies throughout the age spectrum. There obviously are some age-specific features. For example, in prepubertal children, separation anxiety (a reluctance to go to school) may be present. In adolescence, there are various forms of antisocial behavior may accompany depression. Among the elderly, symptoms that suggest a dementia can be quite common, such as inattentiveness, memory loss and apathy; in the elderly, the differential diagnosis of dementia from depression is often a very difficult one.

Prevalence and Course of Major Depressions

The onset of depression is variable. If it is precipitated by a psychosocial stressor, it may develop very rapidly, after just a few days. On the other hand, the onset may be quite prolonged, and there may be prodromal symptoms such as anxiety, phobias, and mild depressive syndromes that can go on for several months.

The length of depression has been altered considerably by treatment. It used to be stated that the average depression would last from six months to a year; modern treatment methods have appreciably shortened this. Still, 50 percent of individuals who recover from a major depression will eventually have another episode. Usually the functioning between episodes of depression returns to normal, which is quite different from what we see in some other disorders, such as schizophrenia. We are now becoming aware that a chronic course with mild residual symptoms is much more common than we had thought, and perhaps as many as 25 percent of depressed patients will have a chronic course.

In terms of the etiology or predisposing factors, there is evidence that chronic physical illness, alcohol dependence, and mild chronic dysthymic disorder predispose the individual to major depression. Frequently, an episode of major affective disorder follows a psychosocial stressor. If an individual has recurrent episodes, however, subsequent episodes may occur, apparently without precipitating factors.

In terms of prevalence and sex ratio, approximately 18-23 percent of adult females and about eight to 11 percent of males have had a major depressive episode at some time in their life. About six percent of females and three percent of males have had an episode severe enough to require hospitalization.

Depression is more common among family members than in the general population, suggesting a genetic predisposition, but the mode of transmission is certainly not known, and a familial pattern does not preclude environmental transmission.

The prevalence of dysthymic disorder (or, in older terminology, depressive personality or character) is unclear, although apparently quite common. Persons entering psychiatric treatment quite often have a major depressive episode superimposed on a dysthymic disorder.

THE PHARMACOLOGICAL TREATMENT OF DEPRESSIVE DISORDERS

Philip Berger, M.D.

In combination with other treatments, and sometimes alone, the drug treatments for depression are remarkably effective. However, they are not effective in every patient, they take from ten days to four weeks to become effective, they have several troublesome side effects, and at least one class of antidepressants can cause a fatal overdose. In the 80 percent of patients who eventually respond to one of the pharmacotherapies of depression, they can restore the patient to normal functioning. Thus, unlike the antipsychotic medications, which often mainly reduce schizophrenic symptoms, the antidepressants resolve or cure the depressive syndrome.

The evidence for the assertion that the drug treatments for depression are effective is based on a massive number of carefully controlled clinical investigations. In one recent literature review which summarized only random assignment double-blind studies, the tricyclic antidepressants were found to be more effective than placebo in 61 of 93 treatment groups studied. While numerous studies have compared one tricyclic to another, none of the seven major tricyclics available in the United States has been shown to be consistently superior to any other.

Another aspect of the efficacy of tricyclics concerns their use as a maintenance treatment for preventing a recurrence of depression. Three large collaborative studies, two in the United States and one in England, reported that tricyclics significantly reduce the relapse rate when used as maintenance treatments in patients initially treated with a tricyclic. Lithium carbonate is also an important maintenance treatment for depressed patients. It is most effective in those patients who experience episodes of both depression and mania (bipolar illness). A number of carefully designed studies have shown that patients with bipolar illness have fewer episodes of both mania and depression.

Well-controlled studies of the monoamine oxidase inhibitors (MAOIs) are not as plentiful. However, several studies have shown that phenelzine and tranylcypromine are superior to placebo in the acute and maintenance treatment of depressive illness. There is some suggestion that the MAOIs are more effective in depression characterized by phobias and panic attacks and in atypical depressions which are characterized by somatic and hypochondriacal complaints, labile mood, reactivity to the environment, and a tendency towards hysterical or dependent features.

Several studies have also shown that the neuroleptic antipsychotics can be useful antidepressants, particularly in patients who suffer from depression with psychosis. In this case,

the term psychosis is not synonymous with severe depression; rather, it is used to describe the depressed patient who has delusions and/or hallucinations. Finally, the minor tranquilizers, particularly the benzodiazepines, have been shown to be effective in the treatment of mild to moderate depression, where anxiety is the predominant or at least a dominant symptom.

Based on this brief review of clinical studies, a summary of the current use of antidepressant medications in the treatment of depression is described below.

Tricyclic Antidepressants

The tricyclic antidepressants are the most common treatment for patients with moderate to severe depression in the United States. They are most effective for depressed patients who have an insidious onset of symptoms; who have anorexia as opposed to those who overeat; who have weight loss and difficulty sleeping, particularly middle night and early morning insomnia; who have a diurnal mood variation of feeling worse in the morning and better in the afternoon; and who have either psychomotor agitation or retardation. Such patients have primary or secondary major affective disorder of the endogenous subtype according to the DSM-III. It is interesting that the original report on the efficacy of tricyclic antidepressants by Roland Kuhn in Switzerland in 1957 noted that patients with endogenous depression were most likely to respond.

Tricyclic antidepressants help approximately 70-80 percent of patients with moderate to severe endogenous depression. However, the drugs are less than ideal for several reasons. The delay of onset of antidepressive action increases the risk of suicide in depressed patients. The toxicity of the tricyclics makes them a potential method for a suicide attempt. In addition, while all of the tricyclics seem to have the same mechanism of action, it is a common clinical experience for a patient to fail to respond to one tricyclic and then to have a complete response to a second tricyclic. Finally, while tricyclic antidepressants have no serious long-term side effects, they do have numerous minor and troublesome side effects that can make compliance difficult.

The most troublesome side effects of tricyclics are due to their peripheral and central anticholinergic activity. The tricyclics can cause severe sedation, dry mouth, blurry vision, urinary retention, constipation, and decreased sexual performance. In addition, the tricyclics produce changes in cardiac electroconduction and contractility that can make them, in some cases, inappropriate for use in patients with heart disease. Finally, a mild withdrawal syndrome characterized by nausea and vomiting can occur. This group of side effects often makes it less

likely for patients to continue a regimen of tricyclic maintenance, even though such maintenance treatment is extremely valuable in preventing a relapse of depression.

Neuroleptics/Antipsychotics

The neuroleptics are also important acute treatments for some depressed patients. Depressed patients with delusions and/or hallucinations are less likely to respond to tricyclic antidepressants. In addition, the neuroleptics can be effective in treating depressed patients who are severely anxious, agitated, or hostile. In general, lower doses of neuroleptics are used to treat depressed patients than would be used to treat patients with schizophrenia. It has been demonstrated that the combination of tricyclics and neuroleptics can be administered to patients with safety and that each drug does not seem to interfere with the pharmacological activity of the other. Thus, it is common in psychotic or agitated patients to use the combination of a neuroleptic and a tricyclic antidepressant.

Once a patient has responded to the combination, it is best to discontinue the neuroleptic but continue the tricyclic. Maintenance neuroleptic treatment is rarely indicated in depressed patients because of the danger that these patients will develop tardive dyskinesia.

Like the tricyclics, the neuroleptics have numerous bothersome side effects. Neuroleptics can cause severe sedation, orthostatic hypotension, dry mouth, blurred vision, urinary retention, and constipation. Neuroleptics also frequently cause extrapyramidal side effects. These are usually manifested as (1) a syndrome resembling Parkinson's disease; (2) a syndrome of uncontrollable restlessness, known as akathisia; and (3) acute dystonic syndromes. The parkinsonian symptoms can include muscular rigidity, "pill-rolling" tremor, altered posture, immobility or akinesia, immobile facies, and shuffling gait. Akathisia is manifested by constant pacing and "fidgeting"; by finger, hand, and foot movements; and by a powerful subjective sense of restlessness. It is often mistaken for psychotic agitation. Acute dystonic reactions often involve spasms of neck muscles (torticollis), occasionally include spasms of the spine and extremities (opisthotonos), and can mimic the oculogyric crises associated with Parkinson's disease, in which spasms of the eye muscles predominate. They tend to be more common in children and young adults and generally appear soon after medication is initiated.

Some neuroleptics, particularly thioridazine, have cardiac side effects. Neuroleptics also lower the seizure threshold, occasionally causing seizures in patients with a history of epilepsy. Most neuroleptics increase serum prolactin levels. This

is the probable cause of the galactorrhea (milk production) which is occasionally seem in women. Amenorrhea is also an occasional side effect. A more common concomitant of neuroleptic medication is weight gain, sometimes to a remarkable degree. Hyperpyrexia can also be bothersome and usually occurs during long hot spells in hospitals without air-conditioning. Finally, neuroleptics rarely cause agranulocytosis.

Lithium Carbonate

Lithium carbonate is used as the primary maintenance treatment for patients with bipolar illness. When a bipolar patient is depressed, the combination of tricyclic antidepressants and lithium carbonate is used as the acute treatment until the depression remits. Then the tricyclic is discontinued and lithium carbonate is continued as a maintenance treatment. When a bipolar patient presents with a manic episode, neuroleptics in combination with lithium carbonate are used for acute treatment. Once the manic episode is under control, the neuroleptic is discontinued and lithium carbonate maintenance is continued for patients who have recurrent episodes.

Unlike the tricyclics and neuroleptics, lithium carbonate has a narrow therapeutic range and therefore its plasma levels must be monitored. Lithium carbonate concentrations of between 0.8 mEq/l and 1.2 mEq/l seem best for preventing recurrent episodes of both mania and depression. In the early stages of treatment, plasma concentrations are determined several times per week. However, once a patient has stabilized, levels may need to be drawn only once per month.

Lithium carbonate has several common early reversible side effects. These include gastrointestinal stress, such as nausea, vomiting, and diarrhea; fine hand tremor; muscular weakness; urinary frequency; dry mouth and thirst; and pretibial and hand edema. Often these side effects disappear without reducing the lithium dose; however, they should be closely monitored, since more serious toxicity occasionally occurs.

More chronic effects of lithium include thyroid effects and renal toxicity. The occurrence of goiter in patients on lithium has been estimated to be about four percent. Individuals with pre-existing low thyroid reserve are particularly predisposed to goiter. Lithium therapy may be associated with a diffuse, nontender thyroid enlargement, hypothyroidism, or both. These effects can be reversed by discontinuation of the drug or by the administration of exogeneous thyroid extract. Consequently, borderline hypothyroidism or other forms of thyroid illness do not constitute a contra-indication to lithium therapy.

The renal toxicity of lithium can be more serious. A significant number of patients taking lithium will notice mild polydipsia and polyuria; however, this is not ordinarily a major problem. Occasionally, some patients develop severe polydipsia and polyuria, which resembles diabetes insipidus. In most cases, this syndrome is fully reversible and not accompanied by changes in other kidney functions or by renal damage. However, there is recent evidence that, in some cases, the defect in the urine-concentrating ability of patients on lithium may be permanent. While this defect should not be fatal, it can be extremely troublesome and may be a reason for discontinuing lithium therapy. Further investigation of the nature, prevalence, and severity of this possible long-term side effect of lithium administration is urgently needed, since lithium maintenance treatment is of such benefit to patients with bipolar illness.

Anxiolytics

Antianxiety agents, particularly the benzodiazepines, can also be useful in the drug treatment of certain depression syndromes. The benzodiazepines are most useful in patients with mild depressive syndromes characterized by anxiety and agitation. Patients who are depressed because of life events or stressful situations often respond to a brief course of treatment with an anxiolytic. Paradoxically, severely depressed patients often experience an exacerbation of their depression if treated with high doses of anxiolytics. The combination of an anxiolytic and a tricyclic antidepressant can be temporarily helpful for the anxious or agitated patient with severe depression, but the tricyclic antidepressant is probably the more important pharmacological intervention in such patients.

The anxiolytics are relatively safe medications for several reasons. The benzodiazepines alone are rarely, if ever, the cause of fatal overdose. This can be particularly important for patients who briefly consider suicide. In addition, the benzodiazepines do not cause the dry mouth, constipation, and urinary retention associated with both the tricyclics and the neuroleptics.

The decision to treat a depressed patient with one of the antidepressants is a clinical judgment which should be based on a careful medical and psychiatric evaluation of the patient. It is extremely important to determine if there is a medical illness or pharmacological condition which is contributing to the depressive symptoms. Any severe physical illness can lead to depressive symptoms because of the disability, pain, and stress associated with disease. However, there are numerous medical illnesses which have been specifically associated with depressive syndromes.

Viral illnesses, such as mononucleosis, hepatitis, and viral pneumonia, often cause depressive syndromes either during the active or the recovery phase of the illness. Over- or underactivity of almost every endocrine organ has been associated with depression. Pituitary-adrenal hyperactivity, the Cushing's syndrome, is also frequently associated with depression, while pituitary-adrenal hypofunction, or Addison's syndrome, is also frequently associated with depression. Both hyper- and hypothyroidism can cause depression, as can hypoparathyroidism. Premenstrual, menopausal, and post-partum depression syndromes are probably related to alterations in female endocrine function. The hyper- and hypoglycemic episodes that accompany diabetes can also mimic depressive symptoms. Finally, while any malignancy can cause a reactive depression, carcinoma of the tail of the pancreas frequently causes depression before the diagnosis of cancer is made. These are but a few examples of somatic diseases that can underlie a depressive syndrome. They illustrate the importance of a careful medical evaluation for every patient with depression.

Abuse of numerous pharmacological agents can also contribute to or exacerbate depression. Alcohol, opiates, amphetamines, and anxiolytics are drugs which are frequently used in futile attempts by depressed patients to treat themselves. In addition, alcoholism, opiate addiction, stimulant abuse, and abuse of anxiolytics can cause depressive symptoms.

A second step in the evaluation of a depressed patient is to determine how severe the depressive syndrome is and what events preceded it. Mild depressive episodes or depressive symptoms which follow a tragic life event probably do not require treatment with pharmacological agents. However, severe depressive symptoms, particularly suicidal ideation even as part of a grief reaction, will often respond dramatically to pharmacological treatment.

Determining the pattern of depressive symptomatology is another important part of the evaluation which precedes drug treatment. If there are symptoms of psychosis, the tricyclics and neuroleptics will probably be necessary for treatment. If the patient is anxious, agitated, or hostile, the combination of a tricyclic antidepressant and an anxiolytic or neuroleptic if the depression is mild or severe, respectively, can be beneficial. The more sedative tricyclic antidepressants, such as amitriptyline and doxepine, can be used in depressed patients with psychomotor agitation, while less sedative tricyclic antidepressants, such as desipramine or protriptyline, may be more useful for the patient with psychomotor retardation.

A careful evaluation of the patient's past psychiatric history is needed before pharmacological treatment is initiated. Patients who have recurrent episodes of both major depressive disorders and

manic disorders respond best to maintenance treatment with lithium carbonate. The acute treatment of these patients may also include either tricyclic antidepressants or neuroleptics. Patients who have recurrent episodes of major depressive disorders will probably require maintenance therapy with tricyclics.

Patients with atypical depression syndromes of several types may respond best to monoamine oxidase inhibitors, such as phenelzine or tranylcypromine. Atypical depression syndromes include phobic anxiety and panic attacks, somatic and hypochondriacal syndromes, and depression syndromes that are characterized by extreme dependency, labile mood, and hysterical features.

In summary, there are five major classes of psychotherapeutic medications that can be useful in treating various depressive syndromes. When used correctly, these drugs can facilitate a complete recovery from depression in the majority of depressed patients. Unfortunately, the drugs are far from ideal. They are slow-acting, have numerous troublesome side effects, can cause fatal overdoses, and do not help every patient. There are a number of new chemical classes of antidepressants which are currently in clinical trials or already in clinical use in Europe. Some of these medications may be as effective or even more effective than the drugs which are currently in use in the United States. In addition, these new agents may be less toxic and have fewer side effects. Mianserin, chlorimipramine, trazodone, maprotyline, and zometapine are but a few of these new and potentially important pharmacotherapies for depression.

The ideal antidepressant medication regimen would differ from current practice in several ways. A more immediate onset of drug action would decrease the risk of suicide and diminish the serious life disruptions that long depression syndromes can cause. Less toxic medications would decrease the utilization of antidepressants for suicide attempts. Predictive laboratory tests would lead to more accurate matching of antidepressant medications and depressed patients. Laboratory tests would also make it easier to safely achieve adequate levels of antidepressant activity. Finally, and perhaps most important, an understanding of the possible biochemical origins of some depressive syndromes would lead to the rational development of antidepressants specifically designed to correct these biochemical defects.

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PSYCHOSOCIAL AND PHARMACOLOGICAL TREATMENTS FOR DEPRESSION: EVIDENCE FOR EFFICACY AND RESEARCH DIRECTIONS

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In clinical practice, the most frequent treatment for the ambulatory depressive is a tricyclic antidepressant and psychotherapy. While clinicians and patients have consistently testified about the value of these treatments, the legitimacy of either treatment has come under heavy attack from many corners.

We have been described as an "overmedicated" society, and drugs for depression have been challenged as a form of social control that encourages women and other groups to adjust to depressing conditions. The most recent attacks, however, have been led by the United States Senate Finance Committee which focused on studies questioning the efficacy of psychotherapies.1,2/

As these challenges have mounted, research evidence has also been accumulating. There is a considerable body of evidence from well designed clinical trials demonstrating the efficacy of the tricyclic antidepressants for the reduction of the acute symptoms and as maintenance treatment in the prevention of relapse.3/ Over the last five years, there has also been an acceleration in the development and testing of psychotherapies specifically designed for ambulatory depressed patients. Description of the psychotherapies has been improved in procedural manuals that record therapeutic techniques and their sequence during the course of the treatment. Scientific standards have been improved for conducting clinical trials involving psychotherapy, with and without pharmacotherapy. As a result of these efforts, evidence for the efficacy and safety of psychotherapy and pharmacotherapy, separately and in combination, for the treatment of the ambulatory depressive, has become available.

The majority of the clinical trials of psychotherapy in depression have been carried out among ambulatory depressed patients who are not psychotic and are not bipolar (i.e., they do not have manic episodes).

Recent epidemiologic studies show that these types of depression are the most common psychiatric disorders in the community, in outpatient general medical practice, in mental health clinics, and in the psychiatrist's office. The current point prevalence rate is high, estimated at about three percent of the adult population, and the lifetime prevalence rate at nearly 20 percent of adults.4/

Moreover, in clinical practice the majority of nonpsychotic, nonbipolar depressives, if treated at all, receive outpatient psychotherapy. Again, this is in contrast to bipolar and psychotic depression where hospitalization, medication, and/or electroconvulsive therapy are the most widely used treatments, with psychotherapy playing a secondary or adjunctive role.

Against this background, I will describe the psychotherapies which have been assigned and tested in clinical trials for the treatment of ambulatory depressed patients; present the research evidence for psychotherapy alone, in comparison with and in combination with drugs; and discuss future areas of research.

Depression as a Clinical Syndrome

Depression as a clinical syndrome is what we are concerned with in this discussion. It includes a number of specific symptoms of certain severity and persistence which produce impairment and/or disability and which occur in the absence of other symptoms or disorders that might better explain the condition.

Table 1 shows the Research Diagnostic Criteria (RDC)* for the syndrome of major depression.5/ Included are dysphoric mood and at least five other symptoms, persisting at least two weeks, producing impairment of functioning or necessity of treatment, and occurring in the absence of schizophrenia or other disorders that might better explain the symptoms.

Description of the Psychotherapies

Whereas many types of psychotherapies, particularly the psychoanalytically-oriented approaches, are widely and appropriately used in the treatment of depression. Unfortunately, as of this writing, only the five described below have undergone scientific testing in clinical trials among reasonably large, homogeneous samples of depressed patients.

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*These criteria have been used by North American researchers for several years. A somewhat less stringent set of criteria has been accepted for broad clinical use in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III).6/

TABLE 1

Research Diagnostic Criteria (RDC)
for a Depressive Syndrome

A through F are required for the episode of illness being considered:

A. Dysphoric mood which is prominent and relatively persistent.

B. At least five of the following symptoms are required for a definite period of time:

1. Poor appetite or weight loss, or increased appetite or weight gain.
2. Sleep difficulty, or sleeping too much.
3. Loss of energy, fatigability, or tiredness.
4. Psychomotor agitation or retardation.
5. Loss of interest or pleasure in usual activities, or decrease in sexual drive.
6. Feelings of self-reproach, or excessive or inappropriate guilt.
7. Complaints or evidence of diminished ability to think or concentrate, such as slow thinking or mixed-up thoughts.
8. Recurrent thoughts of death or suicide, including thoughts of wishing to be dead.

C. Dysphoric features of illness lasting at least two weeks.

D. Sought help from someone during the dysphoric period, or had impaired functioning.

E. None of the following which suggests schizophrenia is present:

1. Delusions of being controlled, or of thought broadcasting, insertion, or withdrawal.
2. Non-affective hallucinations of any type throughout the day for several days, or intermittently throughout a one-week period.
3. Auditory hallucinations in which either a voice keeps up a running commentary on the subject's behaviors or thoughts as they occur, or two or more voices converse with each other.
4. At some time during the period of illness, subject had more than one month when no prominent depressive symptoms were exhibited but had delusions or hallucinations.
5. Preoccupation with a delusion or hallucination to the relative exclusion of other symptoms or concerns.
6. Definite instances of marked formal thought disorder, accompanied by either blunted or inappropriate affect, delusions or hallucinations of any type, or grossly disorganized behavior.

F. Does not meet the criteria for Schizophrenia, Residual Subtype.

Cognitive Therapy

Cognitive therapy is based on the assumption that the affective response in depression is determined by the way the individual perceives experience.7/ As a result of an emergence of maladaptive cognitive themes, the depressed patient tends to regard self and future negatively. Correction of negative concepts is expected to

alleviate the depressive symptoms. For example, an extremely low self-concept can be treated by presenting a hierarchy of cognitive tasks and demonstrating, through these tasks, the invalidity of the patient's self-concept.

Interpersonal Psychotherapy

Interpersonal psychotherapy assumes that the development of depression occurs in a social and interpersonal context and is determined by the interpersonal relations between the depressed patient and important persons in the patient's life.8/

The goals are to improve the quality of the patient's social and interpersonal functioning by enhancing the ability to cope with internally-and externally-induced stresses, by restoring morale, and by helping the patient deal with the personal and social consequences of the disorder.

Behavioral Approaches

Behavior therapy explains the occurrence of depression in stimulus and response terms. A low rate of positive reinforcement elicits certain aspects of the depressive syndrome. It is predicted by negative reinforcing events in the environment and the lack of available positive reinforcements, as well as by the individual's behavior.9/ Several techniques based on behavioral concepts have been developed for depressed patients.

Marital Therapy

Marital therapy attempts to alter the interaction between husband and wife. It is based on the assumption that the marital relation affects thoughts, feelings, and behavior, and that symptom removal can be achieved by changing the transactional marital system.10/

Group Therapy

In group therapy, a psychotherapist and a group of patients attempt to effect changes in the emotional states, attitudes, and behavior of the patient. Currently, explicit definitions of techniques and descriptions of what occurs within the group format are lacking, although there are efforts to develop cognitive therapy in a group context.

Status of Development of the Psychotherapies

Table 2 shows the status of the development and testing of the five therapies. Cognitive therapy has been tested in six trials, interpersonal psychotherapy in three, behavioral approaches in eight, marital and group therapy in one trial each. Of the five therapies, only cognitive and interpersonal and some of the behavioral techniques have been specifically designed for depressed patients. Only cognitive and interpersonal therapies have available procedural manuals.

TABLE 2

Development and Testing of Psychotherapies in Depression

	Cognitive	Interpersonal	Behavioral Approaches	Marital	Group
Number of Trials with Depressed Patients*	6	3	8	1	1
Designed for Depressed Patients	Yes	Yes	(Some)	No	No
Procedural Manual	Yes	Yes	No	No	No

*These trials are not mutually exclusive.

Evidence for Efficacy

Table 3 summarizes the evidence for the efficacy of the five psychotherapies alone, in comparison with, and in combination with drugs for the ambulatory depressed patient. A detailed review of the studies can be found in Weissman.11/

Psychotherapy Alone

There are nine studies testing the efficacy of psychotherapy in comparison with a low-contact or a no-active-ingredient control group.11/ All five treatment approaches are represented. All of the studies support the efficacy of psychotherapy alone when compared with the control group. In none of the studies was psychotherapy alone equal to or worse than a control or no-treatment group; in all of the studies it was shown to be superior.

TABLE 3

Evidence for Efficacy of Psychotherapy and Drugs in the Treatment of Depression

	Number of Studies
Psychotherapy Alone	
Psychotherapy > Control	9
Psychotherapy = Control	0
Psychotherapy < Control	0
Psychotherapy in Comparison to Drugs	
Psychotherapy > Drugs	1
Psychotherapy = Drugs	1
Psychotherapy ? Drugs	3
Psychotherapy > Drugs in Social Functioning	
Psychotherapy < Drugs in Symptom Prevention	
Psychotherapy in Combination with Drugs	
Psychotherapy + Drugs > Psychotherapy > Drugs > Control	4

Psychotherapy in Comparison with Drugs

There are five completed studies in which psychotherapy was compared with a tricyclic antidepressant. All five of the psychotherapies are represented.11/ One study found psychotherapy (cognitive therapy) superior to drugs (imipramine) for the treatment of acutely depressed patients both in terms of attrition and symptom reduction. One study found drugs and psychotherapy about equal for acute symptom reduction. Three studies found drugs superior to psychotherapy (interpersonal, group, or marital) in the prevention of relapse or symptom reduction, but psychotherapy slightly superior to drugs in the enhancement of social functioning. The psychotherapy effect in one study occurred only in those patients who remained in treatment for eight months without relapse.

The results of the comparisons of psychotherapy with drugs are equivocal for acute treatment. The treatments appear to be equal

overall, but to have different targets of action. The one study in which cognitive therapy was found to be superior to drugs requires replication before the results can be accepted.

Psychotherapy in Combination with Drugs

There have been four studies completed which tested the efficacy of combined psychotherapy (interpersonal, marital, or group) and a tricyclic antidepressant. All four studies show the superiority of combined treatment over a control group or over either treatment alone.11/ In none of the studies were there negative interactions in combining drugs with psychotherapy. The effects of the two treatments together were additive. Overall, the combination of psychotherapy and a tricyclic was better than either treatment alone or than no regular treatment. The combination provided a broader spectrum of action, as each treatment seemed to affect different domains.12/ Psychotherapy seems to have its effect on social and interpersonal problems, and had a slower onset of action.13/ Drugs have their effect on vegetative symptoms of depression, such as sleep and appetite, and had a more rapid onset of action.

Research Directions and Limitations in the Data

While there has been rapid progress in psychotherapy clinical trials, there are many limitations in the data which render the studies inconclusive. The limitations are of three types: methodologic problems in the conduct of the studies, absence of comparative studies of particular treatments, or absence of studies in particular types of patients.

Methodologic Issues

Diagnosis. Operationalized diagnostic criteria and standardized clinical assessments of signs and symptoms are quite recent developments in psychiatric research and were not available or widely used when many of these clinical trials were initiated. While most of the studies included moderately symptomatic depressed outpatients, undoubtedly the samples were still heterogeneous.

The key issues in studies testing antidepressant drugs and psychotherapy are which subsample of depressed patients responds to each modality, and whether the patient's symptoms are of sufficient severity and type to respond to each modality. Preliminary findings from one study using precise research diagnostic criteria suggest a differential treatment response to drugs and psychotherapy for different subtypes of depressed patients.14/

Studies should include standardized assessments of signs and symptoms and operationalized diagnostic criteria to ensure the homogeneity of the sample under study and to ensure comparability between studies.

Specificity for Depressions. While some of the treatments (cognitive, behavioral, interpersonal psychotherapy) have been specifically designed for depressed patients, it is unclear whether similar results might be obtained for other patient groups as well. Testing of these treatments in homogeneous samples of patients with other psychiatric disorders would help to answer questions about the specificity of these and other treatments for depression.

Control Groups for Psychotherapy Studies. No definite assessment can be made about the efficacy of a treatment unless there is knowledge of outcomes of similar patients receiving an alternative treatment or no treatment. The latter would determine whether the natural history of the disorder can be altered by the intervention.

The controls for psychotherapy include attention-by-assessment, waiting list, low contact, or nonscheduled treatment. The attention-by-assessment controls for the nonspecific effects of attention. The waiting list, low-contact, and nonscheduled treatment control groups are efforts to maintain contact with the patient by offering no treatment (waiting list), by offering treatment at a reduced rate (low-contact), or by offering treatment at the patient's request although not at a regularly scheduled time (nonscheduled).

All of these efforts provide an ethically feasible method by which to determine how patients who come to treatment would fare without psychotherapy in comparison with the specific effects of receiving psychotherapy. However, these control groups do not entirely resolve the issue of determining the natural history of the disorder without treatment, since persons who come for treatment may be affected by the mere fact that they have volunteered for a study, and, to that degree, there is a shift from the pure natural history. It is conceivable that patients placed on a waiting list may actually deteriorate when compared with untreated persons in the community, because they were disappointed by not getting the treatment they wanted; or they might improve only slightly over time, but not as much as if they had not come to the study at all. The best way to test for the effect of treatment on the natural history of the disorder without the intervention would be to examine the longitudinal course of subjects identified in the community who have the disorder but who have not sought treatment. Such a design requires epidemiologic population data and is often not feasible.

In addition to the inclusion of a no-treatment control group, ideally a specific psychotherapy should be tested against the nonspecific effects of receiving regular attention, but not specific psychotherapy, as well as against the effects of another treatment. Comparisons will provide information on the specificity of the treatment effects for depression.

If a "no treatment" control group is included, provision must be made for maintaining regular contact with the patient so that treatment can be initiated if it is clinically indicated (at which point the patient would be considered a treatment failure of the group); and in order to determine if the patient in the untreated group is in fact receiving treatment elsewhere (and also would be considered a failure from the group). Similarly, if psychotherapy is being compared with drugs, attention should be given to the frequency and type of psychotherapeutic contact in the drug group. Future clinical trials of psychotherapy should include at least one control group, and preferably more than one.

Clinical vs. Statistical Significance. While all results described comparing the various treatments were statistically significant ($p < 0.05$), questions may be raised as to whether they were of substantial magnitude to be of clinical significance. It is widely recognized that treatment differences of quite small absolute magnitude can be demonstrated to be of statistical significance if sufficiently large samples are used. The same significance levels can result from a large effect found in a small sample and a small effect found in a quite large sample. The decision as to when differences in treatment effects are large enough to be of clinical importance involves a complex judgment process. The magnitude of the difference can be examined by taking into account both the size of the difference between the treatment means and the variability about each of the means. This still does not preclude the need for judgment of clinical significance.

In regard to the studies reviewed, for the most part the samples were not large so that the significance values do not reflect small effects. The largest sample was 196 patients in four treatment conditions, or about 49 patients per treatment cell. Ideally, a priori criteria of a clinically significant result, such as a return to work, prevention of relapse, or reduction of symptoms below a certain score, should be stipulated as part of the design.

Consistency and Monitoring of Treatment. Procedural manuals are available for cognitive therapy, some of the behavioral techniques, and for interpersonal psychotherapy. Future psychotherapy trials should require a procedural manual to assist in the training of therapists. Monitoring techniques, such as audiotapes or videotapes of selected interviews, should be introduced to ensure that the therapy under investigation is the one

actually being administered, to ensure that there is comparability between therapists within the same study, and finally, to allow for replication of results.

Absence of Comparative Studies on Particular Treatments

Scantiness of the Data. The data are sparse on any one type of therapy as well as on the actual number of patients studied for many of the therapies. Further testing of all five therapies among depressed patients is indicated. Future studies in the behavior and cognitive therapies should include larger samples as well as drug comparison and combination groups. A replication of the study comparing cognitive therapy with drugs should be undertaken that would include a combined cognitive therapy/drug treatment group in order to test out the observation about the additive effect for the combination.

Untested Psychotherapies. There are many psychotherapies other than the five described, particularly the psychoanalytically-oriented approaches, that are in wide clinical use in depression and may be appropriate and efficacious, but have not undergone testing.

Comparisons Among the Psychotherapies. With the exception of cognitive and behavioral treatment, there are few comparisons of the psychotherapies with one another. A comparison of the cognitive, behavioral, and interpersonal psychotherapy treatments, for which some efficacy has been established and procedural manuals have been developed, would be timely. In the few existing studies of direct comparisons, there has been a tendency for the treatment that is the usual modality of the research group to be shown as more efficacious by that group. These direct comparison studies should be conducted by research teams relatively independent of the development of a particular psychotherapy.

Comparison of Psychotherapy with Drugs. The finding that has generated the most controversy has to do with the comparison of psychotherapy with drugs and the positive finding by Rush et al, for cognitive therapy over imipramine.11/ As noted by Rush et al, unwarranted conclusions about the efficacy of cognitive therapy over antidepressants should not be drawn from one study. This study requires replication, and future studies should pay attention to drug compliance, monitoring of serum levels, and differential response to the treatment by subtype of depression.

Long-term Studies. All of the clinical trials completed were short-term, usually less than four months, the longest having been eight months. A longer trial is especially indicated in studies comparing the efficacy of psychotherapy with drugs, since there have

been suggestions that psychotherapy may have a later onset of action and a different outcome than drugs in the treatment of depression. Moreover, in clinical practice, much of psychotherapy is longer than four months.

Absence of Studies in Particular Populations

Children and the Elderly. Progress has been made recently in the diagnosis and pharmacologic treatment of depression in children and the elderly. However, clinical trials of psychotherapy with these groups are nearly nonexistent and these patients are systematically excluded from clinical trials. The problem of dose and side effects of pharmacologic treatment for the very young and for the elderly and the fact that psychosocial problems of loss, transitions, and identity are common in these groups renders psychotherapy a reasonable approach to be tested.

The Severely Ill and the Bipolar Depressed Patient. The bipolar, severely depressed, psychotic, and/or hospitalized patient generally has not been included in the clinical trial of drugs and psychotherapy. There are preliminary data from a longitudinal study of 65 married bipolar patients who received 12 months of lithium carbonate therapy alone or in combination with couples therapy.11/ Although the study did not include random assignment to treatment, the results suggest the efficacy of combined treatment in the patients' post-hospital adjustment.

It is believed that the more severely ill patients will derive the least benefit from psychotherapy, but this requires testing. The efficacy of drugs as acute treatment for the severely ill depressed patient has been well established. Moreover, the probability of relapse without maintenance drug therapy increases with the severity of the disorder. Therefore, studies which include these severely ill depressed groups should test the efficacy of psychotherapy added to drugs rather than psychotherapy alone.

Conclusions

Evidence for the efficacy of psychosocial treatments alone, in comparison with, and in combination with, pharmacotherapy for the ambulatory non-bipolar, non-psychotic depressive is rapidly developing. In all of the studies reviewed, psychotherapy was more efficacious than a no-active control treatment. The few studies comparing drugs to psychotherapy were equivocal and the studies comparing the combination of drugs and psychotherapy found the combination was more efficacious than either treatment alone or than the no- or low-control treatment.

The limitation and the scantiness of the data available, the developments in specificity of psychiatric diagnosis, the specification of the psychotherapies, and the improved scientific standards in the conduct of clinical trials suggest many promising future research strategies.

A multi-center collaborative trial, which will test the efficacy of several therapeutic conditions with and without drugs in large samples of ambulatory depressives, will begin in 1981. This study was designed by the staff of the Clinical Research Branch, National Institute of Mental Health, in consultation with many experts, and was approved by peer review. In addition, a number of single-center clinical trials of combined treatments in depressives are underway. Over the next five years, more data will become available.

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SOCIAL FACTORS INFLUENCING COMBINED PSYCHOSOCIAL AND PHARMACOLOGICAL THERAPY IN DEPRESSION

Sol Levine, Ph.D.

This paper will not try to assess the value of combined pharmacological and psychosocial therapy for patients suffering from depression, but will aim to illuminate some of the obstacles to the successful provision of combined therapy to those patients for whom it is indicated. These obstacles, as we will see, reside in the social and cultural definitions and responses to illness in the American population, in the structure and financing of the health delivery system, and in the rewards and incentives that shape the behavior of professionals.

If we were to consider the provision of either pharmacological or psychosocial therapy alone, some of these obstacles would be encountered. They tend to obtain even more in the provision of combined therapy to depressed patients.

Studies of people's reactions to symptoms and to illness indicate that, in many instances, people do not turn to the medical system for relief of their health problems and ailments. They may ignore them, attend to them by themselves, or seek help and guidance from friends and family. Indeed, there is much evidence that people make use of a lay referral system: they turn to pharmacists, to bartenders, barbers, friends, and neighbors from whom they get information and guidance as to what symptoms mean, how important they may be, and what should be done about them. People learn about particular therapists, including physicians, who may provide the precise kind of treatment or therapy they may need or prefer.1/

Despite the considerable progress we have made in recent years in educating the public about mental illness, there still are considerable gaps in people's knowledge, and there still is a persistent aura or stigma regarding mental illness. People are thus reluctant to characterize themselves or their friends or relatives as mentally ill.2/ They are more disposed to recognize certain clear somatic complaints as requiring medical intervention, and they are also ready to designate certain kinds of extreme psychological problems as requiring intervention. However, unless individuals demonstrate conspicuous or bizarre behavior or are dramatically unable to perform their basic social roles, their friends and relatives, in many cases, may not perceive or define them as ill, and accordingly may not encourage them to seek assistance.

People may also tend to excuse or overlook inadequate levels of role performance in close friends or relatives when their symptoms or behavior may appear to be attributable to some serious recent event, such as loss of spouse, acute physical illness, unemployment, or retirement. In these cases, low levels of performance may be viewed as understandable or excusable. There are also some, such as recent college graduates or returning war veterans, who may display depressed symptoms for a comparatively long period of time, but whose behavior may not be deemed to merit professional attention. It is also likely for the behavior of depressed patients to receive comparatively little attention in certain kinds of deviant subgroups, such as hobos, some youth gangs, and drug cultures.

Even when depressed individuals become motivated to seek professional help, they often find the road to therapy frustrating and circuitous. Those without a regular primary physician, especially many poor people, frequently turn to the emergency room or the hospital outpatient department where care is often characterized by long waiting periods and brief, abrupt, and often confusing encounters with personnel who, because of their large patient loads, are not disposed or able to provide even minimal components of psychotherapy.

In seeking help, people with mental problems may also try to enter other parts of the health and welfare system, such as family service organizations, community mental health centers, and a host of private and public agencies. The patient's success in getting treatment sometimes may be determined by various kinds of organizational gatekeepers, such as receptionists or telephone operators, who usually are not trained or qualified to make clinical assessments. Depressed individuals seeking help may encounter difficulties in arranging appointments, though their acceptance for treatment may be facilitated if they are referred by a psychiatrist or other physician instead of a nonmedical person like a teacher or a minister.3/ They may also have difficulty in gaining access to some treatment organizations if they are self-referred. Mental patients, in their search for treatment, may sometimes be referred or shunted from one agency to another, going through the well-known "revolving door." Obviously, then, many depressed patients are discouraged at different stages and may give up in their search for help.

In many communities, community mental health centers have made considerable strides in providing readily available care to large segments of mental patients. However, because of their frequently large patient loads, the choice of therapy may not be the preferred one. Depressed patients may often have to enter group therapy and may not feel they are receiving sufficient individual attention and assurance. It is well known that one's income or social position will influence the type of therapy one may eventually receive.

Semi-skilled and unskilled workers or those with relatively little education are customarily known to receive drugs rather than psychotherapy. Those with higher occupational status have a better chance of obtaining some forms of psychotherapy.4/

An overwhelming number of depressed people make their way to the primary care physician--the general practitioner or the internist. Many emotional and psychological problems are masked and presented to the physician as diffuse somatic complaints or ailments. Because their services are sought so frequently, primary care physicians would appear to be in an excellent strategic position to diagnose and to treat many patients who come to them with diffuse complaints, but who in actuality are suffering from depression.

Unfortunately, for a number of reasons primary care physicians customarily fail to realize their potential and fail to fulfill their responsibilities to the depressed patient. Their knowledge and training in psychiatry are often insufficient to permit them to discriminate between somatic and psychological problems and to properly diagnose those who are suffering from depression. They are more likely to dispense some standard drugs which they have used customarily, the properties of which they have learned from their colleagues, advertisements in medical journals, and information from representatives of pharmaceutical firms who aggressively encourage the utilization of these drugs.

Many physicians who have been in practice for several years have not kept up with the literature, nor is there much reason to believe that their intermittent exposures to some form of continuing medical education is very helpful. Thus, a good number of primary care physicians who encounter depressed patients are not sufficiently informed to diagnose them, to treat them, or to refer them to other appropriate specialists.

There are other factors that may be even more formidable. It takes time to talk with patients, even to ascertain their symptoms or to make a diagnosis, let alone to provide them with assurance or to give them more intensive psychotherapy. The earnest physician who seeks to inquire adequately about the emotional problems of his or her patients and to provide anything from verbal assurance to combined therapy, suffers financial loss because third-party payments are made generally for specific medical services rendered, not for time spent with the patient. The primary care physician who devotes time listening to patients, diagnosing them, educating them, or providing them with psychotherapy in addition to drugs is, in fact, losing income. The financial incentives serve to encourage frequent short-term visits. The physician, then, customarily dispenses some medication but avoids the time-consuming aspects of extended verbal interaction.

There are also constraints against the physician even making an appropriate referral to a psychiatrist. There is not sufficient integration of medical and mental health services in the community. Those physicians who send their patients to a psychiatrist may, in fact, find that their patients come to them less frequently or may stop returning to them altogether. Moreover, patients themselves may resist being referred to a psychiatrist in another part of town with all the negative connotations that a psychiatric referral may convey.

There are reasons to believe that the health maintenance organization may have some advantages over solo practice in achieving integrated medical and mental health services. In the HMO setting, it would appear that the psychiatrist would be readily available. The patient, too, would find it easier and probably less unpalatable to obtain psychiatric care in this setting. Moreover, in the HMO setting, the primary care physician who would enlist the psychiatrist in the care of the patient would not suffer financial loss, as would the independent practitioner in the community who is paid on a fee-for-service basis. It would be useful to study intensively the degree to which integrated medical and mental health services is achieved in different organizational arrangements.

Unlike the general practitioner or internist, the psychiatrist in an independent office-based setting may offer combined therapy without suffering loss of income. However, here, too, there are some impediments to the appropriate dispensation of combined therapy. Many psychiatrists have a strong predilection for the pharmacological treatment of mental illness, including depression, and may be reluctant or unable to provide some form of psychotherapy as well.

Some psychiatrists may refer patients for psychotherapy to other psychiatrists but may not wish to make use of other professionals, such as psychiatric nurses or psychiatric social workers, who may also provide effective psychotherapy. Some psychiatrists may have some reservations about psychotherapy being provided by personnel who are not physicians, although they may be inclined to use the services of these other professionals in organizational settings like HMOs where the nonmedical personnel are accountable to a physician or psychiatrist.

As independent professionals, nonmedical professionals generally do not receive third-party payments. In view of the shortage of mental health personnel, the question that naturally emerges is whether nonmedical personnel should be permitted to receive third-party payments for psychotherapeutic services. Of course, the impact on utilization rates and resultant costs should be considered, as well as ways of discouraging unnecessary utilization.

Those therapists on the other side of the spectrum--social workers, psychiatric nurses, clinical psychologists, and psychodynamically-oriented psychiatrists--may also pose problems to the provision of combined therapy for depressed patients. They may be professionally committed to some form of psychosocial therapy but may be less disposed to utilize pharmacological forms of treatment. They may tend to ignore or minimize the patient's need for medication because they know less about, or have less faith in, pharmacological treatments, or, in the case of nonmedical personnel, are not permitted to dispense medications. The possibility of losing a patient to a pharmacologically-oriented psychiatrist must also be acknowledged. Again, these barriers may be surmounted, in part, by health maintenance organizations.

Combined therapy may be viewed as a type of health care innovation. Health scientists and professionals have a rationalistic bias and tend to assume that if the efficacy of an innovation or new mode of treatment can be demonstrated it will be readily adopted by other health professionals. Accordingly, it is believed that therapists will embrace combined therapy if it can be demonstrated, to be more effective than either pharmacological or psychosocial forms of therapy in dealing with depression. However, other studies have shown that there are many factors that impede the acceptance of valid technological innovations.5/

We should remember that in calling upon medical personnel to consider combined therapy, we are really asking a number of psychiatrists and a number of primary care physicians to modify their skills and to change their habits and orientations. However, people like to practice their existing skills, and it is not easy for them to acquire new skills or to change their perspectives. They may resist learning new skills and may be slow in using them even after they achieve proficiency. In promoting the acceptance of combined therapy for depressives, we may not only have to demonstrate its effectiveness, but may also have to consider ways of restructuring the rewards and incentives which influence the behavior of health professionals.

We must remember, too, that the use of psychosocial approaches in combined therapy tends to be limited mainly to those types of services that health professionals themselves can provide. Professionals who provide psychosocial therapy are often not sufficiently attuned to such other relevant approaches as restructuring social relationships and support systems and making proper use of mutual aid groups in the community. The relationship between mutual aid groups and professional care has received little attention in the literature.6/ It would be useful to systematically evaluate the contribution which support systems and mutual aid groups can make to the psychological well-being of depressed patients.

In directing our attention to the broader social factors that may be relevant for psychosocial therapy--factors that are outside of the usual setting of therapist and patient--we also have to ask whether physicians and therapists in general have sufficient knowledge of the social environments of their patients. Do they know enough about their patients' work settings, neighborhoods, communities, or the larger social environments which impinge upon their lives? Do they know enough about the everyday problems with which patients of varying backgrounds must grapple? Despite the strides we have made in sensitizing students to the social and psychological needs of their patients, we have a long way to go. We must not only educate and sensitize therapists; we must make it rewarding for them in their practice settings to know more about the lives and environments of their patients.

We have drawn attention to the beliefs and practices of the public and the helping professions, the segmentation of the health delivery system and the existence of incentives that serve to discourage the adoption of this new technology. The implementation of our research findings on the efficacy of combined therapy depends not only on more effective education of the public and our therapeutic personnel but also on changes in our methods of financing and organizing treatment services, and in the incentive systems we create which ultimately govern the behavior of health professionals.

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A CLINICAL REVIEW OF DIABETES

George F. Cahill, M.D.

Diabetes is the final pathway of a number of processes that end up with either an absolute or a relative deficiency of insulin. Insulin is really the body's fuel "stat." When there is plenty of fuel around, insulin levels increase, telling peripheral tissues to take up and store the fuel. Conversely, when there is not enough fuel around, as in the fasting state, it is the low insulin level that signals the various depots to put fuel back into the circulation because the body needs it. Many fuels are affected, but fortunately the one that appears to be the most affected is blood glucose, and I say "fortunately" because that is easiest to measure and the first to be described as being abnormal in diabetes. It is also the one that is most significant in its abnormality; in excess it causes many of the complications of diabetes.

This overview incorporates three important topics concerning diabetes. The first is a description of the type of diabetes that afflicts children: "juvenile-onset," "insulin-dependent" or "Type 1" diabetes. These are all synonyms for this kind of pathophysiological route for the development of beta cell or insulin deficiency.

This type of diabetes is heterogeneous in origin. In some children, it originates because of a virus which causes a rapid and total destruction of the pancreas. A case of this type was reported one and one-half years ago in the New England Journal of Medicine.* Conversely, in some families an inherited autoimmune process impairs the functioning of the child's endocrine organs--thyroid, adrenal, parathyroid--and diabetes may result. These cases, however, are relatively infrequent. Between these two extremes, the acute viral destruction and the familial autoimmune, lies the common type of juvenile-onset diabetes which is probably a separate entity, partly viral and partly autoimmune, with the virus acting as a trigger.

Some statistics are noteworthy. Data from Michigan and Minnesota suggest that by age 18, one in 300 white children have juvenile-onset type diabetes. In blacks it is less frequent--sound

*Craighead, J.E. Current views on the etiology of insulin-dependent diabetes mellitus. New England Journal of Medicine, 299 (26): 1439-1445, 1978.

data are not available--but the estimates are that it has about one-fifth to one-tenth of the prevalence that exists for white children. The rate for Orientals is even less than that.

The peak age of incidence of this type of diabetes is 12. Although it is rare for it to occur at age one or two, it does occur. Conversely, it can occur at age 90, although it is, again, very rare. With the peak age at about 12 years, by the time a child is 18 or 19, the odds of a child developing this type of diabetes is about one-quarter of what it was at age 12. There appears to be no sex difference in prevalence, at least in this country. In Europe, boys show a slight predilection for diabetes, based on the Danish data.

What do we know about the disease? A large part of this is still anecdotal--that somehow Billy or Mary get some kind of environmental virus which then initiates an autoimmune response whereby the child then turns immune mechanisms against not only the virus, but also against his or her own beta cells on which the virus or virus protein is residing. Thus, an environmental process has initiated this "auto-destruct" of the child's own beta cells. After the development of the acute diabetes--the typical polyuria; polydipsia; weight loss; thirst; bedwetting (which the child may not have done since age five)--most children will go through a second phase after being almost totally decompensated because of the lack of insulin. In the past, this phase of decompensation was frequently fatal, the children dying in ketoacidosis. After this first phase, most will then experience a phase lasting for a month to several months--perhaps as long as a year--in which they still have some endogenous insulin and sometimes they are able to control their diabetes without insulin treatment. This is followed by several years of the so-called "honeymoon" phase when the diabetes may be easily regulated by a single daily insulin injection. The child then enters the final stage in which there is no more endogenous insulin production, and they must have at least one, and usually two, daily insulin injections. The point to be made here is that this is an irreversible process. Under the age of 18, in our experience with approximately 30,000 subjects, we have never seen a permament remission of the disorder.

Over the age of 18, remission can occur, usually in middle-aged males, but it is an extremely rare event. In other words, once the disease process begins, it is essentially irreversible and proceeds to total insulin dependence. Thus, once the child gets the disease, he will have it for life, as far as we know today. This is why the current terminology accepted by the NIH is insulin dependent type diabetes, abbreviated IDDM.

As previously stated, it is much easier for the child to manage the disease during the first few years; then things become more

difficult. Once one loses all thermostat or fuelostat endogenously, one can only depend on exogenous insulin injection, or in some centers by infusion via other insulin delivery systems being developed. It is a grim process to realize and it is difficult to tell the child that he will have it the rest of his life.

The second aspect that must be considered is maturity-onset type diabetes. Recent data show that there are approximately 10 to 15 million maturity-onset diabetics. The statistics are hard to judge, however, since it is a matter of opinion how high a glucose level must be in order to say, "Yes, this is diabetes" or "No, it is not diabetes." An hypothesis, though one with some supporting data, is that human beta cells are gradually dying, as are many other cells in the body. There is also some evidence of earlier senescence of other tissues in the individuals who are predisposed to this type of diabetes. For example, normal fibroblasts in tissue culture will divide only so many times--again, a preprogrammed senescence which is accelerated in individuals with this type of diabetes, suggesting that there may be some kind of ubiquitous early aging for which the beta cells may be the Achilles' heel. This theory is still hypothetical, but the data being gathered generally support it. At the same time that we are losing the capacity to secrete insulin, as aging occurs and the beta cells die, we may need more insulin because the existing insulin is becoming less effective.

There are certain factors which necessitate a greater amount of insulin. Of these, the most significant is obesity. There is evidence that in obese individuals there are fewer net sites for insulin to work. There is other evidence that the secondary effects of insulin inside the cells are insufficient. How earth the cells know that they are residing in an obese individual is what is still unknown!

There is another very important factor here--inactivity. As most people age they are less active, and as they become overweight they are less active. For most people the sensitivity of tissues to insulin is a function of their level of activity.

Thirdly, there is a direct age-related process as well. These three factors added together--obesity, inactivity, and age--will unmask the relative insulin deficiency that occurs, perhaps due to beta cell aging. There is also some very preliminary evidence that damage to the beta cells may result from other factors, such as environmental toxins or chemicals produced not only externally, but also internally in the gut. This is a very active area of research and, unfortunately, one with many emotional and litigational consequences.

The third and last point to be mentioned in this very brief overview concerns the complications of diabetes. Diabetics have two

kinds of complications. Atherosclerosis is found in both juvenile-onset and maturity-onset diabetes subjects, but particularly among maturity-onset subjects, or to use the currently accepted term, in non-insulin dependent diabetes, or NIDDM. If the person is age 50, the blood vessels look like they come from a 60- or 70-year old with more atherosclerosis, more myocardial infarction, more strokes, and almost 100 times the prevalence of peripheral vascular problems. In addition, the youngster with diabetes, is more afflicted in the capillaries, particularly in the retina and in the kidney. The grim statistics collected in the 1940's and 50's suggested that the average juvenile diabetic would live only 36 or 38 years from the time of diagnosis. Thus, if diabetes occurs in children at age 12, by age 48 half of them would will be dead. Of those, half would have died of renal failure due to the specific small blood vessel complications in the kidney. About one-fifth would be legally blind, and all would have evidence of nerve damage.

The evidence today suggests that these specific complications, which also afflict the maturity-onset diabetic, may simply be a function of too much sugar in the body. It is as simple as that. There is more evidence accumulating, and it has been proven in experimental animals that hyperglycemia, the increase in blood glucose as a result of deficient insulin, may be the provocateur for not only the eye problems and the kidney problems but also the nerve problems which I have mentioned.

The evidence is that the glucose molecule binds chemically with proteins to sort of "glop up" the proteins. An appropriate biochemical analogy is the toast we eat each morning. The toast browns as it is heated because glucose (derived by the yeasting of the starch) reacts with proteins from the wheat. It is this chemical process of the aldehyde of the glucose molecule reacting with proteins, which more and more evidence suggests as the cause of the eye, kidney, and the increased capillary permeability problems. Indeed if this concept holds true in humans, as it has in experimental animal studies, then maintaining blood glucose levels near normal will prevent the eye, nerve, and kidney problems. A prospective study has not yet been done in man. The question now is whether ethics will allow it to be done.

Among identical twins in which one twin has juvenile-onset diabetes, the other does not get it in two-thirds to three-fourths of the cases in this country. In 50 percent of the pairs in Scandinavia and the United Kingdom the second twin does not get it. If one gets diabetes and the other does not, we will note 30 years later that the one having had diabetes has the eye problems, the kidney problems, and delayed nerve conduction, the increased atherosclerosis, and so forth. The other identical twin is 100 percent normal; in other words, no retinopathy, no nephropathy, and

so on, which again supports the fact that diabetes is not a genetic preprogrammed situation, but a process influenced by hyperglycemia. There is enough anecdotal information that kidneys transplanted from diabetic animals to normal animals lose their specific lesions to a limited degree. Conversely, kidneys transplanted from normal individuals into diabetics assume the lesions that are present in the diabetic-- again, supporting diabetes as a metabolic process and perhaps simply due to hyperglycemia.

The problem that challenges those interested in diabetes, and which all data support, is that if the aforementioned is true, we are forced to bring the blood glucose as close to normal by whatever maneuver we can. Since the individual is usually charged with the responsibility of taking care of his or her own diabetes, the question of patient compliance and of educating the patient regarding the disease challenges us all. Patients very often ask: "Doctor, if I take care of my blood sugar, will I have no problems?" I cannot say irrefutably "Yes," because the data are not absolutely certain in humans. All that I can say is that I can assume that all of the experimental data to date support this concept. The British have experimented with an automatic insulin-delivering device in four cases of juvenile-onset diabetes with advancing problems in the eye. A striking regression of the problem was noted in all four patients. This is only anecdotal, however, not statistically proven. But what is clear is that there is an important need to improve the quality of our management. Evidence is accumulating daily that bringing the glucose levels to normal is worthwhile.

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CURRENT TRENDS OF PHARMACOLOGICAL TREATMENT

Juanita Archer, M.D.

The pharmacological approach to the therapy for diabetic patients is perhaps more extensive than ever before. We still see, however, many complications in our patients and we realize that these approaches are much too limited. As was pointed out,* we know that the underlying defect in diabetes is that of abnormal insulin action. This single underlying defect is present no matter what type of diabetes mellitus exists. Recently, efforts to better define how abnormal insulin action is associated with the various syndromes and their complications have been productive enough to demand some improved alterations in the pharmacological therapeutics for our diabetic patients.

This discussion will center around these improvements; specifically, recent methods of making more insulin physiologically available at the cell receptor site. It is here and only here that insulin can be adequately utilized. Since most United States diabetologists feel that the role of sulfonylurea is restricted to carefully selected patients, I will spend only a moment discussing these oral agents, then conclude after discussing pharmacological treatment of the chronic complications.

About 20 years ago, with the advent of radioimmunological assays, direct measurement of hormones brought us to the point of realizing that the insulin we gave our patients consisted not only of good insulin that the cells could easily use, but also of pro-insulin, or other products produced in the pancreas prior to the time that insulin is released, as well as insulin dimers, split insulin products, and unidentified proteins. Now, with further technical advances, we know that some of those unidentified proteins are other pancreatic hormones that stimulate glucose production.

Approximately ten years ago, investigators who had access to improved electrofluoretic and chromatographic techniques obtained mixed beef and pork insulins almost free of other insulin forms and other pancreatic hormones. When these more pure insulins were given to patients, it was found that their total insulin dose requirement decreased. Thus, an attempt was made to get away from the so-called "contaminated" insulins. Investigators and pharmaceutical houses producing insulin then began attempting to improve the purity of insulin, so that insulin obtained from both mixed beef and pork

*See presentation by George Cahill, p. 117.

pancreas, as well as from pork only, was as pure as possible, containing as much pure insulin as could be obtained. Their aim was to produce (1) insulin that had very little antigenicity, and (2) insulin that would act more efficiently at the cell level. Subsequently, two pure forms of insulin became available. One form had the chromographic profile of a single, isolated peak. This form was designated "single peak" insulin. It still contained minimal amounts of pro-insulin and pancreatic polypeptides. Single peak insulin also contained glucagon and somatostatin, the aforementioned hormones that may stimulate insulin production.

Today, single peak insulin is produced with minimal amounts of pro-insulin contamination. It may contain as little as one one-thousandth percent pro-insulin; other contaminants are also markedly reduced.

By further purifying the single peak insulin, a second type of very pure insulin has been derived. This is called monocomponent insulin. Monocomponent insulin is so pure that patients who are switched from the conventional types of insulin to monocomponent require 20-30 percent less insulin.

One of the major advantages from utilization of monocomponent insulin has been total eradication of the three major side effects of both conventional and single peak insulin: (1) insulin allergy, (2) insulin resistance due to antibodies produced against insulin and "contaminating" insulin products, and (3) the so-called "secondary" lipoatrophy. None of the patients who have been treated with monocomponent insulin have evidence of secondary insulin resistance, insulin allergy or lipoatrophy. Further, when any of these occur while patients are receiving other kinds of insulin, they can all be alleviated if patients are switched from their usual insulin to monocomponent insulin. Thus, monocomponent insulin can prevent or reverse insulin resistance, insulin allergy and lipoatrophy.

The major therapeutic advancement expected in the future will be obtained with continued improved production techniques that will make purer insulin easily and inexpensively available to all diabetic patients.

What about the other forms of insulin production? Recombinant DNA technology has resulted in altering the genetic constitution of E. coli bacteria, so as to cause them to produce human insulin and insulin products. In addition to government regulations controlling recombinant DNA research, the problem with the production of insulin from DNA is one of cost of production as opposed to the quantity of insulin needed, and there are similar cost problems when one considers other forms of delivering insulin to its cell site. For example, the potential exists, but is extremely costly in relation

to the extent of the patient population which can benefit from it at present. It is anticipated, however, that future research will help alleviate the problems associated with the methods for delivery of insulin. At present, delivery of insulin for most diabetic patients is best accomplished by daily multidose therapy with both an intermediate- and a short-acting insulin.

As for oral agents, today most diabetologists will employ them for only a few carefully selected Type 2 patients; that is, patients who are not insulin dependent. These patients are carefully selected non-obese patients who do not respond to diet alone and require minimal alterations in their insulin secretion. The agents used all contain sulfonylurea groups and act by stimulating the pancreatic beta cells. They also stimulate peripheral cell insulin sensitivity. Thus, sulfonylureas may act by stimulating beta cell activity or by stimulating peripheral cell insulin sensitivity.

There are two new sulfonylureas. One is called glyburide and one glypazide. These are now awaiting approval for clinical use in this country. These drugs have half-lives of approximately six to eight hours. However, they may, in fact, have their glucose-lowering effect after only one or two daily doses for 20-24 hours.

Finally, let us briefly look at the current drug treatment of those with special problems and complications. For the problem of insulin resistance, we have already mentioned the effect of switching from a very contaminated insulin to a pure insulin. In addition, when resistance is solely on the basis of an autoimmunological defect, that is, a defect subsequent to the patient's body producing antibodies against itself, immunosuppression may be indicated. This may be accomplished by adding prednisone to the daily insulin dose for 10 days. However, a rare cause of insulin resistance with antibodies produced to the insulin receptor has been reported. Symptomatic patients with this rare cause of insulin resistance may respond to prednisone alone or combined with cyclophosphamide.

As for the chronic complications of diabetes mellitus, there are only a very few pharmacological approaches. With retinopathy, the approach remains that of surgery, as well as other mechanical interventions; with nephropathy, surgical or mechanical intervention is also the only available therapy. When diabetic nephropathy reexpresses itself in a transplanted kidney, immunosuppression may suppress this expression for a temporary period. With diabetic neuropathy we do, in fact, have some pharmacological agents for alleviation. This alleviation of the neuropathy is directed not at the neuropathy itself but at alleviation of the pain that it causes. Several agents have recently been used to offer some aid in alleviating this pain. Among these agents are fluphenazine decanate, a drug that has the trade name of Prolixin Decanate, and

tricyclic antidepressants. These and other agents have been successfully used when nothing else would offer relief of pain to the diabetic with severe incapacitating neuropathy. There are suggestions now that other drugs may be on the way.

In summary, for the diabetic patient, the main pharmacological trends are toward the effective use of technical advances to better provide pure insulin for the direct maintenance of physiological cellular metabolism.

Fortunately, included in these trends are attempts to prevent chronic diabetic complications and to better treat those patients with already existing complications.

MANAGEMENT OF MATURITY-ONSET DIABETES

John K. Davidson, M.D., Ph.D.

At the present time, at least 90 percent of the patients who develop diabetes in this country are overweight. Thus, for those who treat diabetes, the number one problem is attempting to control excessive caloric intake. How excessive caloric intake influences certain diseases, especially diabetes, is the focus of current research.

The beta cells have a remarkable capacity to increase their insulin production when body weight goes up and more insulin is needed to keep the blood sugar level normal; but they do have a limit which they cannot exceed. In people who are grossly obese, it is estimated that the prevalence of diabetes is about 40 times as great as it is in those who are at normal body weight.

The insulin receptor number goes down in patients who are overweight. With fasting or weight loss, the insulin receptor number comes back to normal or near normal and the tissues regain their insulin sensitivity and are no longer resistant to the effects of the endogenous insulin that the patient can produce.

Among the most feared complications of diabetes are atherosclerosis and gangrene of the lower extremity. Gangrene, which terminates with amputation, can develop in both maturity-onset diabetes and in juvenile-onset diabetes. In the hopes of preventing the development of microangiopathy, arteriopathy and neuropathy, maximum efforts should be made to keep blood sugar, lipids, and other intermediates at normal levels. For the patient who is overweight, the clearcut objectives of therapy are to attain and to maintain ideal body weight and normoglycemia. There is increasing evidence that this can be accomplished.

In 1970, the Diabetes Unit of Emory University discontinued the use of oral insulin agents and expanded its nutritional care program. A team (physician, podiatrist, dietitian, nurse) has been used since that time to evaluate and educate patients, and to provide continuous follow-up care. Physicians have tended to delegate responsibility to the dietician for prescribing diet. It appears that this is no longer the best practice. In some instances, the patient may interpret the physician's lack of involvement in this diet-prescribing process as an indication that it is unimportant; the patient will downgrade the importance in his or her own mind and adherence will drop. Hence, physicians should work closely with the dietician in this aspect of the treatment plan.

The Emory Diabetes Unit uses a "stepped" approach to the treatment of diabetics who are obese. The usual first step is trying conventional low-calorie diets. If the patient loses weight, a low-calorie diet is prescribed along with an exercise routine and continuous follow-up care. If the low-calorie diet does not work, a fast is instituted with medical supervision. Follow-up of this enforced weight loss includes a low-calorie diet and exercise routine with continuous support. The continuity of care has been found critically important. From 1970 to 1978, patients at Emory have lost an average of 20 pounds each, and this represents 40 percent of the excess weight. The hospital has saved money as a result of fewer amputations, fewer episodes of care of diabetic crises, and using less insulin in the treatment. At the present time, 81 percent of our patients are on diet therapy alone, and 19 percent are on insulin. This contrasts with the national average of only 26 percent of patients who are on diet therapy alone with the rest being on medication.

These experiences with diet therapy made us curious about what would happen if overweight patients with no history of ketoacidosis were taken off insulin. We studied 37 hyperglycemic patients, all of whom were overweight and were abruptly taken off insulin and fasted for one week. Four of the patients were classified as failures. Two of them developed diabetic ketoacidosis during the fast and insulin therapy was promptly resumed. Consequently, it is important to recognize that if one uses this approach, one should monitor the patients carefully. One patient lost 67 pounds and the plasma glucose returned to normal. However, she regained 40 pounds while eating compulsively, and she resumed insulin therapy on her own. One died of coronary insufficiency four months post-fast, although the death was not related to it. The average weight loss over a 20-month follow-up period in 33 patients who were classified as successes was 40 pounds. The mean plasma glucose after this was 120 milligrams per deciliter, which was a highly significant decrease ($p < 0.01$) from the 237 mg/dl when they were on insulin.

The point that this study clearly makes is that insulin therapy in the overweight diabetic will not attain or maintain normoglycemia in many patients. It is clear that in this group of patients weight loss is more successful in attaining the goal of normoglycemia.

In other research, a group of patients who were taken off oral agents in 1970 were followed until 1978. In each case, those who lost the most weight had the greatest lowering of plasma glucose. The group that had transiently been placed on insulin and then on diet alone after the oral agents were discontinued lost an average of 33 pounds, and their average plasma glucose in 1978 was 101 mg/dl, lower than it had been on oral agent therapy in 1971. The same is true for those who have been on diet therapy alone since

1971, and for those who were on insulin therapy in 1978. If one looks at the individuals who had the greatest increase in plasma glucose from 1971 to 1978, the diet-treated group was nearly 140 percent of ideal body weight in 1978. Those who had insulin therapy discontinued and who became more hyperglycemic from 1971 to 1978 were above 130 percent of ideal body weight in 1978, and those that were on insulin in 1978 and who were the most above ideal body weight had the greatest plasma glucose increase from 1971 to 1978. This, again, tends to indicate that controlling the plasma glucose involves more than just giving insulin.

The number of patients who have come to the clinic from 1971 to 1978 has increased seven-fold. This increase can be accounted for by continuity of care; once you have seen them, you continue to see them. However, the expanded nutritional care program is cost-effective. While it costs about two and one-half times as much as the original basic nutritional care program, the saving comes about by not using oral agents. Using less insulin, the hospital actually saved almost $100,000 over that eight-year period.

In order to teach patients about good nutrition, we produced the Diabetes Guidebook: Diet Section. The book is color coded to simplify use by many of our patients who cannot read or write. Special efforts were made to utilize foods that the patients liked. For example, we analyzed fried chicken and found out that the fried drumstick fits into the low-fat meat exchanges. The hog maw is an item that is the greatest favorite among our patients, and we demonstrated that it also could be used in the diet.

With the assistance of a dietician to instruct the patient and changing the strategy from medication-oriented to diet-oriented therapy, the number of severe DKA has fallen from 502 in 1969 to 112 in 1978. The number of amputations have fallen from 172 in 1973 to 86 in 1978. This has saved the hospital an estimated $3.2 million by decreasing the prevalence of these two directly diabetes-related complications alone.

In summary, we can say that in the treatment of the maturity-onset diabetic, it is important to be aware that there have been changes in thinking about how these individuals should be treated. These patients are at risk for all of the complications associated with diabetes. It is important to detect them early. If they are overweight, they should lose weight; if they need insulin, they should be treated with insulin, but only after diet therapy has been utilized as aggressively as possible. There is reason to believe that in maturity-onset diabetics, weight loss will, in fact, reverse fasting hyperglycemia to normoglycemia.

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BEHAVIORAL AND PSYCHOSOCIAL ISSUES IN THE MANAGEMENT OF THE CHILD AND ADOLESCENT WITH DIABETES MELLITUS

Allan L. Drash, M.D.

Diabetes mellitus is one of the more common serious chronic diseases of childhood and adolescence. It occurs at a frequency in excess of one per 1,000 children under 17 years of age.1/ It is uncommon in early infancy, increases with increasing age, with peak incidence achieved in early adolescence, somewhat earlier in girls than boys, followed by a decline in the early adult years. Diabetes occuring in the child and adolescent is usually of the classical insulin-deficiency form. The symptom complex at the time of presentation usually includes polyuria, polydipsia, polyphagia, weight loss, and fatigue. The duration of these symptoms rarely exceeds three weeks prior to diagnosis and a history of preceding viral infections is common. Fifteen to 20 percent of the patients present with severe metabolic disturbances, including ketoacidosis, while the remaining have somewhat lesser metabolic alterations and less compelling clinical symptoms.2/

The initial clinical course is of special interest. In excess of 75 percent of the newly diagnosed patients will have a period of declining insulin requirement and spontaneously improving metabolic status during the period of one to three months following diagnosis. This interval has been referred to as remission or "the honeymoon phase." The duration of this period is variable but may last from several weeks to several months and, in some cases, in excess of two years. The mechanism for this spontaneous improvement appears to be improved endogenous insulin secretion due to recovery of beta cell function. Unfortunately, it is not clear whether anything available in the therapeutic area can increase the frequency or duration of this phase. Almost invariably with the passage of weeks, there is either a gradual or abrupt loss of endogenous beta cell function associated with increasing insulin requirement and increasing difficulty of moment-to-moment and day-to-day regulation of metabolic homeostasis.

The primary objective of the practice of medicine is prevention and cure of disease. In our current state of knowledge, we are incapable of either preventing or curing insulin-deficiency diabetes mellitus. Consequently, the physician, in concert with the patient and family, must establish secondary therapeutic objectives. The therapeutic objectives in our clinic include the following:

1. Complete elimination of the overt acute symptoms of diabetes mellitus, including polyuria, polydipsia, and polyphagia.

2. Prevention of ketonuria, ketonemia, and ketoacidosis.

3. Prevention of hypoglycemia.

4. Control of hyperglycemia and glucosuria to the extent that caloric losses are minimized. (A 24-hour urinary glucose loss of less than seven percent of ingested carbohydrates is a reasonable goal which can be achieved in a high percentage of patients.)

5. Maintenance of blood lipid concentrations within the limits normal for age.

6. Achievement of normal growth and development, including normal timing of development of secondary sexual characteristics.

7. Maintenance of a high level of physical fitness.

8. Avoidance of obesity.

9. Full participation in activities appropriate to age and interest.

10. Acceptance of a diet to help minimize postprandial hyperglycemia and prevention of hyperlipidemia.

11. Education of the patient and family regarding diabetes and its treatment so they can effectively participate in all management decisions.

12. Assumption by the patient of progressively more responsibility for insulin administration, urine testing, and dietary or other daily management activities.

13. Development by the patient of sound psychological acceptance of the problems of diabetes, including a positive outlook for the future.

14. Eventual achievement of full intellectual and emotional potential as a contributing member of society.

15. Prevention of cardiovascular complications of diabetes, including atherosclerosis and microvascular disease.

Insulin-deficiency diabetes mellitus is unique in terms of the requirements placed upon the patient and family from the point of view of intimate involvement in management activity and decision-making. Undoubtedly, these management requirements are significant factors in the high frequency of behavioral and psychiatric problems associated with diabetes mellitus in children and adolescents. It has been well-documented that chronic disease carries with it increased risk for psychopathology. This has been documented in both the pediatric and adult medical literature in such conditions as cancer, chronic renal failure, leukemia, congenital heart disease, cystic fibrosis, epilepsy, and asthma.3/ In none of these conditions are the patients required to participate significantly in their therapeutic management and decision-making. In all of these diseases, with the possible exception of asthma, the decision-making is almost exclusively in the hands of the physician.

An analysis of the management requirements of the child with diabetes will provide some insight into the demands placed upon the patient and family. The basic therapeutic ingredients include insulin administration by injection one or more times daily; dietary management which eliminates or minimizes many of the highly desirable foods in our environment, traditionally so appealing to children; and physical activity of a daily regulated amount. From a biochemical point of view, the objective of management is the achievement of biochemical normality, including blood glucose variations within the normal limits, as well as lipids, proteins, amino acids, and other biochemical substances. Given our current modes of therapy, it is impossible to achieve continuous biochemical normality in the completely insulin-deficient patient. The pressures generated by either the physician, the patient, the family, or all in concert to achieve goals which are practically unachievable, obviously generate high levels of stress. Conversely, the setting of inadequate therapeutic goals will invariably lead to the increased likelihood of recurring acute and chronic medical complications. Traditionally, the patient with diabetes administers his own medication, insulin, by injection. This is true of children as well as adults. In our clinic, we expect our young people to assume this responsibility sometime between 10 and 12 years of age. They are expected to do biochemical determinations of urinary glucose concentration three or four times daily, keeping a careful record of this information to provide periodically to their physician; but even more important, to use the information to adjust their insulin dose on a daily or weekly basis. They are provided with detailed dietary directions and are expected to become much more knowledgeable about nutrients, diet construction, spacing of meals, and so forth than most physicians or health professionals learn in a lifetime. They are expected to involve themselves in a program of physical fitness involving daily physical activity, but carried out in such a way that hypoglycemia will be avoided. In addition to having all these demands made upon them, they are also

expected to avoid those activities which might be injurious to their health. It is not surprising that behavioral problems occur commonly in these young people. Indeed, it is surprising that so many of our young patients get through the stresses and strains of growing up with diabetes without serious emotional handicaps.4/

The Complications of Diabetes

Although there is increasing evidence that the chronic complications of diabetes mellitus, particularly those involving the microvascular circulation, are related to the metabolic disturbance of diabetes, it has not been unequivocally demonstrated that these are a direct result of persistent hyperglycemia. The possibility that insulin deficiency per se is a direct factor in development of complications has not been adequately assessed, nor have other possible factors, such as genetic predisposition. Increasingly, however, diabetologists have focused on improving metabolic control as a means of minimizing serious complications. Acute or short-term complications include ketoacidosis and hypoglycemia, both a direct result of alterations in glucose metabolism and impaired growth and maturation, an intermediate type complication seen in children who receive inadequate insulin therapy. The pregnant diabetic presents unusual challenges and clear evidence that metabolic homeostasis is a factor in the complications which may occur in the infant born to the diabetic mother. It is now well established that the "syndrome of the infant of the diabetic mother," including the excessively heavy, floppy infant with increased susceptibility to hyaline membrane disease and neonatal hypoglycemia, is a direct result of maternal hyperglycemia. Unresolved as yet is the question of whether the increased rate of congenital malformations in these infants is also an expression of inadequate glucose control early in pregnancy. This issue is currently being approached by a multi-center grant from the National Institute of Child Health and Human Development (NICHD).

The chronic complications include accelerated atherosclerosis, cerebral vascular accidents, renal hypertension, and gangrene, all of which in turn result from large vessel disease and retinopathy, leading to blindness, nephropathy leading to chronic renal disease, and neuropathy, all expressions of microvascular disease. The National Institutes of Health are planning a multi-center long-term study in an attempt to resolve the long-term controversy as to whether metabolic control is responsible for, or is a major factor in, the development of vascular complications. However, in advance of these final conclusions, many workers in the field are vigorously pushing forward with new techniques to improve metabolic control.5/

New Approaches to Insulin Delivery

The ultimate hope is for the transplantation of a healthy pancreas into the diabetic, thus resulting in permanent cure of the disease, or the development of a totally implantable mechanical pancreas which can completely substitute for the pancreatic beta cells, resulting in complete normalization of energy homeostasis. Neither of these two possibilities is at hand. However, as an interim step, increasing interest and enthusiasm has been demonstrated for the use of the "open loop pump" in the treatment of insulin-deficiency diabetes mellitus.6/ A number of investigating centers, our own included, are now utilizing relatively crude insulin infusion pump systems to continuously administer insulin subcutaneously to adolescents and young adults with insulin-deficient diabetes mellitus. Considerable promise has resulted from these early efforts, demonstrating that in at least some patients, near normal energy homeostasis may be achieved by such approaches. However, these techniques have not by any means been, uniformly successful and must remain at this time as research tools rather than practical means for management of large numbers of patients. Of particular interest is the fact that, to date, no one has carried out adequate psychological evaluation of patients who are being considered for open loop pump therapy, nor have there been studies to determine the extent of psychological stresses associated with living attached to a mechanical device. We know, for example, that suicide rates are clearly increased in patients with chronic renal disease requiring chronic renal dialysis. Studies need to be developed to determine whether the use of the open loop pump system carries with it such increased hazards.

Almost concurrent with the application of the open loop insulin infusion systems have come other developments of major importance in diabetic management. One of the major difficulties we have had in diabetes management has been the inadequacies of the techniques available to assess metabolic control over time. The patients may check three or four individual urine specimens daily for semiquantitative glucose concentration, 24-hour urine glucose spill may be checked periodically, and fasting or postprandial blood glucose determinations may be made three or four times yearly. Such techniques have clearly been demonstrated to have very limited utility in assessing long-term control. The recent development and application of the technique for measuring the percentage of red blood cell hemoglobin in the glycosylated form has provided a sensitive and highly valuable technique for indirectly assessing the degree of hyperglycemia over a period of three or four months from a single blood determination. This has provided, for the first time, a satisfactory method for assessing long-term control. In addition, in conjunction with the emphasis on improving day-to-day management,

home glucose monitoring is now becoming a fairly routine part of diabetic management. This method involves blood glucose determinations by the patient, utilizing capillary blood glucose obtained from a finger stick and assessed using glucose oxidase impregnated paper strips. This can be done in the home with reasonable accuracy.7/ However, it does place additional stress and demands upon the patient with diabetes and the family.

The Therapeutic Alliance

The keystone to successful diabetes management is education of the patient, the family, and other relevant individuals in the patient's environment. The educational process must involve an adequate grasp of the pathophysiology of diabetes mellitus, awareness of symptom complexes, clear understanding of the rationale for adjusting insulin dosage, detailed knowledge about nutrition and its application on a day-to-day basis in the choosing of food, and the integration of exercise in the overall management program. It is quite clear that few physicians today possess the time, inclination, or the requisite skills to meet all the educational requirements of the patient. Consequently, the team approach of diabetes management has evolved and is the accepted mode of therapy for most diabetes treatment units. The central figure of the diabetes management team is the patient, who must participate actively in the educational process and bring back to the therapeutic team problems and issues which he or she cannot or will not resolve. If success is to be achieved, a contractual relationship, either overt or covert, must develop between the patient and the other members of the team, in terms of each meeting certain necessary aspects of management.

The physician functions as captain of the therapeutic team. Of great importance is the diabetes nurse/clinician or diabetes educator, who is the individual who spends the greatest amount of time initially and on an ongoing basis with the patient and family, insuring that they understand the basic information and providing periodic updates of this. The nutritionist or dietician is also essential, either as an integral part of the team or a readily available consultant. The psychiatric social worker brings unique skills to the team in assessing the family and its resources, as well as having knowledge of the resources of the community which may be of benefit to the family. Finally, the team should include either a skilled psychologist or psychiatrist for the many problems which arise in the behavioral area in these patients.

Although education is essential, it is not enough to insure therapeutic success. Many patients with inadequate management as demonstrated by recurrent hospitalization with ketoacidosis,

hypoglycemic reactions, poor growth and maturation, and so on, have accumulated the necessary factual information, as documented by paper and pencil tests, yet do not use this information in making rational and appropriate decisions regarding their management. In such patients, psychological factors clearly impair the application of factual knowledge. One of the most difficult aspects of patient management, particularly in the adolescent, has to do with psychological acceptance of the diagnosis as a permanent part of the patient's future and the integration of that information in a positive way into their daily lives. The poet Bobby Burns defined maturity as "the ability to make peace with necessity." It is the inability to come to grips with the finality of the diagnosis of diabetes mellitus which leads many patients to behavior which is exceedingly difficult, if not irresponsible.

Periods of Special Stress

Living with diabetes mellitus is a constant emotional stress. The patient and family will come to know this is a serious, incurable disease which sets frustrating limitations on lifestyle and life choices and leads to life-threatening complications as adults. Patients are aware that 80 percent of them will eventually develop some expression of early heart disease, and so forth. They are also aware that they may face discrimination in the job market and may not be able to provide for the family they are fearful of having. However, in addition to these constant emotional stresses, there are certain times in the life of the individual with diabetes mellitus which carry with them increased stress.

The Diagnosis

The diagnosis of diabetes in a child almost invariably carries with it an initial reaction of shock followed by depression in the parents though less so in the child. As the sense of depression slowly begins to moderate, it may be followed by a sense of guilt and/or by anger. Marital problems between the parents may be aggravated as each points to the other as the guilty party in the development of diabetes in their child. For the most part, the preadolescent patient handles the diagnosis and initial phases of therapy appreciably better than do his parents. The adolescent, however, may go through a period of depression or grief response for "loss of self." It is Dr. Maria Kovacs's working hypothesis on studies carried out on our teenage diabetics that this process of grieving may be a positive coping mechanism.

The Remission Phase

The remission phase, occuring a few weeks or months after the initial diagnosis, is associated with declining insulin requirement and improving metabolic control. The patient is returning to normal

activities and seems to have recovered much of his or her "old self." Not infrequently, the parents begin to question the diagnosis of diabetes and develop false hopes that the disorder is not really permanent. A secondary period of depression results when the remission is lost and insulin requirements rise, with increasing difficulties in day-to-day management.

Hypoglycemia

Hypoglycemic reactions may result in generalized convulsions and irreversible brain damage in the diabetic child. Although such severe reactions are exceedingly uncommon, they do occur, and the fear of brain damage is an ever-present concern of the parents of diabetic children. Indeed, it is this overconcern that in many families leads to inadequate increases in insulin administration, resulting in chronic poor diabetic management. The families may make the decision that they would prefer their children's blood glucose to be "high" rather than chance the possibility of hypoglycemia.

Adolescence

Adolescence is a difficult, if not turbulent, time for most young people with good health. The stresses of normal adolescence become markedly accentuated in young persons with diabetes mellitus for many reasons. Their disease and its management places upon them certain restrictions of time, place, and activity which are inconsistent with the freedom of lifestyle that most adolescents with to adopt. It makes the teenager with diabetes different. A variety of behavioral responses may be seen during this period. Most frequent is hostile, acting-out behavior with the denial of their disease, linked to excessive risk-taking. They appear to want to force the system to its ultimate, and prove they are good enough to meet any of the demands of society. Another common reaction is depression. The young person views his or her medical situation as incurable, with only increasing medical problems and death ahead. They become isolated, withdrawing from their usual social contacts, and become less involved in their medical management. Their school work begins to decline and other interpersonal relationships are reduced.

A special problem seen most commonly in adolescent girls is the condition referred to by Minuchin and Baker 8/ as "psychogenic diabetes mellitus." This is not to mean that the diabetes in these patients is caused by psychological disturbance, but rather that the course is a direct result of inadequately handled psychological stresses. These patients characteristically have severe recurrent ketoacidosis requiring hospitalization, sometimes several times a year during the adolescent years. This may be a result of a

psychiatrically disordered family and requires intensive family therapy in order to improve the overall support and management of the child with diabetes mellitus.

Identification

The chronic vascular complications of diabetes rarely reach clinically significant proportions during the childhood or adolescent years. However, the initiation of these alterations may be identified in the adolescent who has had diabetes for five years or more. The most commonly identified initial lesion is in the eye, where the earliest changes are microaneurysms. Using the technique of fluoroscein angiography, it is possible to detect alterations in the eye at an even earlier time than can be identified by direct ophthalmoscopic examination. The time when the young person and the family are informed that early diabetic complications have been identified is frequently a time of acute stress and anxiety. It may lead to at least a temporary period of angry rejection of the disease with a sense of hopelessness about the future. Fortunately, however, in many cases this initial identification of the beginning of clear diabetic complications results in a final acceptance of the disease by the young person and the family, and the development of a sense of determination to assume control of their future health by improving day-to-day management of their diabetic state.

The Job Market

Although federal guidelines clearly prohibit job discrimination based on medical diagnosis that does not impair function, it is quite clear that young people with diabetes mellitus frequently meet rejections as they apply for jobs. In addition, dismissal from jobs may result under circumstances which may not have led to loss of jobs in individuals who did not carry a medical diagnosis. The young people are aware of these problems as they approach the job market, and they do so with considerable anxiety.

Marriage and the Family

Young persons with diabetes mellitus frequently have a poor self image. Seeing themselves as "damaged goods" leads to lack of self-confidence in interpersonal relationships and, frequently, avoidance of appropriate interpersonal relationships which should lead to courtship and marriage. In addition, they frequently carry excessive concerns about giving diabetes to potential offspring, and women diabetics have great anxiety about their health during the course of pregnancy and the effect their diabetes may have on offspring. Factual informtion as well as emotional support is vitally needed during these periods of increasing stress and anxiety.

The Needs for Research in the Behavioral Issues of Diabetes Mellitus

The research opportunities available in the field of diabetes mellitus to the behavioral scientist are great. The recently published proceedings of the national conference "Behavioral and Psychosocial Issues in Diabetes" should be consulted for details of the numerous identified research needs in the field.9/ However, I will mention a few issues which are of special concern to me as a pediatric diabetologist. We regularly see our patients, particularly teenagers, developing progressively more serious behavioral problems, and in some cases, clear psychiatric disturbance. We would like to prevent the development of such problems rather than attempt to meet them in crisis situtions. We need predictive tests which can be utilized in the evaluation of the entire family of newly diabetic patients which will allow us to determine family and individual family members' strengths and weaknesses, and hopefully predict those families who should be entered into preventive counseling early. In addition, we should learn from those young people with diabetes and their families who have learned to cope in an effective and even victorious way with the demands and stresses of this serious chronic illness. Can we learn from them and apply very adaptive techniques to less fortunate families? The relationship between emotional stress and the body physiology is most dramatically seen in the adolescent diabetic who may be transformed from excellent metabolic control to severe ketoacidosis in a period of a few hours when placed under excessive stress. The whole area of the relationship between cortical, hypothalamic, and endocrine interrelationships and the central nervous system and the mediation of stress remains an area requiring increasing careful scientific input which will demand the collaboration of the behavioral scientist, the endocrinologist, and others.

Education is the framework on which diabetic management must be built. The educational psychologist has had little input into the development of teaching techniques for the diabetic and his family, and little input into the assessment or evaluation of the effectiveness of such techniques. This is badly needed. In addition, even though education--that is, the accumulation of factual information about diabetes and its management--may appear to be adequate, the application of this information is frequently lacking. The patient is noncompliant or does not adhere to the therapeutic regimen. Techniques which will allow for assessment of the causes for failure and the development of successful modes of operation are clearly needed. The skills of the behavioral modification psychologist are particularly relevant in this area and can provide a scientific basis for altering behavior toward health-giving, rather than self-destructive, ends.

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APPENDIX A
ANNOTATED BIBLIOGRAPHY:
PRE-CONFERENCE BACKGROUND REFERENCES*

Becker, Marshall H. Understanding patient compliance: The contributions of attitudes and other psychosocial factors. In S.J. Cohen, Ed. New Directions in Patient Compliance. Lexington, MA: D.C. Heath and Company, 1979.

Given the array of reasonably efficacious therapies, the critical problem facing health-care providers is often not one of finding an appropriate medication or other treatment regimen but obtaining the patient's cooperation with the required preventive or therapeutic program. Early studies have shown that the phenomenon of noncompliance is found among patients in all demographic, social, and personality groups, as well as at all levels of patient knowledge about an illness and its treatment.

Findings from studies related to the determinants of compliance indicate that a multifactorial approach to understanding and increasing patient cooperation with health and medical advice is needed. Practitioners and organizations are encouraged to improve patients' knowledge concerning the specifics of their therapies; reduce the costs, complexity, duration, and amount of behavioral change required by regimens; increase the efficiency and convenience with which care is provided; improve levels of patient satisfaction, particularly with the provider-patient relationship; encourage staff to monitor patient noncompliance; create new methods of supervising the patient, including involvement of the patients' families; and attempt, where appropriate, to modify patients' inappropriate health beliefs. Although more research is needed on determinants of patient cooperation and on methods for increasing adherence, the knowledge base already exists for rational programs that health care providers and organizations can implement to improve compliance.

*Prepared by Caren Carney, M.A., Research Associate

Etzwiler, Donnell D. Why not put your patients under contract? Prism, January 1974, 26-29.

Dr. Etzwiler presents results from a Minneapolis experiment showing that a simple written document can stimulate many persons to cooperate more fully in their own health care. He asserts that health care professionals should be aware not only of the need for cooperation with the patient, but also must encourage the individual to become involved in his or her own care. Dr. Etzwiler presents an example of a physician-patient contract for treatment of diabetes mellitus. The contract requires that both physician and patient understand, agree to, and accept responsibility for performing their respective tasks. Another essential component of the contract includes communicating the fact that a required task has been completed.

Etzwiler, Donnell D. and Sines, Lloyd K. Juvenile diabetes and its management: Family, social, and academic implications. Journal of the American Medical Association, 181(4): 304-308, 1962.

Questionnaires completed by 72 juvenile diabetics, their parents, teachers, camp counselors, and physicians gave further insight into the family, social, academic, and medical implications of the disease. The practices of management and roles of the various family members in the care of the child's disease, and the child's adjustment are described. Many of the children and their parents lacked knowledge of the fundamental principles of the disease. This suggests that the physician should take a more aggressive role in the supervision and teaching of the young diabetic and the family.

Green, Elmer E.; Green, Alyce, M.; and Norris, Patricia A. Self-regulation training for control of hypertension. Primary Cardiology, 6(3): 126-137, 1980.

Over the past 10 years, controlled clinical studies have demonstrated that antihypertensive medication can prevent deaths from stroke, congestive heart failure, peripheral vascular disease, and kidney disease, even in patients with borderline (140/90-160/95) hypertension. Today, a new treatment method of psychophysiologic self-regulation developed over a five-year period suggests that many patients are able gradually to eliminate these medications while restoring or maintaining normotensive blood pressure levels. Follow-up indicates that a healthier homeostatic balance is achieved and stress management maintained without need for continued daily practice of self-regulation.

Subsequent to the writing of this report, an additional 50 patients have been treated with this method, both individually

and in groups, with equally good results. Results indicate that 75-80 percent of patients will find it possible to comply with the training regimen, as taught at The Menninger Foundation, and will become normotensive without drugs.

Hollister, Leo E. Tricyclic antidepressants. The New England Journal of Medicine, 299(20): 1106-1109, 1978.

About 70 percent of prescriptions for tricyclic antidepressants are written by non-psychiatrists, largely physicians in family practice or internal medicine. Depression seems to be encountered frequently in medical practice. Despite this widespread recognition of depression and prescription of antidepressant drugs, many believe that depressed patients either are frequently not recognized or that they are inadequately treated. Depression is readily diagnosed when that is the patient's chief complaint; unfortunately, it rarely is. A host of complaints may mask the true underlying disorder. Patients with many vague complaints, most or all of which defy explanation, and those who may be thought to be "neurotic" or "crocks" should be suspected of being depressed. Diagnosis is not as easy as that of hypertension, nor is treatment with drugs likely to be as beneficial, but depression may rival hypertension in being both underdiagnosed and undertreated.

Controlled comparisons of the tricyclics have usually concluded that they are roughly equivalent drugs. Although they may be equally effective across various groups of patients, individual responses of these drugs may vary considerably. Individual patients may fare better on one drug than on another, for reasons that are uncertain. Finding the right drug for the patient is accomplished empirically at present. The past history of the patient's drug experience, if available, should be used as the major guide. At times, such a history may lead to the exclusion of tricyclics, as in patients who may have responded well in the past to monoamine oxidase inhibitors.

Hosten, Adrian O. Hypertension in black and other populations: Environmental factors and approaches to management. Journal of the National Medical Association, 72(2): 111-117, 1980.

Hypertension is a major health problem for industrialized as well as developing countries, especially those with sizeable black populations. If this was not the case for developing countries, it has become increasingly true in recent years. The fact that the complications of hypertension, especially coronary artery disease, are not as great a problem in developing countries as in the industrialized ones is little consolation when one reflects that myocardial infarction was once considered uncommon among American blacks.

Data seem to suggest that there is no intrinsic ethnic immunity to hypertension. Given a baseline genetic predisposition, a factor with which people of Negroid background seem heavily endowed, together with the right mix of environmental influences, one might expect hypertension to be prominent. Therefore, no developing society, least of all one with a black heritage, should feel secure against this potential killer. Rather, as their people's way of life becomes more complex, leaders in these communities must be vigilant and encourage a simple lifestyle based on a prudent diet, physical activity, avoidance of obesity, and a relaxed mental attitude. Current victims must be identified and treated. Even if hypertension may not finally be preventable, it can be controlled.

Luborsky, Lester. Combined pharmacological and psychosocial approaches in hypertension: Conceptual issues. Unpublished position paper prepared for the National Academy of Sciences, Institute of Medicine, Conference on Psychosocial and Pharmacological Treatment Approaches: Issues and Interrelationships, held on May 28-29, 1980, in Washington, D.C.

The pharmacological approach in the treatment of essential hypertension has been the established standard treatment for controlling elevated blood pressure in the past 15 years, ever since it has been shown that even small increases in blood pressure increase the danger of a variety of cardiac diseases as well as cerebral, renal, and peripheral vascular diseases. The idea that psychosocial treatments can be valuable supplements or alternatives to pharmacological ones has been proposed but not nearly so well established as the pharmacological approach. In the past few years, there have been some evaluations of the psychosocial approaches, especially of the "behavioral techniques." Progress in arriving at the relative value of each approach and of the combination has been slowed by the fact that the practitioners of each come from very different traditions. This review is aimed at examining conceptual issues with the hope of furthering integration of knowledge and approach by discussing three questions:

(1) What are the main psychosocial interventions?

(2) What are the relative contributions of the psychosocial as opposed to the pharmacotherapy treatments?

(3) What are the benefits of the combination as opposed to the individual treatments?

Mertens, Charles A. Psychological risk-factors in the management of cardiovascular diseases. Unpublished paper prepared for the National Academy of Sciences, Institute of Medicine, Conference on

Psychological and Pharmacological Treatment Approaches: Issues and Interrelationships, held on May 28-29, 1980, in Washington, D.C.

Dr. Mertens reviewed the data from experimental findings and clinical observations regarding the appropriate management of cardiovascular patients. Factors deemed relevant to experimental findings include the secondary importance of psychological traits in causing cardiovascular disorders, the primary importance of ego-defensive mechanisms, the role of intervening variables on the link between psychological and bioclinical risk-factors, and the cumulative effects of psychological and bioclinical risk-factors.

From clinical practice, Dr. Mertens discusses five important aspects in treating and preventing cardiovascular disorders. These include integrated teamwork, a multidisciplinary approach, permanent care, physician coaching of the patient, and the patient experiencing the uselessness of his or her own defense of passivity toward his or her illness.

Pfefferbaum, Adolf. Psychotherapy and psychopharmacology. In: Jack D. Barchas, Philip A. Berger, Roland D. Ciaranello, and Glen R. Elliott, Eds., Psychopharmacology, From Theory to Practice. New York: Oxford University Press, 1977.

Knowledge of psychological responses to the pharmacological process comes from astute observations by clinicians. These phenomena are not universal and take varied forms, depending on the psychopathology and personality structure of each individual. Perhaps this variety makes the task of "proving" an interaction between psychotherapy and pharmacotherapy so difficult. To date, it has not been possible to demonstrate this interaction, especially with insight therapies; but clinical experience and observations leave many convinced that it exists. There are neurophysiological and neurochemical counterparts to thoughts and emotions, and, therefore, the actions of psychopharmacological agents on biological substrates should influence the effects of psychotherapy on psychological substrates. Perhaps some psychiatric disorders begin with changes in the psychological substrate, thus altering biological mechanisms, while in others the process is reversed. Unraveling this interaction is one of the great challenges of psychiatry, as Sigmund Freud recognized when he wrote: "In view of the intimate connection between the things that we distinguish as physical and mental, we may look forward to a day when paths of knowledge and, let us hope, of influence will be opened up, leading from organic biology and chemistry to the field of neurotic phenomena."

Schwartz, Gary E. Behavioral medicine and systems theory: A new synthesis. National Forum, Winter 1980, 25-30.

Dr. Schwartz discusses the role and implications of systems theory for the emerging field of behavioral medicine. He also describes some potentials, problems, and controversies inherent in the system approach. He indicates that system theory represents a way of approaching science in general. Thus, it is not a specific theory per se, but a metatheory. One advantage of its metatheoretic status is that it has the potential to resolve controversies resulting from differences in orientation between researchers and clinicians trained in biomedical versus behavioral models. When a systems view is adopted, major differences caused by specialized training disappear. Specific models of disease or health become subsets of a more general and comprehensive approach to science. The real similarities across disciplines become clear, while the remaining discrepancies emerge as true differences among levels of analysis. For example, the behavioral psychologist's emphasis on learning and conditioning is appropriate at the organismal level, while the cardiologist's emphasis on fluid dynamics is appropriate at the organ level. Thus, if future students in the behavioral and biomedical sciences are exposed to general systems theory early in their careers as part of their specialty training, the goal of developing a general theory for behavioral medicine may be achieved.

Schwartz, Gary E.; Shapiro, Alvin P.; Redmond, Daniel P.; Ferguson, Donald C.E.; Ragland, David R.; and Weiss, Stephen M. Behavioral medicine approaches to hypertension: An integrative analysis of theory and research. Journal of Behavioral Medicine, 2(4): 311-363, 1979.

This article compares behavioral and biological approaches to hypertension; highlights some of the practical, semantic, and theoretical issues involved; and attempts a constructive, behavioral medicine integration of these approaches. The major behavioral approaches to hypertension are described, with a focus on their conceptual limitations as stimulants to research into psychobiological mechanisms. A biobehavioral system analysis of hypertension is outlined, emphasizing the role of the central nervous system as a common pathway relating environmental and behavioral factors to cardiovascular regulatory dynamics and disease. Schwartz's concept of blood pressure disregulation is discussed, by which behavioral "feedback loops" may be included in the pathogenesis of homeostatic disorders. A detailed discussion of concepts underlying the clinical pharmacological approach to

hypertension is provided; parallels are drawn between the conceptual framework and the theoretical and practical questions facing behavioral researchers concerned with hypertension. Synergistic interactive effects of drug and behavioral treatments are proposed. A biobehavioral overview, which links pressor and depressor stimulus patterns to both pathogenesis and therapy, can serve to integrate the previous biobehavioral system analysis, the conceptual framework of clinical pharmacology, and the notion of biobehavioral disregulation of blood pressure. Implications for future behavioral medicine research in hypertension are provided.

Seer, Peter. Psychological control of essential hypertension: Review of the literature and methodological critique. Psychological Bulletin, 86(5): 1015-1043, 1979.

Recent studies (1971-1978) that investigated psychological approaches to the treatment of essential hypertension are reviewed. Twenty studies that use techniques of biofeedback, relaxation, and meditation training are summarized in table form. They are subjected to a detailed methodological critique, and suggestions for methodological improvements and directions for future research are proposed. Most experiments demonstrated blood pressure reductions too small to be of clinical significance. A combination of biofeedback and relaxation/meditation with other behavioral techniques appears most promising, and suggestions for a more comprehensive approach to assessment and training are made. Although studies comparing biofeedback and relaxation/meditation were inconclusive, relaxation/meditation is suggested to hold more promise because it requires no sophisticated technology and has been reported to simultaneously reduce other stress-related complaints.

Shapiro, Alvin P. Behavioral and environmental aspects of hypertension. Journal of Human Stress, 4(4): 9-17, 1978.

Relationships of behavioral and environmental influences on the development and maintenance of hypertension have been reviewed. The evidence for such influences arises from studies in five areas, namely, retrospective correlations between emotional events and hypertensive disease; acute changes in blood pressure with stress in animals and man; chronic blood presure change following stress in animals and man; changes in blood pressure produced by behavioral modifications; and the personality patterns and particular behaviors of hypertensive subjects.

Data from these studies have been briefly but critically reviewed with emphasis on the interactive nature of the environmental, behavioral, genetic and other biological factors

which eventuate in hypertension. It is emphasized that the issue for the future is not whether behavioral factors play any role in hypertension, but rather to what extent, under what circumstances, and in which individuals behavioral factors are acting as important pressor stimuli in the overall homeostatic distortions that result in hypertension.

Shapiro, Alvin P.; Schwartz, Gary E.; Ferguson, Donald C.E.; Redmond, Daniel P.; and Weiss, Stephen M. Behavioral methods in the treatment of hypertension: A review of their clinical status. Annals of Internal Medicine, 86(5): 626-636, 1977.

Behavioral methods to lower blood pressure include biofeedback, relaxation, psychotherapy, suggestion and placebo, and environmental modification. Reported data for each method have been examined, applying the clinical pharmacologic format used to study other therapeutic agents. Most studies have been Phase I type, small numbers of subjects in acute (short-term) treatment situations. Phase II studies, controlled trials employing comparison with known effective agents, are sparse; and Phase III studies are not yet appropriate. The Phase I studies indicate blood pressure effects that are small, with minimal data about their duration and their relation to the use of pharmacologic agents. The methods are adjunctive and not alternative, while the compliance problem is similar to that with pharmacologic agents. The major difference between the methods is the ease with which they can be used. Widespread application of the nonpharmacologic methods cannot currently be recommended, but further basic and clinical research into mechanisms and outcomes is encouraged.

Simonton, O. Carl; Matthews-Simonton, Stephanie; Sparks, T. Flint. Psychological intervention in the treatment of cancer. Psychosomatics, 21(3): 226-233, 1980.

In a preliminary study of the effects of psychological intervention in the treatment of advanced cancer, it was found that patients so treated survived up to twice as long as would have been expected based on national averages. Better patient motivation, greater confidence in the treatment, and overall positive expectance are thought be have contributed to the results. An educational model has been developed employing the psychological processes used in the study, and further investigations are underway to assess the effect of the patient's mental health on the course of cancer.

Stason, William B. and Weinstein, Milton C. Allocation of resources to manage hypertension. The New England Journal of Medicine, 296(13): 732-739, 1977.

The finding that an intervention to improve patient adherence may be a better use of limited resources than maximum efforts to detect hypertension should give pause to the current nationwide exuberance for screening programs. Public programs to screen for hypertension are indicated, on cost-effectiveness grounds, only if adequate resources are available to ensure that detection is translated into effective long-term blood pressure control. The importance of problems with adherence suggests that efforts to improve long-term follow-up observation and medication adherence should receive priority. Improved access to care, patient and provider education, and provision of incentives for patient adherence all are potential means to this end. It should be stressed, however, that the arguments leading to this conclusion are based on cost-effectiveness grounds alone. Clearly, there are issues of social equity that may be countervailing, and may result in a higher priority for screening.

The possible relation between the effectiveness of antihypertensive treatment and the presence of other cardiovascular risk factors, such as obesity, serum cholesterol and smoking habits, is not examined in this analysis. A priori, one might expect that the effectiveness of hypertension treatment might be enhanced in the presence of other risk factors. No direct evidence on this point exists, however.

Weissman, Myrna M. The psychological treatment of depression. Archives of General Psychiatry, 36: 1261-1269, 1979.

In this article, 17 clinical trials are identified that test the efficacy of various psychological treatments (behavioral, cognitive, group, marital, interpersonal) alone, in comparison with, and in combination with pharmacotherapy in homogeneous samples of depressed outpatients. Despite the limitations of the available data, conclusions can be drawn about the efficacy of psychotherapy. In all of the studies reported, psychotherapy was more efficacious than a no-active-treatment control group. The studies comparing drugs with psychotherapy were equivocal. One study found psychotherapy more efficacious than drugs. One study found them about equal, and three studies found that drugs and psychotherapy had different effects. These three latter studies found that drugs effected symptoms and psychotherapy had more of an effect on social functioning, although in one of the three studies the effect for psychotherapy was not strong and in another it occurred only in patients who remained in treatment eight months and did not relapse.

The four studies examining the combination of drugs (tricyclic antidepressents) and psychotherapy found the combination additive, and no negative interactions were noted, suggesting that combination treatment was the most efficacious as compared with either treatment alone or no treatment.

These results do give reasonable direction to the treatment of ambulatory nonpsychotic, non-bipolar, moderately ill, depressed patients. Drugs and psychotherapy together maximize efficacy and seem to be the treatment of choice on the average. However, in clinical practice, many patients will not or cannot tolerate tricyclic antidepressants. Alternately, other patients do not wish to enter into psychotherapy. Under either of these conditions, the patient should not be denied treatment but should be offered the alternative. There are not sufficient data yet to say which of the psychotherapies should be used, which patients will recover quickly with no treatment, or which subtype of depressive disorder will benefit from drugs and/or psychotherapy.

Weissman, Myrna M. Combined pharmacological and psychosocial approaches in depression and in hypertension: Conceptual issues for consideration. Unpublished position paper prepared for the National Academy of Sciences, Institute of Medicine, conference on Psychosocial and Pharmacological Treatment Approaches: Issues and Interrelationships, held on May 28-29, 1980, in Washington, D.C.

In her position paper for the IOM conference, Dr. Weissman notes that pharmacotherapeutic and psychosocial approaches for medical and psychiatric disorders derive from different theoretical bases. Opinions about their relative importance for various disorders have fluctuated over the years. Decisions about optimal treatment modalities are affected by changing research evidence, and with equal frequency, by changing ideologies. Regardless of the vogue in clinical practice at any particular time, most patients receive and probably require some combination of both approaches.

Further, Dr. Weissman indicates that any discussion of combined pharmacotherapeutic and psychosocial treatment or in review of the research evidence for efficacy, three concepts should be clarified:

(1) The nature of the psychosocial intervention: Is it psychological management (including the psychological, as distinct from the pharmacological, effects of taking a pill), or it is a specific psychotherapy? If it is the latter, which one?

(2) Which of the treatments--psychosocial or pharmacotherapy--is primary and which is adjunctive? Or are the treatments coequal?

(3) What are the anticipated effects of combining treatments? Are they additive, neutral, antagonistic, or synergistic?

Dr. Weissman presents these three concepts for discussion.

Williams, Redford B. Jr. Complementarity between biofeedback and consultation-liaison psychiatry. Psychiatric Annals, in press.

In this paper, Dr. Williams reports the emergence of understanding between two clinicians that their respective approaches, biofeedback therapy and insight-oriented psychotherapy, are actually complementary. Each therapist is learning to recognize problems that may be more amenable to the type of therapy the other practices. Dr. Williams illustrates some of the mutual benefits accruing to such cooperation within a hospital setting and then describes mechanisms and procedures instituted to incorporate this orientation into clinical training and practice.

APPENDIX B

PSYCHOSOCIAL AND PHARMACOLOGICAL TREATMENT APPROACHES: ISSUES AND INTERRELATIONSHIPS

Robert J. Haggerty, M.D., Chair

Wednesday, May 28, 1980

8:30	Welcome	David A. Hamburg, M.D. President Institute of Medicine
8:45	Overview: Conceptual Issues in Combined Treatments	Gerald L. Klerman, M.D. Alcohol, Drug Abuse, and Mental Health Administration Rockville, Maryland
9:15	Hypertension	
	a. Clinical Review	Stevo Julius, M.D., Sc.D. University of Michigan School of Medicine Ann Arbor, Michigan
	b. Pharmacotherapy (Efficacy Problems, Long-term Treatment)	Adrian O. Hosten, M.D. Howard University School of Medicine Washington, D.C.
	c. Behavioral Treatment of Hypertension	Redford Williams, M.D. Duke University Medical Center Durham, North Carolina
	d. Role of Patient Attitudes and Beliefs in Patient Compliance	Marshall Becker, Ph.D. University of Michigan Ann Arbor, Michigan
10:35	Coffee Break	
10:45	Discussion	Discussion Leader: R. Brian Haynes, M.D., Ph.D. McMaster University Medical Center Hamilton, Ontario, Canada

Wednesday, May 28, 1980 (continued)

12:30	Lunch		
1:30	Depression		
	a.	Clinical Review	Robert Spitzer, M.D. New York Psychiatric Institute New York, New York
	b.	Pharmacotherapy	Philip A. Berger, M.D. Stanford University School of Medicine Stanford, California
	c.	Efficacy of Treatment (with drugs, without drugs)	Myrna Weissman, Ph.D. Institute of Medicine Washington, D.C.
	d.	Social Factors Influencing Combined Treatments	Sol Levine, Ph.D. Boston University Boston, Massachusetts
	Discussion		Discussion Leader: Myrna Weissman, Ph.D.
5:00	Adjournment		

Thursday, May 29, 1980

9:00	Diabetes		
	a.	Clinical Review (subtypes not restricted to juvenile onset)	George Cahill, M.D. Howard Hughes Medical Institute Boston, Massachusetts
	b.	Current Trends in Pharmacological Treatment	Juanita Archer, M.D. Howard University School of Medicine Washington, D.C.
	c.	Management of Maturity Onset Diabetes	John K. Davidson, M.D. Emory University School of Medicine Atlanta, Georgia

Thursday, May 29, 1980 (continued)

	d. Psychosocial Issues in Diabetes: Special Focus on Child and Adolescent Diabetics and Their Families	Allan Drash, M.D. University of Pittsburgh School of Medicine Pittsburgh, Pennsylvania
10:45	Discussion	Discussion Leader: Ruth T. Gross, M.D. Stanford University School of Medicine Stanford, California
12:00	Lunch	
1:00	Discussion: Policy Implications	

How can the collaboration between biomedical and behavioral sciences be stimulated in order to enhance knowledge for clinical care?

a. Research problems/promising topics

b. Research approaches

c. Researchers:
   - Composition of team
   - Training

d. Obstacles:
   - Academic
   - Funding
   - Interdisciplinary

3:00 Adjournment

APPENDIX C

PSYCHOSOCIAL AND PHARMACOLOGICAL TREATMENT APPROACHES: ISSUES AND INTERRELATIONSHIPS

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