COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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HEARINGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

OF THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

NINETY-FIRST CONGRESS

FIRST SESSION

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

JULY 16, 29, 30, AND OCTOBER 27, 1969

PART 13

PSYCHOTROPIC DRUGS

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July 16, 1969:
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July 29, 1969:
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October 27, 1969:
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*The testimony for May 15, 16, 17, June 7 and 8, 1967, appears in pt. 1 of these hearings; the testimony for June 27, 28, 29, July 24, and Aug. 8, 10, 1967, appears in pt. 2 of these hearings; the testimony for Sept. 13, 14, 29, and Oct. 13, 1967, appears in pt. 3 of these hearings; the testimony for Oct. 31, Nov. 9, 15, 16, and 28, 1967, appears in pt. 4 of these hearings; the testimony for Dec. 14, 19, 1967, Jan. 18, 19, and 25, 1968, appears in pt. 5 of these hearings; the testimony for Nov. 29, 1967, Feb. 6, 8, 27, 28, and 29, 1968, appears in pt. 6 of these hearings; the testimony for Apr. 23, 24, and May 1, 1968, appears in pt. 7 of these hearings; the testimony for May 2, 3, and Sept. 17, 1968, appears in pt. 8 of these hearings; the testimony for Sept. 18, 19, and 25, 1968, appears in pt. 9 of these hearings; the testimony for Dec. 11, 17, 18, 19, 1968, and Jan. 23, 1969, appears in pt. 10 of these hearings; the testimony for Feb. 19, 20, 26, 27, Mar. 13, 18, 25, and 26, 1969, appears in pt. 11 of these hearings; the testimony for May 6, 7, 20, and 27, 1969, appears in pt. 12 of these hearings.

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, JULY 16, 1969

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:40 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Dole.

Also present: Benjamin Gordon, staff economist; Elaine C. Dye, clerical assistant; and James P. Duffy III, minority counsel.

Senator NELSON. The Small Business Committee will resume its hearings now. We have three witnesses this morning, Dr. Stanley Yolles, Director, National Institute of Mental Health, of HEW; Dr. Jerome Levine, Chief of Psychopharmacology Research Branch of HEW; and Prof. Bernard Barber, chairman of the Department of Sociology, Barnard College.

I had an opening statement but, in order to move along here, I will just place it in the record.

(Senator Nelson's statement follows:)

OPENING STATEMENT BY SENATOR GAYLORD NELSON

When Aldous Huxley wrote his fantasy concept of the world of the future in the now classic "Brave New World", he created an uncomfortably, emotionless culture of escapism dependent upon tiny tablets of tranquility called soma.

It was chillingly disconcerting to read Huxley's book as it described an emotionless society populated by robot-like figures frantically hiding from reality. It was comforting, however, that the book was after all only science fiction. But in the nearly 40 years since Huxley created his classic the fiction began to read like reality. It became a prophetic insight into the kind of society we seem to be moving toward today.

In our complex society we have our soma to escape the frustrations. We find our psychotropic drugs of escape in barbiturates and tranquilizers. Over the past few years, if we can believe only a small part of what has been written, Americans have been insulating themselves from the pressures of modern life by using tranquilizing drugs in rapidly increasing numbers.

Our problem is that we don't really know very much about the tranquilizing drugs or what they are doing to us as individuals and to our society as a whole. These hearings will be seeking answers to what many thoughtful people believe to be vitally important questions. To my knowledge, no one has gathered the best information available in one place on psychotropic drugs. We hope to begin that compilation today.

The witnesses today are Dr. Stanley Yolles, Director, and Dr. Jerome Levine, Chief of the Psychopharmacology Research Branch, both of the National Institute of Mental Health, and Professor Bernard Barber, of the Barnard College, Columbia University Sociology Department.

Dr. Yolles and Dr. Levine will discuss the nature and extent of psychotropic drug usage in the United States, and Professor Barber will discuss the sociological problems that are caused by the use of the drugs.

Senator NELSON. Tomorrow's witness, Dr. Edward Pinckney, former associate editor of JAMA, Journal of the American Medical Association, will not be able to testify because of illness. His prepared statement will be submitted for the record and questions I had planned to ask will be sent to him. His answers will also be printed in the record and any questions by any other committee members will also be sent to Dr. Pinckney for his response and printed in the record.[1]

Our first witness this morning will be Dr. Stanley Yolles. Dr. Yolles, we are very pleased to have you here this morning. You may present your statement in any fashion you desire.

STATEMENT OF DR. STANLEY F. YOLLES, DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE; ACCOMPANIED BY DR. JEROME LEVINE, CHIEF, PSYCHOPHARMACOLOGY RESEARCH BRANCH, NATIONAL INSTITUTE OF MENTAL HEALTH; AND DR. MITCHELL BALTER, CHIEF, SPECIAL STUDIES SECTION, PSYCHOPHARMACOLOGY RESEARCH BRANCH

Dr. YOLLES. Thank you, Mr. Chairman. I am very happy to appear today to introduce and generally discuss psychotropic drug usage in the United States. I am accompanied today by Dr. Jerome Levine, Chief of the Psychopharmacology Research Branch of the National Institute of Mental Health and Dr. Mitchell Balter, Chief of the Special Studies Section of that Branch. Dr. Levine has a statement which he will give a little later.

In 1969, we are rapidly moving into an area of understanding of brain function. The synthesis of protein, the breaking of the genetic code, increased experiments in RNA and memory functions, increased understanding of chemical functions within the brain, and the effects of drugs on brain and body functions, the understanding of learning behavior which has progressed in animal studies to the point where animals can be conditioned to control bodily functions—all of these lead toward the artificial alteration of human behavior.

We have arrived at the point where the uncontrollable is becoming subject to control. The mission of the National Institute of Mental Health is the improvement of the mental health of the people of the United States. From its inception the mental health program has supported the development of research, the training and production of manpower in the mental health field, and the initiation and expansion of community-based treatment services. One of the primary purposes of the NIMH, therefore, is to support the search for new knowledge in the field of drugs as in many others.

In the 20 years of its existence, the NIMH has strongly stimulated research in psychopharmacology and the utilization of drugs in treatment. This year, the Institute is supporting more than 300 projects

[1] The statement of Dr. Edward R. Pinckney, former associate editor of the Journal of the American Medical Association, appears in pt. 14.

relating directly or indirectly to psychopharmacology in the amount of $12 million. During these years the impact which the large-scale introduction of new psychotropic or psychoactive agents has had on hospital, community, and private practice of psychiatry has been enormous.

Just 15 years ago, psychiatry possessed no clearly useful drug treatment—either for schizophrenia or any of the other forms of mental illness. Today, in large measure through the Institute's efforts, the treatment arsenal of the clinical psychiatrist is a powerful one. Collaborative hospital studies—widely hailed as models of clinical research—have helped define the relative value of specified drugs. Drugs have shortened the patient's hospital stay, and they have allowed treatment and rehabilitation in the community of an increasing number of the mentally ill without serious disruption of family relationships and work.

A measure of our progress——

Senator NELSON. May I interrupt a moment? Are these drugs that were discovered through the research of NIH?

Dr. YOLLES. Many of them have been. Many of them are not. But all of them have been involved in grant-supported studies where we have evaluated their efficacy in the treatment of various mental illnesses. This has been going on since early 1948. As a matter of fact, one of the earliest grants of the NIMH dealt with the effect of drugs on human behavior.

Mr. GORDON. Dr. Yolles, do you know if any of these drug efficacy studies financed by NIH have been used to support the efficacy requirements in the New Drug Applications of the various drug firms?

Dr. YOLLES. If you do not mind, I would rather have that answered by Dr. Levine, who is more knowledgeable about that specific subject than I.

Dr. LEVINE. Yes. The studies which we support have been used as evidence in NDA applications to the FDA. Most of the psychopharmacologic agents which have come on the market recently have been studied through our early clinical drug evaluation units program and the information from those studies I assume have been included in NDA applications.

Senator NELSON. You may proceed.

Dr. YOLLES. A measure of our progress is reflected in the continuing decrease in the number of Americans residing in the Nation's mental hospitals. Thirteen years ago, that number was well over one-half million. Today, after more than a decade of steady advances in research and treatment, there are 401,000—a reduction of nearly 30 percent. Last year alone saw a decline of 25,000 patients or 5.9 percent, including, for the first time, a decrease of 2 percent in the crucial 15–26 age group. Had the rising mental hospital population seen before 1955 gone unchecked, we would today be confronted by 731,000 patients in our mental hospitals—or nearly twice the actual number. This reduction in hospital patient population represents a saving to the States and communities of some $5 billion in patient care and capital improvements.

I mention these developments only as background. Other witnesses, I am certain, will discuss specific areas of drug use. I would like to

spend my time this morning in discussing what has truly become a national concern resulting from the use and abuse of drugs by the people of the United States. Certainly, this is the concern of research investigators and clinicians, as well as those who translate social policy into public policy.

It is one thing to reverse situations in an illness, but the ability to change what has been considered normal in order to improve the norm is something else again. The choices among evils, dangers, and eventual good resulting from such manipulations can and will be made; but the questions are by whom and for what purpose?

In both clinical and experimental studies, behavioral scientists have not been satisfied simply to refer to a behavioral change brought about by a compound. They also want to state whether or not this change is desirable or undesirable.

Making these value judgments requires either some general understanding of health itself, or favorable individual adjustment, or the acceptance of certain value standards from some outside frame of reference.

It must be pointed out that there are other drug-using cultures that lie outside the domain of conventional drug use and outside the healer's purview. This would suggest that there may be something in common among the various kinds of drug use.

In order to determine such values, a conceptual theory which shows how values are established by systems—more inclusive than the individual or the examiner—is essential. This approach may be characterized as a wedding of clinical pharmacology and social psychology, a union which some have referred to as sociopharmacology.

To what extent would Western culture be altered by widespread use of tranquilizers? Would Yankee initiative disappear? Is the chemical deadening of anxiety harmful? To what extent are the Peyote cultures different because of the use of mescal, or Central American tribes unique because of their hallucinatory mushrooms?

The use of drugs may indicate changing attitudes toward illness and what the quality of life should be. For example, one thesis is that "suffering is going out of style"; that it is no longer the virtue it once was throught to be—or at least stated to be. If we examine the purposes for which drugs are given and taken, almost all Americans would agree that taking a psychotropic drug to offset severe psychiatric symptomatology is entirely legitimate. But how about the use of drugs for the enhancement of performance? For example, should athletes take drugs which will enhance their prowess on the track? Should truck drivers take stimulants so that they can drive for longer periods? Should fatigued executives take drugs which will allow them to enjoy the theater at night or be the life of the party at the end of an exhausting day?

In terms of social consequences there is a cost-benefit ratio associated with all drug usage—be it licit or illicit. The cost-benefit question applies to the use of drugs versus other coping mechanisms, the use of one drug versus another, and the use of even very dangerous drugs in an otherwise hopeless situation. A person can seek relief of the same problem inside or outside the medical system and thus cost-benefit thinking can also be applied to the potential narcotic drug addict.

To the extent that the individual cannot solve his problems within the legitimate societal system for personal, economic, social, or cultural reasons, he may appear in some other system where he gets a drug that meets his needs. In the case of the narcotic addict, obviously, the long-term cost-benefit ratio is much too high and in fact leads to the destruction of otherwise potentially productive lives.

Concern over the use of drugs other than narcotics is highlighted by nationwide college surveys revealing that approximately 20 percent of college students, and more lately—we have reason to believe that this should be about 35 percent nationally—have used marihuana one or more times, and that roughly 8 percent have used LSD or other hallucinogenic drugs: data from one university show a dramatic rise in the use of marihuana—from 21 percent of students in 1967 to 57 percent currently, with a predicted level of 70 percent during 1969 and 1970—although most students included here use marihuana only once or twice, with only a small proportion being chronic users.

Senator NELSON. Who did the survey?

Dr. YOLLES. This was done under support from the National Institute of Mental Health by investigators on the west coast.

Senator NELSON. NIMH?

Dr. YOLLES. It was done by Dr. Blum on the west coast, supported by the National Institute of Mental Health.

The growing dependence on both sleeping pills and stimulants also poses an increasing threat to the Nation's health. The problem of drug abuse is increasingly apparent among children at the junior high school level and, because of the potency of "fads" in early adolescence, the problem begins to affect students in the upper grades of elementary school as well.

What standards of social behavior do we wish to maintain? We already have an example of broad social action and reaction to a drug in our experience in the United States with LSD.

Society was suddenly faced with a monster when a heretofore esoteric chemical became a social problem. Social decisions and public policy were made too late to forestall events of which we have not seen the last, since both social and public policies in this regard are still ambivalent.

With Hollister, who wrote in Chemical Psychoses, I can only regard the psychedelic drug movement as a new brand of anti-intellectualism.

Just as the ancients were fearful of the unknown mysteries of nature, many people today are fearful of the information explosion which is so difficult to understand and assimilate.

Fear of reality, known or unknown, has always been the major impetus for seeking escape through drugs. The prophets of the new drug cults are convinced that modern man needs to think less and feel more. Drug taking is a sensual, not an intellectual, experience. Indeed, the title of a recent psychedelic happening starring the cult's leader was appropriately titled "The Death of the Mind."

Psychedelic drugs are solvents of the logical, formal mind ordinarily used by intellectuals; and words and numbers are supplanted by random, unorganized, and often meaningless, images. As the prospective Christ of the cult has so aptly described it, LSD is a "powerful, non-

verbal, metaintellectual agent." Clearly, the escape represented by these drugs involves abdication of the intellect.

The emergence of LSD into the public consciousness as either a threat or a boon to mankind is neither the worst nor the best of happenings, as humans learn to alter their own behavior artificially. It is, however, a good example of what the future can be expected to produce and there is more to come.

As scientists involved in drug phenomena, we are in somewhat the same dilemma which faced the nuclear physicists who split the atom. We have their example before us, and we should profit by it. No amount of breast beating and cries of "mea culpa" will put the stopper back in the pill bottle, any more than it put the old-fashioned atom together again.

The judicious use of mind-changing drugs may require a simultaneous awareness by the investigator in the laboratory and the political and social activists in the community. The fact that this has been a rare happenstance in the past makes it no less imperative.

Science and humanism can and will march together in the future; for, as Lord Horder write in The Appeal of the Common Man, "Surely, science was made for man, not man for science."

To make medicine a complete science in the service of man we must see that it infiltrates this important and now more clearly perceived sphere—as yet largely neglected—of social need.

This sphere lies between that in which the diseases of the individual patient are presented and treated by the individual doctor and the sphere in which the preservation of the public health is achieved by the methods of the State health officer.

The manipulation and control of human behavior by drugs cannot, in the future, be left to investigators isolated in the laboratory. The people have already proved that drugs developed in the laboratory are self-prescribed by the general population. Neither science nor law has yet learned to control this situation; and, as a result, the National Institute of Mental Health is faced with a double responsibility.

Mr. GORDON. Doctor, what do you mean by the statement: "People have already proved that drugs developed in the laboratory are self-prescribed by the general population"?

Dr. YOLLES. Well, LSD is a good case in point, though there are others. These drugs were developed in the laboratory for laboratory use. They were research drugs. Their efficacy in effecting changes in behavior were being investigated but they escaped from the laboratories is the best way I can put it. Clandestine laboratories were developed to produce LSD. It was used illegally throughout the country by segments of the population.

The same is true for the informal or illegal use of the stimulant drugs; amphetamines, for example. We have a clear example of this in Sweden where the drugs were introduced for strictly medical purposes as central stimulants but were soon picked up and used illegally throughout the country for production of what is called a "high."

The primary purpose of the NIMH is to support the search for new knowledge—in the field of drugs as in many others. It has also, however, been charged by the Congress with a major responsibility to assist in the control of the abuse of drugs, today, at the same time that it helps to develop the drugs of tomorrow.

It is to be expected that the use of drugs in the next 10 years will increase a hundredfold. It is necessary, therefore, to develop effective processes to control their abuse.

One is not dealing here with a simple, unitary phenomenon. Drug use and abuse is a health, legal, social, economic, and moral problem. These are complex phenomena in which the major interacting factors are the characteristics of the drug used, the characteristics of the person using the drug, and the characteristics of the society within which the drug is used.

It is evident that there will be no simple solutions to problems posed by drug use. Substantial effort must be devoted to discovery of new knowledge and to development of imaginative and innovative approaches and testing of these.

Achievement of the total range of objectives for a program to deal with the drug-abuse problem is dependent not only on the development of new knowledge but, perhaps just as critically, on the ability to bridge the research utilization gap by rapidly feeding these findings into the treatment system, and having the necessary trained manpower to work in this area. The responsibility of the medical community at this time is to accelerate the kind of research which will yield the basic knowledge required for a more rational approach to the problem.

Dr. Robert Livingston has put it most aptly:

> These problems are historically recent and are still changing in their emergent form. They are inadequately understood and patently resistant to easy solution. Problems that resist solution may be insoluble; yet, if you will believe the history of science, it is most likely that the means of solution being attempted are inadequate. In the absence of fresh insight, sheer devotion is powerless to do more than provide momentum for our shortcomings and our ignorance. We must seek out that which can lead to a more fundamental level of understanding.

Only through research can we develop more fundamental understanding.

Drug use and abuse touches our deepest values, hopes, aspirations, and fears. It is an emotionally charged area. For every false prophet advocating drug use there is a viewer-with-alarm prone to sensationalism and to advocating simplistic solutions.

It is the task of the National Institute of Mental Health to mount the programs needed to deal flexibly with the many problems of drug use and abuse. As the problem is complex and changing, so must be the strategies designed to understand and cope with it.

I would like to close with two quotes that are most appropriate to this subject.

The first is a thought that Oliver Wendell Holmes expressed over 50 years ago in an address to the Harvard Law School:

> An ideal system . . . should draw its postulates from science. As it is now, we rely upon tradition, on vague sentiment, on the fact that we never thought of any other way of doing things as our only warrant for rules which we can enforce with as much confidence as if they embodied revealed wisdom.

The second is an appropriate philosophy for persons who work in this field, beautifully expressed by Robert L. Duffus, one of the editors of the New York Times:

> We need humility among the so-called leaders of opinion. We need tolerance, tolerance that arises from a scientific recognition of the high percentage of

fallacy and irrationality in our own beliefs. The wisest man at this stage of the world's affairs is he who knows that none of us is wise.

Senator NELSON. Thank you, Doctor.

What is the jurisdiction and authority of NIH in the control of drugs?

Dr. YOLLES. Let me clarify a point, Senator. The National Institute of Mental Health is no longer a part of the NIH. We have been separated off for a period of 2½ years.

Senator NELSON. You are not a part of NIH in any way?

Dr. YOLLES. No, sir; we are not. The area of jurisdiction of the National Institute of Mental Health in terms of the mental health program can be stated to be a total program. We are responsible—we are one of the few programs in the Public Health Service that is a total program, in that we are responsible for all elements of the program ranging from basic research through applied research, the production of manpower both for research and service, for demonstrations, for construction of mental health facilities for treatment and rehabilitation, and for the staffing of such facilities. So that in the area of psychotropic drugs we have a major responsibility both for leadership to see that these drugs are produced—the necessary drugs are produced—to treat the mental illnesses and we have a supporting service responsibility to people working in the field to provide information and services and help in any way we can, through consultation, in furthering their programs.

Senator NELSON. If a new drug or psychotropic drug of some kind comes along, who has the authority to classify its use, to decide whether——

Dr. YOLLES. The legal decision for drugs other than those controlled, which are considered controlled and dangerous drugs, rests with the Food and Drug Administration of HEW. Those drugs which fall in the classification of stimulants, depressants, narcotics, marihuana, that classification, now rests with the Bureau of Narcotics and Dangerous Drugs in the Justice Department.

Senator NELSON. How long has that authority rested there?

Dr. YOLLES. I suppose it is about a year now. It was changed by the Congress in the Reorganization Plan No. 1 of last year.

Senator NELSON. Previously HEW had that jurisdiction?

Dr. YOLLES. In regard to all of the so-called dangerous drugs, controlled substances, stimulants, depressants, LSD, et cetera, this rested with the FDA in HEW; yes. This was transferred to the Justice Department last year.

Senator NELSON. May I ask you a question to which you may not wish to respond? I, myself, am curious as to whether Justice is the proper place for making such a determination. In your opinion, where should that responsibility lie? Was it a mistake of Congress, in your judgment, to change it?

Dr. YOLLES. Well, the Congress in its wisdom made its decision last year.

Senator NELSON. Everything we do is not necessarily wise.

Dr. YOLLES. Well, this field of use of drugs and abuse of drugs has a long history, and there have been a number of very eminent commissions established over the years to look into these very problems

which we are trying to solve today. One of the most definitive ones was the Prettyman Commission of about 5 years ago, which recommended a whole series of changes in the way the Federal Government administered the control of the use and abuse of drugs.

Now, many of the recommendations of the Prettyman Commission have been implemented and we at the NIMH have been endeavoring to implement as many of them as we possibly can. Among them was a clear definition and statement of principle which we supported at that time and continue to support, that all of the determinations which are strictly medical should be made by that part of the Federal Government which has the medical responsibilities—in other words, the Department of Health, Education, and Welfare.

The Commission also stated that all of those functions which are purely control functions and law enforcement functions should be transferred from the Department of HEW to the law enforcement agencies, in this case the Department of Justice.

Now, we have always supported that principle. We still do. And I do personally, as a physician, feel very strongly that those decisions which are medical decisions should be made by medical persons.

Senator NELSON. Well, what resources does Justice have to make these medical decisions under the current law?

Dr. YOLLES. I believe the Justice Department has an advisory group which they work with and they also do work with the Department of Health, Education, and Welfare. We act as consultants to them. But the final decision is that of the Attorney General.

Senator NELSON. Thank you very much, Doctor, for your very fine statement.

Senator DOLE. Mr. Chairman——

Senator NELSON. Excuse me. I did not see you come in, Senator.

Senator DOLE. I think perhaps Dr. Levine covers this in his statement, but I am a novice in this area. I am not certain that I understand just what we talk about when we talk about psychotropic drug usage. If you cover that, I will not take your time.

Dr. LEVINE. Yes, I will cover that.

Senator DOLE. I think I generally know what drugs we are talking about. I am not certain. Then, certainly, on page 2 of your statement you talk about psychopharmacology and about some 300 projects relating directly or indirectly to psychopharmacology. Now, would you give me some examples of what we are spending $12 million on?

Dr. YOLLES. These projects are related primarily to basic and applied research on the efficacy of drugs as used in treatment of the mental illnesses, such as schizophrenia.

For example, roughly half of the hospital beds in the United States are occupied by mentally ill patients. About half of those beds are occupied by schizophrenics. This is a chronic mental illness, the most severe of the mental illnesses, and to date one of the most resistant to treatment. Consequently, it has a very high priority in the efforts of the National Institute of Mental Health in finding means for treatment, adequate treatment, and we have been quite successful.

We have not achieved any cures, speaking as a professional at this point, but we have been able to release many schizophrenics from hospitals and have them adjust in the community. This is a result of

the development of drugs which are tailored to the treatment of specific kinds of mental illnesses, in this case specific kinds of schizophrenic syndromes. Some drugs work well in certain cases of schizophrenia, others work better with other types of schizophrenia.

The development over the years and the support of research to develop these drugs has been a function of the National Institute of Mental Health. Extending from that point, in the treatment of schizophrenia, for example, we have been able to support and come to the point where now we can satisfactorily maintain chronic schizophrenic individuals in the community through the use of drugs and keep them from returning to the State hospitals and filling up those beds I spoke about.

This also extends to the treatment of the depressions. For example, the development of agents which will alleviate the depressions. The emotional problems, for example, of hyperactive children. Drugs tailored to improving the adjustment of the aged in terms of their mental problems, and to make them more amenable to treatment. I could go on for a long period of time. All of these are subjects of a good deal of psychopharmacology research. This has been a major concern of the National Institute of Mental Health—not the total concern but certainly one of our major interests has been in the treatment and cure of mental illnesses.

Senator DOLE. You referred to development of drugs—do you carry on the developments yourself?

Dr. YOLLES. We do this under a number of different systems. We occasionally do it by contract, more often by grant to investigators around the country.

In many cases in terms of evaluating the efficacy of a new drug which has come on the market we support collaborative studies. This technique has been one of the singular succcesses in the Institute's programs. This collaborative program enlists the aid of a large number of individual clinics or hospitals who work together using the same protocol and same drug. We can then pool the results and establish the efficacy of the drug.

Senator DOLE. Do you have any contact with the Food and Drug Administration?

Dr. YOLLESS. Yes, quite a bit.

Senator DOLE. Maybe Dr. Levine will go into that.

Thank you very much.

Senator NELSON. Dr. Levine, you may present your statement in any way you desire.

Dr. LEVINE. Mr. Chairman, I am pleased to be here today to present to you and the subcommittee some information on the extent and nature of psychotropic drug use in the United States. My prepared presentation is fairly long, detailed, and technical. However, after having been associated with work to develop information in this area over the past 3 to 4 years, I am convinced that a thorough consideration of the issues is important.

A proper understanding of the drug-prescribing process requires an intimate knowledge of the patient being treated, including such things as age, diagnoses, previous medical history, prior exposure to psychotropic drugs, and the circumstances which brought the patient into

treatment. It is also important to know how long patients are maintained on drugs, how frequently they return to the physician, what other drugs may have been prescribed by this or some other physician, and so on. Detailed longitudinal data on patients and physicians is difficult to obtain and seldom, if ever, available on a national basis.

Senator NELSON. Are you talking about all drugs here?

Dr. LEVINE. Yes. This will hold true for all drugs. We will present information on psychotropic drugs specifically.

More commonly available are data on physicians' prescribing behavior which cover a limited time period and provide only limited information on the patient, usually no more than age, sex, and current diagnosis. In those instances where longitudinal data on prescribing behavior are available, it is seldom possible to follow individual patients over time. Thus, most data currently available on prescribing behavior must be interpreted with caution.

THE NATURE OF PSYCHIATRIC ILLNESS

Before proceeding to a discussion of the extent of drug use in the treatment of psychiatric disorders, it is important to point out that the etiology of the major psychiatric disorders is essentially unknown. Psychiatric disorders, therefore, are descriptive constellations of psychological symptoms or psychopathology shown by an individual. In some cases the psychopathology may be observable by others in the behavior of the individual, but in other cases it is only by the patient's description of his subjective experience that the disorder is detected.

For example, in some patients with depression we may observe that the individual's movements and thinking are slowed. There may be a loss of appetite evidenced by lack of eating and an inability to have normal sleep characterized by early morning awakening. If the patient is asked, it is likely that subjectively he will report feeling blue and unhappy, a loss of energy and interest in his surroundings, feelings of guilt, and perhaps even a desire to be dead. The point to be made is that the diagnosis of mental disorders is difficult because the etiology is unknown, no objective laboratory tests exist, and heavy reliance is placed on the subjective report of the patient. Treatment, therefore, is directed for the most part at relief of subjective symptomatology and the guidelines for when medication should or should not be used are not as clear and definite as, for example, indications for the use of antibiotics, diuretics, or antihypertensive agents. Psychotherapeutic agents act by unknown mechanisms to reduce the level of symptomatology of patients but do not, to our knowledge, directly affect the causative agent of the illness in the same manner as antibiotic agents attack the microbes which cause infectious diseases.

CLASSIFICATION OF PSYCHOTROPIC AGENTS

For purposes of orientation to our presentation, I would like to present a classification of psychotropic drugs which is based primarily on clinical use of these agents and secondarily on their chemical structure. Other classifications based on pharmacological action or other parameters are possible and perhaps more comprehensive, but we have

selected this simpler, operationally defined classification as best serving present needs.

Psychotropic drugs are defined as those substances which have their main or principal effect on mood, thought processes, or behavior. The first chart—I have a blowup over here on the table—shows six classes of psychotropic agents; namely, major tranquilizers, minor tranquilizers, antidepressant agents, stimulants, sedatives, and hypnotics.

(The chart referred to follows:)

CHART 1

MAJOR CLASSES OF PSYCHOTROPIC DRUGS

Major tranquilizers:
- Phenothiazine derivatives (Ex.: chlorpromazine, thioridazine).
- Butyrophenones (Ex.: haloperidol).
- Thioxanthines (Ex.: thiothixene, chlorprothixene).

Minor tranquilizers:
- Substituted diols (Ex.: meprobamate, tybamate).
- Benzodiazepines (Ex.: chlordiazepoxide, diazepam, oxazepam).
- Miscellaneous (Ex.: hydroxyzine, buclizine).

Antidepressants:
- Tricyclics (Ex.: imipramine, amitriptyline).
- MAO inhibitors (Ex.: isocarboxazid, phenelzine).
- Others (Ex.: combination of amitriptyline and perphenazine).

Stimulants:
- Amphetamines (Ex.: dextro-amphetamine, methamphetamine).
- Others (Ex.: methylphenidate).

Sedatives:
- Barbiturates—long- and intermediate-acting (Ex.: phenobarbital, butabarbital).
- Others (Ex.: bromisovalum).

Hypnotics:
- Barbiturates—short-acting (Ex.: pentobarbital, secobarbital).
- Nonbarbiturates (Ex.: gluthethimide, ethchlorvynol).

Dr. LEVINE. The major tranquilizers, of which the phenothiazine-related compounds compose the bulk of the class, were introduced into widespread use in the mid-1950's. They are primarily thought of as agents useful in the treatment of the major or most severe psychiatric disorders; namely, the psychoses. The class of drugs is, therefore, also known as antipsychotic agents. Their use in schizophrenic patients leads to a decrease in agitation, thought disorder, hallucinations, and delusions.

The most common side effects include drowsiness—usually transient in nature—extrapyramidal symptoms such as are seen in Parkinson's disease, and orthostatic hypotension, or lowered blood pressure. Drug dependence of a psychological of physiological type leading to addiction does not occur. Rather rare toxic effects of agranulocytosis and liver damage occur and prolonged chronic use in high dosage has led to increased skin pigmentation and eye opacities which fortunately do not usually result in impaired vision.

The minor tranquilizers also referred to as antianxiety agents became available in the early and mid-1950's. These drugs are thought to represent an advance in the treatment of disorders which have a large

anxiety component because they alleviate anxiety without inducing the degree of drowsiness which other agents such as barbiturates cause. While at first they were not thought to produce physiological dependence and true addiction, it is now clear that, with prolonged usage and/or high dosage, physiological dependence of the type known to occur with barbiturate drugs is produced. This is most clearly seen with several compounds of the substituted diols subclass.

The antidepressant class of drugs was introduced a few years after the major and minor tranquilizers. Imipramine, a drug from the tricyclic series, was first investigated as a potential major tranquilizer but instead was found to be effective in the treatment of depression, especially of the endogenous type. Side effects are generally mild and include dry mouth, blurred vision, and orthostatic hypotension. If tricyclic antidepressants are given concurrently with drugs from the MAO—monoamine ovides inhibitor—subclass, there have been occasions when there was a marked drug interaction and a toxic state leading to death occurred. It is also known that eating foods which are high in certain amines, such as tyramine, while receiving MAO inhibitors can lead to a marked hypertension resulting in a cardiovascular accident and death. Physiological dependence does not occur with this class of drugs.

The stimulant class of drugs of which amphetamines constitute the bulk are primarily used in the treatment of obesity but have marked central nervous system effects in increasing activity and reducing fatigue, and are used to some extent n the treatment of symptoms of depression. These drugs have recently been subject to marked illicit use and when taken in high enough quantities lead to a psychotic paranoid state. Psychological dependence and minor physiological dependence have been demonstrated.

The sedative class of drugs is primarily composed of the long- and intermediate-acting barbiturates. They have been available for a long period of time and were used extensively as antianxiety and calming agents before the introduction of the major and minor tranquilizers. Drowsiness is a common side effect and physiological and psychological dependence does occur.

The hypnotic class of drugs is used for the treatment of sleep disturbances. Both the barbiturate and nonbarbiturate subclasses, when taken in large amounts, produce marked intoxication and depression of respiration which can result in death. Likewise, they produce marked psychological and physiological dependence. The withdrawal syndrome seen after stopping these drugs in physiologically dependent individuals is extremely severe and can also lead to death.

These, briefly, are the classes of drugs we will deal with in today's presentation.

A MODEL AND SOURCES OF DATA NECESSARY TO CHARACTERIZE THE NATURE AND EXTENT OF PSYCHOTROPIC DRUG USE

At the time we were invited to testify, it was indicated that a major focus of these hearings was to try to ascertain whether psychotropic drugs were being overprescribed and overused in the United States. Certainly this concern has been expressed frequently in the mass media

and is an important issue to consider. Unfortunately, this issue is more easily raised than answered if conclusions are to be documented and factual rather than opinionated and judgmental. For the past 3 years Dr. Mitchell Balter, Chief of the Special Studies Section of the Psychopharmacology Research Branch, has been formulating precise questions about the extent and character of psychotropic drug use and has been collecting the extensive data that are required to provide accurate and comprehensive answers to these questions at the national level. The work is still in progress but some answers are currently available and will be presented today.

The critical questions are fairly simple: To whom are psychotropic drugs being prescribed? For what purposes are psychotropic drugs being prescribed? In what manner are they being prescribed, and, finally, in what manner are they being used by the patients?

Several sources of data and types of information are needed to answer these questions satisfactorily. In our working model the physician is viewed as a gatekeeper who issues a prescription to a patient who then has a number of options. He may go on and fill that prescription at a drugstore or elsewhere, or he may not. He may not use all the medication provided in the original prescription or he may not obtain all the refills permitted. Given the range of possibilities, it becomes necessary to study the prescribing behavior of the physician and to gather accurate information on drugstore outflow. It is also crucial to obtain information directly from patients, former patients, and others in the general population who are using psychotropic drugs, whatever the source. This requires a broadly based survey approach in that the individual can move about from place to place, can change physicians, can borrow drugs, or buy them licitly or illicitly without consulting a physician. Without obtaining information on the pattern of use directly from the individual, the true significance and character of the drug use cannot be assessed. Through a series of studies supported by contracts and grants and analyses conducted within the Institute, a large body of information on physicians' prescribing, drugstore outflow, and patients' and others' use of drugs is being steadily developed. It is from these carefully coordinated ongoing activities that the data to be presented today has been derived.

EXTENT OF USE OF PSYCHOTROPIC AGENTS

Initially, let us consider a representative period and characterize prescription drug use during a single year. In 1967 it is estimated that a total of 1.1 billion prescriptions for drugs of all types were filled in drugstores throughout the United States at a retail cost of $3.9 billion. Psychotropic drugs, as previously classified, made up about 17 percent of this total or 178 million prescriptions at a consumer cost of $692 million. Forty percent of this total was accounted for by new prescriptions; 60 percent by refills. These figures for psychotropic drugs do not include those preparations which are mixtures of a psychotropic drug plus a nonpsychotropic drug such as an antispasmodic agent, or a coronary vasodilating agent. If these combinations were added, the percentage accounted for by psychotropic drugs might rise to almost 25 percent of all prescriptions. Parentheti-

cally, I might add that at this point we are not considering drugs sold over the counter—so-called OTC—for the same indications as prescription psychotropic agents. We will return to these OTC preparations later.

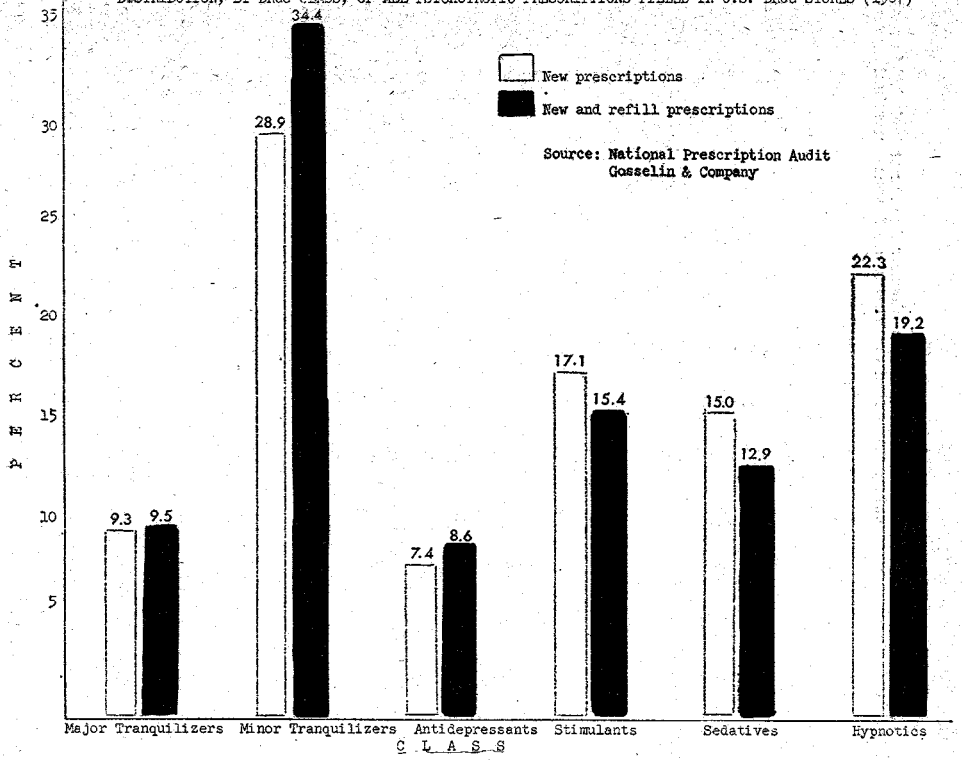
Chart 2 [1] shows the percentage of all psychotropic prescriptions filled in U.S. drugstores attributable to each of the major drug classes in the year 1967.

(Chart 2 follows:)

[1] In this and subsequent charts and analyses prochlorperazine is not included in the major tranquilizer class since it is mainly prescribed for treatment of gastrointestinal dysfunction.

CHART 2

DISTRIBUTION, BY DRUG CLASS, OF ALL PSYCHOTROPIC PRESCRIPTIONS FILLED IN U.S. DRUG STORES (1967)



Dr. LEVINE. The left bar in each case refers to the percentage of all new prescriptions accounted for by the class, and the right bar shows the percent of new and refill prescriptions—that is, total prescriptions—for the class. In that year there were 54.1 new prescriptions for psychotropic drugs filled for every 100 of adult population.

Senator NELSON. What was that figure?

Dr. LEVINE. 54.1 new prescriptions for psychotropic drugs filled for every 100 of the adult population. The analogous figure for total psychotropic drug prescriptions, both new and refill, was 133.1. It should be pointed out that these acquisitions are obviously not equally distributed per person, meaning that 1.33 prescriptions were not given to every individual adult, but some individuals got many more than 1.33 prescriptions.

From this chart it is clear that the minor tranquilizers and hypnotic drugs are the classes acquired most frequently.

Let us now turn our attention to trends in drug acquisitions over the past 10 years.

Between 1958 and 1967 the number of new psychotropic drug prescriptions filled in U.S. drugstores rose from 42.7 million to 70.6 million, an increase of 65 percent. During that same period, new prescriptions for all other drugs increased by 35 percent. However, it should be pointed out that a marked increase in new psychotropic drug prescriptions observable in 1966 is largely artifactual, due to the passage of the Drug Abuse Control Amendments of 1965. These amendments set limitations on the number of refills for sedative, stimulant, and hypnotic drugs and this resulted in a sharp increase in new prescriptions. This was so because you could not give more than five refills on any one prescription and your prescription totally could not extend more than 6 months, and, therefore, more new prescriptions would be written.

From 1958 to 1965, in the 8-year period preceding the legislation, the rate of increase for new psychotropic drug prescriptions was 31 percent as opposed to 21 percent for all other drugs.

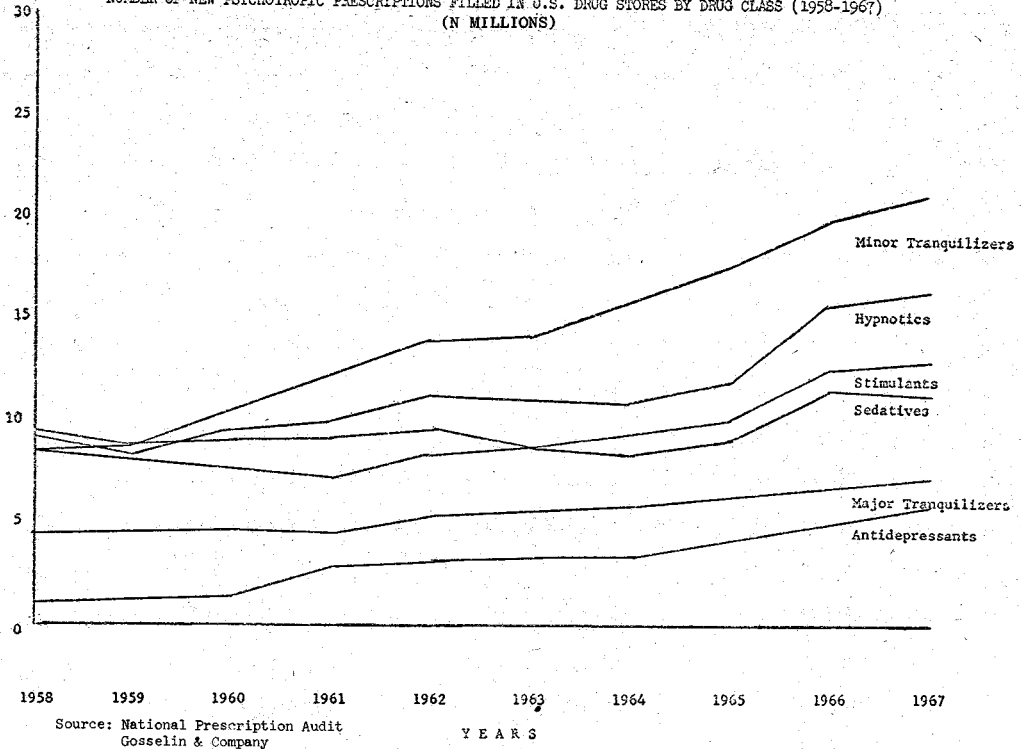
Because of the passage of the Drug Abuse Control Amendments of 1965, current trends for psychotropic drugs are better represented by the combined total for new and refill prescriptions. Between 1964 and 1967, the years for which we have data available, the total number of psychotropic prescriptions filled increased by 16 percent, from 149.1 to 173.6 million, while those for all other drugs rose by 26 percent. Thus, in recent years, prescriptions for psychotropic drugs have advanced at a slower pace than for all other drugs.

When trends for new psychotropic drug prescriptions are broken down by major drug class, and up to this point I have been talking about psychotropic drugs as a unit, when we now break them down by drug class, it becomes apparent that the large overall increase—31 percent—that occurred between 1958 and 1965 is mainly attributable to minor tranquilizers. If you look at chart 3 either in the handout or up here, this can be seen.

(Chart 3 follows:)

CHART 3

NUMBER OF NEW PSYCHOTROPIC PRESCRIPTIONS FILLED IN U.S. DRUG STORES BY DRUG CLASS (1958-1967)
(N MILLIONS)



Source: National Prescription Audit
Gosselin & Company

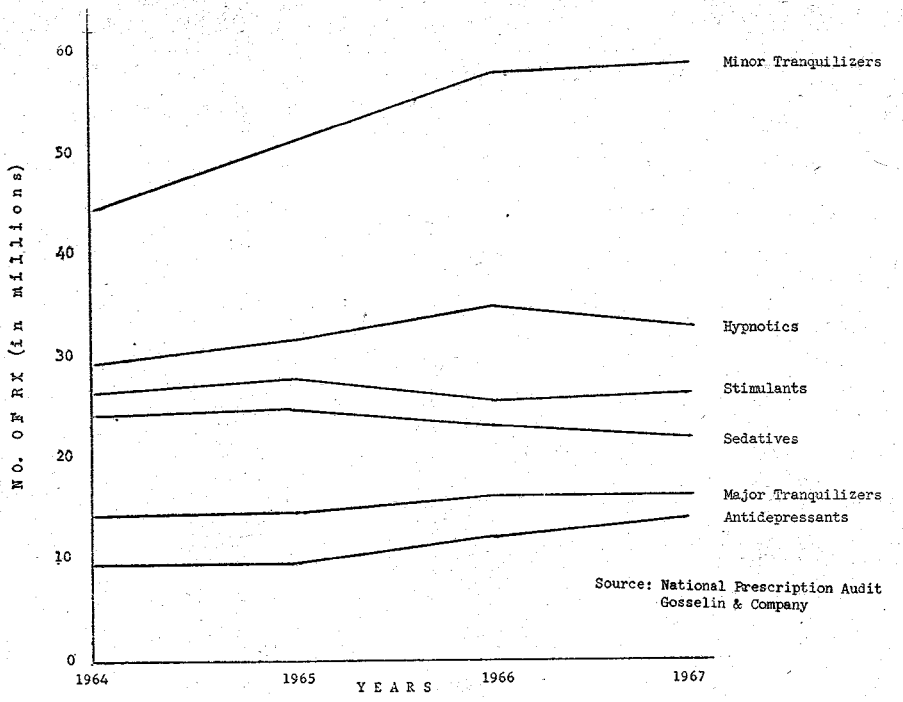
Dr. LEVINE. By 1967, the last year on which we have complete data, the number of new prescriptions for minor tranquilizers filled in U.S. drugstores had risen to 20.4 million. From 1958 to 1965, the 8-year period preceding enforcement of the drug abuse legislation, new prescriptions for minor tranquilizers were advancing at the expense of the sedatives, mainly the barbiturates.

Growth rates for the individual classes of psychotropic drugs were also differential between 1964 and 1967. In terms of new and refill prescriptions, minor tranquilizers have shown the greatest rise, from a total of 45.1 million in 1964 to 59.7 million in 1967. This is shown in chart 4.

(Chart 4 follows:)

CHART 4

NUMBER OF NEW AND REFILL PSYCHOTROPIC PRESCRIPTIONS FILLED IN U.S. DRUG STORES BY DRUG CLASS (1964-1967)



Dr. LEVINE. Total prescriptions for antidepressants also rose sharply from 9.4 to 14.8 million, but their percentage of all psychotropic drug prescriptions remains small. The total number of acquisitions for the stimulant and sedative classes has actually declined while major tranquilizers have remained relatively stable. Hypnotics have shown a small increase in total acquisitions over these years. Up to this point we have been talking about prescriptions.

Let us now turn our attention from the number of prescriptions filled to estimates of the actual number of adults—over 18 years of age—who have used psychotropic drugs in the United States. Information of this type is mainly available from probability-based survey studies in the general population. In one such study, performed in October 1967 by the Social Research Group of the George Washington University, respondents were asked the following:

Here are three questions about the types of pills that people use. For each of the three types of pills listed below, circle how recently you have used that type.
(a) Pills that help you sleep at night, like Sleep-Eze, Phenobarbital, and the like;
(b) Pills to calm you down and keep you from getting nervous and upset—pills that are often called tranquilizers, like Equanil, Compoz, and the like;
(c) Pills that pep you up, help you stay awake, make you more alert and less tired, that help you lose weight—pills that are often called stimulants, like Dexedrine, Dexamyl, No-Doz, Preludin, and the like.

Results of this national survey indicate that approximately one out of four adults have taken a psychotropic agent in the past 12 months and about one out of two have taken a psychotropic at some time in their lives.

Senator NELSON. Are you talking about those who get it both by prescription and illegally or——

Dr. LEVINE. No. I am talking about those who get it by prescription and over the counter.

Similar surveys performed in 1967, both national and regional, have yielded almost identical results. It is important to point out that the results of this survey, and you anticipated the point, include the use of over-the-counter—OTC—preparations as well as prescription psychotropics. When I answered by saying no, I meant that we are not talking about the large bulk of illicit use but we did sample from the general population and, to the extent that someone may have obtained one of these drugs from their mother, their daughter, their friend, they would be included. I do not think we want to call that necessarily illicit use in terms of narcotic drug abuse and other abuses.

In evaluating figures for psychotropic drug usage in the general population, both prescription and over the counter, it is important to make a distinction between use of a drug at one time or another and fairly regular or frequent use. Data collected in a recent statewide survey in California indicated that 51 percent of the adults had used a tranquilizer, sedative or stimulant—either a prescription or over-the-counter drug—at some time in their lives but only 17 percent had done so frequently. In a more detailed study of 1,104 respondents in San Francisco, investigators from the Family Research Center of the Langley-Porter Neuropsychiatric Institute found that 54 percent of those who had used a prescription psychotrope at any time had done so only on an irregular or occasional basis or for periods of less

than 1 month. At the other extreme, 21 percent of the drug users reported regular daily use of a prescription drug for a period in excess of 5 months; 90 percent of those reporting use of over-the-counter psychotropic agents had used them on only a few occasions or a number of occasions of short duration.

During the coming year a much more comprehensive national survey than any previously carried will be undertaken by the Social Research Group of George Washington University with NIMH grant support to pinpoint in detail the extent and character of psychotropic drug use in the United States.

So much for the extent of psychotropic drug use. Now, let us try to answer some of the more detailed critical questions posed earlier.

TO WHOM ARE PSYCHOTROPIC DRUGS PRESCRIBED?

This question has as many answers as the ways in which it is possible to characterize people. Today we will only talk about two of the more important characteristics related to psychotropic drug usage; namely, age and sex.

The large bulk of psychotropic drug prescribing occurs in the over-20 age group, principally for ages 40–59. Further, it is clear that stimulant drugs are used much more extensively during young adulthood while the sedatives and hypnotics are most frequently used in advanced ages. Use of minor tranquilizers and antidepressants is greatest in the age range of 40–59. These data coincide with clinical knowledge that somatic disorders with stress components such as cardiovascular and gastrointestinal disorders, which are frequently treated with sedative drugs, occur in later life as do general problems of insomnia. The use of stimulants at an earlier age is strongly related to their use as appetite suppressants and anti-obesity agents.

Shifting our attention now to the sex distribution, females receive a much higher proportion of psychotropic drugs than do males. On an overall basis they account for approximately 67 percent of all psychotropic drug usage, whereas on nonpsychotropic drugs they account for 60 percent. Exactly why this differential exists is not clear and it certainly deserves closer study. It is interesting to note that stimulants and antidepressants are overwhelmingly "female drugs" and females account for 82 and 74 percent of the use respectively. Cross-tabulation of the age and sex variables indicates that with increasing age the male-female imbalance in receipt of psychotropic drugs tends to diminish.

BY WHOM ARE PSYCHOTROPIC DRUGS PRESCRIBED?

Although psychiatrists and neurologists as a specialty group prescribe psychotropic agents at a greater rate than any other physician specialty, over 70 percent of all prescriptions for psychotropic agents are written by general practitioners, internists, and surgeons. Psy-

chiatrists and neurologists prescribe major tranquilizers and antidepressant agents at a rate five times that expected from their numbers in the overall population of physicians in private practice. General practitioners also employ psychotropic drugs at a high rate and we find them consistently overrepresented on use of all classes of psychotropic agents. On an overall basis osteopaths employ psychotropes at about the rate expected for their representation in the total physician population. But when distribution of prescribing among the major drug classes is considered, they are found to employ stimultants at three times the rate expected. More understandable is the high rate of prescribing of hypnotic drugs by surgeons and the high rate of prescribing sedative drugs by general practitioners. Because of the extensive use of psychotropic drugs among almost all types of physicians, serious efforts must be made in undergraduate and postgraduate training to insure the rational use of psychotropic agents.

In interpreting data on the extent of psychotropic drug usage, it should be recognized that neither drug prescribing nor drug acquisitions are uniformly distributed among the individuals in the reference populations; namely, physicians and patients. The top 25 percent of the prescribers may account for as much as 50 percent of the prescriptions written, and similarly a small proportion of the patients, as little as 28 percent in a recent study, may account for 48 percent of the acquisitions.

FOR WHAT ARE PSYCHOTROPIC AGENTS PRESCRIBED?

In some ways this question comes closer to the issue of overprescribing and overuse than any other. Unfortunately, it is a difficult issue on which to obtain meaningful data and the interpretation of the data must be done very carefully so as not to jump to erroneous conclusions. Ideally, one would like to be able to discuss with the physician at the time of his prescribing a psychotropic drug the reason for this decision or to review well-kept clinic records in order to obtain information on the rationale for prescribing a psychotropic drug. Short of this, however, we can ask what is the diagnosis of the patient receiving a psychotropic drug and, perhaps even more importantly, what was the desired action of the medication prescribed. For example, at first glance the prescribing of a minor tranquilizer for a patient with a diagnosis of coronary artery insufficiency may seem inappropriate. But, when the desired action is known to be anxiety reduction to try to prevent an increased cardiac load due to heightened anxiety, then this becomes an understandable and rational procedure.

For the year 1968 chart 5 gives the main diagnoses for which representative drugs in each of the six major classes of psychotropic agents were given.

(Chart 5 follows:)

CHART 5.—USE OF MAJOR CLASSES OF PSYCHOTROPIC AGENTS BY DIAGNOSIS (1968)[1]

All mental disorders	Major tranquilizers 50	Minor tranquilizers 25–34	Anti-depressants 60–70	Stimulants 5	Sedatives 10	Hypnotics 6
Schizophrenic disorders	27	3	6–9			16
Depressive reactions	21	8–20	61–64	40	4	33
Anxiety reaction	17	42–46	7–8		46	16
Psychoneurotic disorders	5	9–15	3–5		24	
Senile psychosis	4		2–3			
All other mental disorders	24	24–30	16		26	35

[1] Representative drugs of the class and not the entire class tabulated.

Source: National Disease and Therapeutic Index of Lea and Associates.

Dr. LEVINE. Considering the appropriateness of the diagnosis to the drug class, we find that the use of these drugs is, by and large, rational. For example, in the minor tranquilizer category only 3 percent of the representative drugs are prescribed for schizophrenia while 27 percent of the major tranquilizers are prescribed for this disorder. Likewise, up to 64 percent of the time when antidepressants are given for a psychiatric disorder, they are given for depressive reactions, whereas minor tranquilizers are given only 8–20 percent of the time and major tranquilizers 21 percent of the time for this same disorder.

Mr. GORDON. Dr. Levine, may I ask a clarifying question here? Are you saying that when these psychotropic drugs are used for psychiatric problems they are used rationally?

Dr. LEVINE. When we look at the psychiatric disorders, we find a good correlation between the classes of drugs which are known to be effective in treating those disorders and, in fact, the disorders for which they are being prescribed. We find only 3 percent of the minor tranquilizer category being prescribed for schizophrenia, one of the major psychiatric disorders. The minor tranquilizers should be used in treatment of anxiety neurosis, a less severe disorder. This is the kind of data that leads me to the conclusion that overall this is a rational use of that class of drugs.

Somewhat surprising at first glance is the frequency with which these representative drugs are employed in nonpsychiatric diagnoses. Sixty-four percent of all prescriptions for the antidepressant category are for psychiatric diagnoses but only 10 percent for the representative drug in the sedative category. In the minor tranquilizer category the percentage ranges between 25 and 34 while for major tranquilizers there is a 50-percent use for mental disorders.

The caveat presented earlier, however, must be kept in mind before any conclusions are reached regarding the appropriateness or inappropriateness of these therapeutic practices.

Chart 6 presents data on the same representative drugs of the major psychotropic classes but this time cross-tabulated with desired action rather than diagnosis.

(Chart 6 follows:)

CHART 6.—USE OF MAJOR CLASSES OF PSYCHOTROPIC AGENTS BY DESIRED ACTION (1968)[1]

Desired action	Major tranquilizers	Minor tranquilizers	Anti-depressants	Stimulants	Sedatives	Hypnotics
Tranquilization	36	43–58	1–6		7	
Sedation	16	20–27	0–4		68	
Antidepression	2		80–85	5		
Antiemetic	18					
Anticonvulsant					14	
Antihypertension					3	
Antiinsomnia						88
Antiobesity				90		

[1] Representative drugs of the class and not the entire class tabulated.

Source: National Disease and Therapeutic Index of Lea & Associates.

Dr. LEVINE. The minor tranquilizer class is prescribed 70 to 78 percent of the time for tranquilization or sedation while the previous table showed that by diagnostic categories the minor tranquilizers were prescribed for mental disorders only 25 to 34 percent of the time. Likewise, in the sedative class, while these are prescribed only 10 percent of the time for mental disorders, the desired therapeutic action is tranquilization or sedation 75 percent of the time. Hypnotic drugs are used almost exclusively for sleep induction while the vast use of stimulant drugs is for appetite suppression to aid in weight reduction with 5 percent of stimulant drug prescribing aimed at relief of depression. The conclusion drawn is that psychological or psychiatric symptomatology occurs to a large extent in patients who are not diagnosed as having a mental disorder and physicians prescribing reflects the treatment of these symptoms in patients who are not primarily mentally ill.

The data presented so far on the question of "For what are psychotropic drugs prescribed?" have only been for the year 1968. But what has been the trend over the past several years? Data on this question unfortunately are not available for each of the separate major classes of psychotropic agents but for a conglomerate grouping referred to as ataraxics consisting primarily of the classes major[1] and minor tranquilizers. Data on this topic are available from the year 1960. The percent of prescriptions for ataraxics written for conditions diagnosed as mental disorders between 1960 and 1968 has fluctuated very mildly between 31 and 41 percent. In 1968 the percentage stood at an intermediate 37 percent. The distribution of subdiagnoses within mental disorders—as listed in chart 5—over the past 5 years indicates that there has been little change in this aspect of psychotropic drug therapy.

Considering desired actions of the ataraxics over the 8-year period between 1960 and 1967, we find that, if anything, there has been an increase from a low of 73 percent in 1960 to a high of 85 percent in 1967 for indications dealing with mental symptomatology. This 85-percent figure for desired actions pertaining to mental symptoms can be contrasted with the 39-percent use of psychotropes in patients who were diagnosed as having mental disorders. Taking both these figures into consideration, we again conclude that psychotropic drugs are being prescribed overwhelmingly for psychiatric symptomatology but a large part of this symptomatology is occurring in patients with diag-

[1] Prochlorperazine is included in this class.

noses other than mental disorders. The number of properly controlled studies in which psychotropic drugs have been evaluated for efficacy in patients with nonpsychiatric disorders is, to our knowledge, very small and more attention should be given to studies of this type in view of the fact that this is the group for whom a majority of prescriptions for psychotropic agents is being written. These studies should also attempt to provide data on any possible dangerous drug interaction between agents of other therapeutic classes and the psychotropes being used. The enzyme-inducing effect of phenobarbital on the rate of metabolism of anticoagulant agents is the kind of interaction to which I refer.

The final critical question to which we will address ourselves is: "In what manner are psychotropic drugs being prescribed and used?"

Among private practitioners prescribing patterns for psychotropic drugs are fairly uniform. For both major and minor tranquilizers the modal prescription provides for 40 to 45 tablets or capsules to be taken at the rate of three per day for a period of 12 to 14 days. Daily dosages tend to be moderate to low and the mechanics of consumption so arranged that a patient usually takes only one pill per administration. Prescribing practices differ with the medical setting and the average days of therapy provided in the original prescription may vary depending on whether the physician is dealing with patients that are well known to him, or whether the system encourages phone contacts and reports, and similar factors. Among internists and general practitioners, minor tranquilizers are often prescribed on an as-needed basis rather than on a regular extended regimen which probably reflects a prophylactic intent where stress has serious implications for an organic illness such as heart disease.

Average prescription sizes for the antidepressants tend to be larger than those for the tranquilizers, approaching 50 units, and the average number of days of therapy provided is closer to 17—a probable reflection of a common therapeutic belief that antidepressants are fairly slow acting. The average number of days of therapy allowed on prescriptions for hypnotics and sedatives is larger than that for either antidepressants or tranquilizers. In the case of hypnotics, days of therapy average close to 25 and for sedatives close to 1 month.

Prescription sizes for the sedatives, principally phenobarbital, are much larger than those for any other class of psychotropic drugs, averaging close to 80 units of medication. However, it should be pointed out that sedatives and hypnotics are frequently used in middle-aged and older patients with more chronic illnesses.

In general medical settings it is not uncommon to find one-third of the patients being treated with psychotropic drugs for a single acute episode of 1 to 3 months' duration, another one-third being treated for several episodes of similar duration that occur over a period of several years, and one-third or less who are chronically ill and receiving psychotropic drugs on a fairly continuous basis.

Preliminary data at our disposal also indicate that outpatients often do not obtain all the refills they are permitted and frequently reduce the prescribed daily dosage when they begin to feel better in what appears to be a self-titrating procedure.

ATTITUDES TOWARD PSYCHOTROPIC DRUG USE

We have found that attitudes toward psychotropic drugs and mental illness along with demographic variables influence psychotropic drug usage in the general population. We suspect that attitudinal factors also influence prescribing behavior and hope to study the problem in detail in the near future. We emphasize attitudinal considerations because we feel that many of the judgments about overprescribing, inappropriate prescribing, and overuse of psychotropic drugs will turn on value issues that go beyond the specific medical consequences of drug ingestion.

Early returns of recent survey studies indicate that the attitudes of the American public toward the use of psychotropic drugs remain generally conservative and a majority of those currently taking psychotropic drugs or who have done so in the past express some discomfort with the idea. As might be expected, attitudes toward the use of psychotropic drugs tend to be more conservative in the middle and older age groups, who, paradoxically, because of a greater need, are more prone to obtain psychotropic drugs from a physician. Nonetheless, negative attitudes toward psychotropic drugs are more likely to act as a deterrent to use among the middle and older age groups than in the younger generation who seem to have fewer compunctions about using a psychotropic drug if they feel they need it. Final conclusions on these matters will have to await the outcome of current studies and an upcoming national survey that will be carried out by the Social Research Group of George Washington University as part of our program of collaborative research on the extent and nature of psychotropic drug usage in the United States.

The data available to us at this time do not indicate that a large proportion of Americans are becoming chronic or dependent users of psychotropic drugs, or are in danger of becoming so in the near future. On the other hand, we suspect that the occasional use of psychotropic drugs to improve adequate social functioning and offset or prevent mild discomfort may very well be on the rise.

We hope this information will be of value to the subcommittee and ultimately will result in even better health care for the Nation.

Senator NELSON. Thank you very much, Doctor. You did not comment very much on any of the side effects. Are there side-effect implications in all of these psychotropic drugs, and what are they?

Dr. LEVINE. Yes. As I tried to point out in the capsule presentations of the drugs class by class, there are side effects that do occur with all these classes of psychotropic agents.

Senator NELSON. On the charts?

Dr. LEVINE. In the capsule presentations accompanying chart 1. That would begin on page 3 of the testimony. For example, with regard to major tranquilizers, the most common side effects include drowsiness. This is usually of a transitory or temporary nature. Extrapyramidal symptoms such as are seen in Parkinson's disease are also frequently seen and the occurrence of low blood pressure in response to standing or getting up quickly, so-called orthostatic hypotension, does occur. Some toxic effects such as agranulositosis and the occurrence of liver damage are rare but do occur with these drugs.

Senator NELSON. But in most cases, I take it, then, they are temporary side effects without permanent injury to the patient.

Dr. LEVINE. In most cases this is so. Of course, in the case of agranulositosis it is a dangerous side effect.

Senator NELSON. Of which drug?

Dr. LEVINE. Chlorpromazine in particular has been shown to give rise to agranulositosis but other drugs in the phenothiazine class also give rise to this side effect.

With regard to the extrapyramidal symptoms—this is rigidity of muscles and tremor, masklike facies which are the symptoms of Parkinson's disease—we can treat these with anti-Parkinsonian agents.

Senator NELSON. You can?

Dr. LEVINE. Yes, we can treat these symptoms with anti-Parkinsonian agents or with reduction in level of the psychotropic medication and this leads to a relief of these symptoms. When phenothiazine drugs are given in large amounts for prolonged periods of time, another neurological manifestation which has been called tardive dyskinesia and which is shown by unusual movements of the mouth and tongue and choreiform-type movements of the fingers are seen. They are thought to be related to large and continued phenothiazine usage and they are not as reversible or controllable as the extrapyramidal symptoms.

The symptoms of Parkinsonian, I might mention, Senator, are less often seen on an outpatient basis, since the amount of drug that is given is much lower than that given in a hospital. It is much more common in hospitals to see the extrapyramidal side effects and the other side effects that I discussed.

Mr. GORDON. I have a public health monograph called "Facts Needed To Assess Public Health and Social Problems in the Widespread Use of Tranquilizing Drugs." It is quite old. This was in a publication that came out in 1957 or 1958, and on chlorpromazine it says, "A large variety of toxic effects produced by chlorpromazine in man are well known. Among these are severe hypotension, dermatitis, Parkinsonism, jaundice, and agranulositosis, to name only a few. Because of the way many of the results are reported, it is difficult to compare incidence of complications between studies by age, sex, type of disorder, and so on."

Dr. LEVINE. Yes, Mr. Gordon, if I can interrupt here, I think those are precisely the effects I mentioned, orthostatic hypotension, lowering of the blood pressure, increased pigmentation, liver damage, and agranulositosis, so I think that older document in fact picked up the same kind of side effects that we know about today.

Mr. GORDON. Do you use reserpine or rauwolfia today?

Dr. LEVINE. No, not to any great extent. Reserpine came out about the same time chlorpromazine did and was found to be effective in reducing the symptomatology associated with major psychoses, but over the years it has been found that the phenothiazine-type drugs are more effective and have fewer side effects than reserpine. If a patient shows an allergic reaction to phenothiazine-type drugs, fortunately we have the reserpine drugs to fall back on as well as some newer classes of drugs that have been developed, the thioxanthine category of drugs and the butyrophenone category of drugs.

Mr. GORDON. At the top of page 21 you say that many people who have taken psychotropic drugs have, in the past, expressed a discomfort with the idea. Why are they discomforted by the idea of using the psychotropic drugs?

Dr. LEVINE. If I might, I would like to refer that question to Dr. Balter, who is a social psychologist and I think best prepared to answer it.

Dr. BALTER. My remarks are based on partial data since we are still in midstream on our survey research program, although I think there are some basic findings that can be discussed.

The attitude structure looks something like this. In the main Americans seem to agree that psychotropic drugs work well, the minor tranquilizers in particular. They tend to reject the idea that the use of these drugs is a sign of weakness. They also agree, and this includes drug users as well as nonusers, that the use of drugs tend to cover up the real problem, that the use of willpower and some old-fashioned methods of self-control might be better.

They express qualms about the side effects of the drugs and many believe that they may be addicting. They have mixed feelings about using drugs for long periods of time. Some fear that there may be physical danger involved. Over half have vague questions about whether the drugs are appropriately tested before they get to the market.

Overall about 8 percent of the respondents say they would never take a tranquilizer under any circumstances. About three-quarters of the public say that they would take one but only on the prescription of a physician. And only 17 percent say they would take one if they felt they needed it with or without the doctor's permission.

It is also interesting that about one-third of the respondents could not define a tranquilizer, but this is less than was the case, say, 5, 8, or 10 years ago. Americans are becoming more sophisticated about psychotropic drugs.

Tranquilizer users are generally more positively disposed toward the drugs than are nonusers; but, interestingly enough, a majority of them harbor the same kind of fears and trepidations. Younger people, who are even more sophisticated than others about psychotropic drugs, express similar attitudes, share the notion that it would be better to use willpower and similar techniques to solve personal problems; but they tend to be less stoic. They tend to subscribe less to the idea that the enduring of hardship is a virtue, that one's character is formed in adversity, and the like, and as a consequence they are more prone to use the drugs if they feel they need them, whereas the middle and older generation seems to be in a conflict situation where their attitudes may be quite negative but their need is quite high.

Mr. GORDON. I would like to read something to you. This is a bulletin of the New York Academy of Medicine, April 1957—it goes way back. And it is a report on tranquilizing drugs by the Committee on Public Health of the New York Academy of Medicine. Let me read a paragraph to you:

In some minds this widespread use of tranquilizers in meeting everyday situations raises a question about the rationale underlying it. Anxiety and tension seem to abound in our modern culture, and the current trend is to escape the

unpleasantness of its impact. But when has life ever been exempt from stress? In the long run is it desirable that a population be ever free from tension? Should there be a pill for every mood or occasion? It has been noted that when the drug is used satisfactorily in an emergency, there is a tendency among some persons to regard more and more of life's situations as emergencies until the pattern results in everyday usage of tranquilizing drugs. Their use is said to be becoming more and more common among persons in certain occupations.

Would you comment on that, please?

Dr. LEVINE. With regard to the widespread use of minor tranquilizers in particular, the desired action by persons taking them is not one of escape from the situation that they are in but rather to help them cope more effectively with the situation that they are in. My observations, and I cannot substantiate them with data at this time, are that the drugs are used, by and large, to help people perform better and to cope with life more effectively rather than using them as agents to dull them and to help them escape from their problems.

Now, to be sure, there probably is a small percentage of people who take too much drugs, and an even larger percentage who take too much alcohol, to escape from their problems, but I think the use of psychotropic drugs generally is to help people cope more effectively with problems of everyday life rather than to escape them.

Senator NELSON. Senator Dole?

Senator DOLE. I think your statement indicated that many of the stimulants were used for weight-reduction purposes.

Dr. LEVINE. That is correct.

Senator DOLE. I have a friend who was taking dexadrine and he was told about some of the harmful side effects. What are the side effects of continued use of dexadrine?

Dr. LEVINE. One of the common side effects is the irritability associated with the drug, a kind of jitteriness, inability to sit still and concentrate. It is well known that these drugs are sometimes used to help one stay up to study longer before examinations.

Senator DOLE. Good for campaigning sometimes?

Dr. LEVINE. This sometimes works well but other times makes the individual more jittery and more uptight and less able to concentrate on the task at hand. This would be one of the side effects.

Now, if the stimulant drugs, amphetamines in particular, are taken in very large and increasing doses, as I mentioned in the prepared statement, there have been cases reported, fairly widespread, of paranoid psychosis. The individual becomes very suspicious, fearful that someone is after him or threatening him, and actually goes into a psychotic state which is quite a dangerous one. A person must be hospitalized for treatment of that. But that occurs generally with high dosage.

Senator DOLE. Do you build up a tolerance to these drug things over a period of months or years to a point where they have no effect at all?

Dr. LEVINE. Yes; there is a tolerance built up to amphetamines. That is, if you take the same amount day after day after day it does not seem to have the same effect, so that individuals who take it chronically, if they want to have the same effect and feelings, do tend to increase the dosage and this does lead to problems that I mentioned.

Senator DOLE. If taken by prescription for weight reduction and properly prescribed—there are really no harmful effects; is that correct?

Dr. LEVINE. There are not major harmful effects. It certainly should be given with the supervision of a physician and for specific purposes and not for an unlimited amount of time.

Senator DOLE. I think probably one problem is that, though they do reduce your appetite, you stay awake longer. You could take in four meals instead of three, you know, if you take enough of those dexadrines.

Dr. LEVINE. Especially on the campaign circuit.

Senator DOLE. I think he stopped taking them. I will report to him he can probably start again.

Thank you.

Senator NELSON. Thank you very much.

Mr. DUFFY. Mr. Chairman, may I just ask a question? Doctor, I note at the bottom of page 21 of your statement that you say occasional use of psychotropic drugs to improve adequate social functioning—I am dropping out a few words here—may be on the rise. I would assume you would include within this kind of taking of this drug the tired business executive so he can enjoy his theater more, as Dr. Yolles suggested.

Dr. LEVINE. Precisely.

Mr. DUFFY. And I think, if I understood your response to Mr. Gordon a moment ago, that you feel there is nothing necessarily objectionable about the use of these drugs to improve personal performance. Am I interpreting you correctly?

Dr. LEVINE. I would say that this is a decision that society is going to have to make and these are the other frames of reference to which Dr. Yolles referred which must be taken into account.

This is, in a sense, beyond the medical opinion. Medical opinion is treating illness, but if society—and physicians are a part of society and only a part of society—decide that this is a legitimate use of drugs, that the enhancement of normal performance is a legitimate use of drugs, yes, this would be considered legitimate.

Society may decide that it is not. For example, the use of amphetamines and other drugs to help athletes perform better on the track or to give drugs to horses in horseraces, society does not condone these actions as being beneficial to society.

So that I think society will have to aid in saying what is legitimate use of drugs. It is not solely a medical decision.

Mr. DUFFY. Just one other question. This is prompted by nothing other than curiosity, but if I discovered alcohol today, would that be a psychotropic drug?

Dr. LEVINE. Yes, indeed it would, and it would probably fall in the minor tranquilizer class. It probably would not be put on the market because it leads to damaging liver effects when taken in large doses over prolonged periods of time.

Mr. DUFFY. It is a good thing it was discovered a long time ago.

Senator NELSON. Thank you very much, Doctor. We appreciate your taking time to come here this morning.

Our next witness is Mr. Bernard Barber, professor and chairman of the Department of Sociology, Barnard College, Columbia University. Professor Barber is also a member of the Drug Research Board of the National Academy of Sciences.

Professor Barber, we are very pleased to have you here this morning. You may present your statement in any way you desire.

STATEMENT OF BERNARD BARBER, PROFESSOR AND CHAIRMAN, DEPARTMENT OF SOCIOLOGY, BARNARD COLLEGE, COLUMBIA UNIVERSITY

Mr. BARBER. Thank you, Mr. Chairman. I have been a close student of the printed proceedings of these hearings and I am pleased to be here to make a contribution myself today.

I have been asked to "discuss the sociological aspects of psychotropic drug use." I would like to do so by talking to three separate but interrelated problems. First, I want to answer the question which is often raised, indeed is often answered in the affirmative. Is this a "drugged society"? Second, I want to say something about what I consider the desirable social policy with regard to abuse of the psychotropic drugs. And, finally, I want to describe why I think it is true that doctors may be overprescribing tranquilizers. If my description rings true, it may be possible for some doctors to cut down on the prescription of these drugs.

I should make it clear, before proceeding, that I am trying to be as brief as possible about these three problems in this prepared statement. I am assuming that your questions will lead to any amplification and clarification of my remarks wherever that is desirable.

Is this a "drugged society"?

Affirmations that the United States is a "drugged society" rest on an interpretation of what is an undoubted fact, the very widespread and very large recent increase in the use of both the major and the minor tranquilizers. Pilot studies of tranquilizer use, not based on nationally representative samples but probably pretty representative nonetheless, show that as many as one in four adults have used tranquilizers within any preceding 12 months and that as many as one adult in every two has used them at some time in the recent past.

If I may interpolate, I am using data from other sources than those referred to by Dr. Levine. I am very much impressed with the way in which the excellent research which they are doing now simply bears out the patterns which have been reported up to now.

The final report of the Task Force on Prescription Drugs, Department of Health, Education, and Welfare, indicates that in 1966 prescriptions for tranquilizers were the second most frequent category of all prescriptions, with cardiovascular preparations first, and diuretics, sedatives, and antibiotics in third, fourth, and fifth places.

I do not agree with those who infer from this large use of tranquilizers that America has become a drugged society; that is, a society that is sinking into passivity, escapism, and the hedonistic pursuit of exotic experiences of mood and mind. It is my impression—and I venture to offer you impressions only because nothing better is available to any of us yet, including those who are affirming that this is a drugged

society—that Americans are still, both in their values and in their actual activities, an activistic, performance-oriented, striving, achievement-minded society. It is my inference that, apart from those who are so psychologically ill that they need the major tranquilizers to permit them to function at even a minimum level, most Americans are using the minor tranquilizers to ease some of the stresses of their achievement-oriented activities and to permit them to engage more successfully in those activities.

Health—both psychological and physiological—is an indispensable asset for successful performance in our high-standard society. In considerable measure, though obviously not entirely, the tranquilizers are probably being used in the pursuit of better health in an activistic society. I cannot agree that there is anything but a tiny minority in this country that is seeking the passivity, the escapism, and the pursuit of unusual personal experiences that would constitute a drugged society.

Mr. GORDON. Professor Barber, Dr. Yolles stated on page 10 of his statement as follows:

"It is to be expected that the use of these drugs in the next 10 years will increase a hundredfold." What do you think would be the effect of this?

Mr. BARBER. I raised my eyebrows at that statement. I do not know whether Dr. Yolles meant, as I hope he does, that new drugs will be discovered, much more specific ones than we now have. I am very much impressed with the statements of our knowledgeable colleagues here that most of our presently available psychotropic drugs are just for the relief of symptoms, that they are not specific as to any causative agents. I hope he means that.

I think another thing he may mean is what is implied in Dr. Levine's figures, that there are somewhat different, not radically different but somewhat different, attitudes between the age groups. I think the younger people have somewhat less uptight, somewhat more rational attitudes toward a variety of matters of this kind, and it seems to me that in this respect, although fundamentally oriented to achievement, they may be less ambivalent about taking the drugs and, therefore, you would get an increase just by the change in the age structure of our population.

Mr. GORDON. But if he means what he actually says, would you start worrying?

Mr. BARBER. Well, I am not sure—if you are implying that he intended to imply that there was going to be a great deal more harmful use, I do not think I would agree with that but I am not sure that he means that either.

A second point I wanted to talk to is a desirable social policy for control of abuse of the psychotropic drugs.

Though it is probably only a minority, then, that abuse the psychotropic drugs, these drugs are, at least to that extent, a danger. Indeed, all drugs are in some measure dangerous. Aspirin is dangerous under certain conditions. Among other things, for example, it is the largest single cause of infant mortality.

Abuse of the psychotropic drugs is dangerous both to the abuser and possibly to others, as when the abuser is not in adequate control of himself when driving an automobile. We need to do something to pro-

tect the abuser and those whom he might harm. What should we do? What kind of social policy should we have?

Senator NELSON. Did I understand you to say——

Mr. BARBER. I should have said child mortality. Accidental ingestion. Aspirin is the largest single cause of child mortality.

Senator NELSON. It is?

Mr. BARBER. Yes.

Senator NELSON. I have never heard that before.

Mr. BARBER. I will try to get the evidence for that if you would like.[1]

Senator NELSON. Yes; if you would submit evidence for the record that aspirin is the most frequent cause of child mortality.

Mr. BARBER. That is right. Yes. The drug industry at the present time is working on all kinds of devices for safety; that is, bottles that are extremely hard to remove the caps on, single-dose packaging, things of that sort.

I am not competent at this point to speak to the details of a social policy in this field, but I do wish to say something about its general characteristics. As strongly as I can, I wish to urge that we continue to pursue the present *social-medical policy* that we have toward psychotropic drug abuse and that we avoid turning to the *police-punitive policy* which has been so ineffective, perhaps I might even say so disastrous, with regard to other "dangerous drugs" such as marihuana and heroin.

People who abuse the psychotropic drugs, like those who abuse marihuana and heroin, are sick people, disturbed in their social and psychological functioning, as well as in their physiological functioning. They need the kind of treatment that various kinds of physicians and other socially rehabilitative agencies can give them. We know, of course, that the treatments that are available to them are far from being as effective as we should like them to be. Often, too often, the best they can do is to prevent further harm. But, nonetheless, they are much better than the consequences of a police-punitive policy. A police-punitive policy has little beneficial effect on the disturbed social and psychological functioning of the abusers. And worse, it is a policy that leads to a whole set of harmful secondary consequences for society. Without helping the abusers, we heap on ourselves a new set of troubles.

We get racketeering; we get police brutality and corruption; we often get prostitution and petty crime to acquire money to pay the racketeers their exorbitant prices for the banned drugs; and we get disrespect for the law and for a society which obviously enforces ineffective and unnecessarily harsh laws. If we should mistakenly move to a police-punitive policy with regard to the psychotropic drug abuse, we shall bring upon ourselves the troubles that we had under prohibition and that we now have with our heroin and our marihuana laws.

Please note that a social-medical policy toward abuse of the psychotropic drugs or any other kind of drugs does not mean the abandonment of all controls. Because the psychotropic drugs are dangerous in some measure, as is the abuse of alcohol in probably a greater meas-

[1] Material not received at time of going to press.

ure, we have to have some controls for the former as we still do for the latter, even though we have abandoned the prohibition laws. We shall need rules as to prescription, as to distribution, as to conditions of use, and the like, for psychotropic drugs. But such rules should be formulated within the context of a social-medical policy, not a police-punitive one. And such rules should be accompanied by the kind of rational education in the uses and dangers of psychotropic drugs—education, incidentally, for both doctors and users—that is so often replaced by the "scare-'em-to-hell" education of the police-punitive approach.

My last point, do doctors overprescribe psychotropic drugs?

In pursuit of good health to function well in their activistic society, Americans go to get help from their doctors. Recently, as we have seen, a larger part of this help has taken the form of prescriptions for tranquilizers. There has been some criticism, often from doctors themselves, that much of this prescribing of tranquilizers is unnecessary; there is the charge that doctors are overprescribing the psychotropic drugs.

Unfortunately, there probably is something to this charge. But we need to understand why some doctors do overprescribe before we can suggest remedies for the problem. Overprescription, it seems to me, does not result from casual carelessness or incompetence but from something that lies deeper in the situation of medical practice.

An observant doctor is once said to have remarked that, until about 50 years ago, the average patient with the average disease consulting the average physician had only a 50–50 chance of getting some help from him. In the period since then, the amount of help that the average doctor can give his average patient has increased enormously. New drugs and other new therapeutic techniques have greatly increased the control that the physician has over ill health, both physiological and psychological. Nonetheless, there remains a great deal of uncertainty and lack of control in the situation with regard to both diagnosis and treatment that the average doctor faces every day.

This uncertainty and lack of control, which we easily tend to forget, were interestingly revealed in a little study which one practitioner made of his own prescribing patterns. We do not know how representative these data are, but my guess is that they are fairly representative. This practitioner kept a record of his prescriptions for a period of 4 months. For each prescription he made an estimation of therapeutic intent, or what he felt was the degree of his certainty and control. His five categories of prescribing intent, with examples, are as follows: Specific (insulin in diabetes), probable (antibiotics in infections), possible (corticosteroids in bronchial asthma), hopeful (mixed corticosteroids and tranquilizers), I take it for the same disease, and placebo (any preparation given with the intention of relieving mental stress and which the prescriber believes possesses minimal pharmacological activity). The results are shown in the accompanying table:

Intention, specific, (number) 44, (percentage) 7.55; intention, probable, (number) 87, (percentage) 15.03; intention, possible, (number) 149, (percentage) 25.69; intention, hopeful, (number) 124, (percentage) 21.38; intention, placebo, (number) 176, (percentage) 30.35; total (number) 580, (percentage) 100.

Now, it is pretty clear from these figures, especially if we take the middle categories to express uncertainty in diagnosis and treatment, and the placebo category to indicate minimal control, that the physician is constantly facing these two conditions in his use of therapeutic drugs.

Facing frequent uncertainty and lack of control, the doctor is still under pressure to do something for his patient. I should like to stress it is a double pressure from his own wish to be helpful and pressure from the patient's appeal, often urgent, for some help. In this situation, the doctor is under a structured pressure which results in some patterned responses. First of all, he can respond by using a drug or technique which he knows is helpful in some cases and might possibly be in this one. Or he can respond by prescribing a placebo, something which does no harm. It is an old medical maxim, first of all, do no harm, and which allows the healing power of nature to take its course.

The history of medicine is filled with responses of both these kinds. Some recent examples have been the fads for tonsillectomies or for the antibiotics. The psychotropic drugs would seem to satisfy both of these responses. That is, they can be thought of as either possibly effective for a broader range of ills than has been demonstrated by research or they can be thought of as placebos. It is no wonder that they have been very widely prescribed in recent years.

Doctors could probably reduce the amount of prescribing of tranquilizers—that is, could reduce "overprescribing," if one prefers to view it that way—by being more aware of why it is that they often seize on new drugs and new techniques in a fadlike fashion. If they educated themselves and their patients to the considerable uncertainty and lack of control that does exist even today in medical practice, both they and their patients might better be able to tolerate it without recourse to unnecessary and costly prescriptions. For those who cannot tolerate the uncertainty or lack of control, of course, whether doctors or patients, the prescribing of tranquilizers cannot be viewed as "overprescription" but rather as a possibly effective way of dealing with the anxiety this uncertainty and lack of control generates.

Thank you.

Senator NELSON. Thank you very much, Professor Barber.

Mr. Gordon, do you have any questions?

Mr. GORDON. On page 5 you say, "We shall need rules as to prescription, distribution, conditions of use, and the like, for psychotropic drugs."

If special controls are necessary for the prescription and use, how about for the promotion of these drugs?

Mr. BARBER. Well, there might be that, too. For example, we see now in the case of tobacco requests for controls on advertising to the young. There might be prescriptions of that sort of drugs, too.

I hate to be specific about details because I think these are hard problems. Age differences would be one of the central foci of careful people sitting down to think about the controls. Obviously, you would have different rules for young people as against older people. You might require parental permission, for example.

The same things are true in the case of alcohol. That is, in some States the age at which people may purchase alcohol is 18 and others 21. We would obviously have to have controls on whether people might drive, since drowsiness is a common side effect of some of these psychotropic agents. Things of that sort are what I have in mind. Unfortunately, the question of controls is often posed as a choice between extremes, no controls or excessive controls.

Mr. GORDON. How about TV advertisements for over-the-counter psychotropic drugs?

Mr. BARBER. Again, of course, we presumably already have some controls over those. As you know, the FDA has recently set up a series of guidelines for drug advertisers, ethicals, in his prescriptions. Over-the-counters do not come under FDA. They come under the Federal Trade Commission. There might very well be some investigation of desirable controls for both those classes.

But with respect to all of these things, I would like to see them done within a social-medical policy and I would like to see them based on the kinds of specific information about use, prescribing, and consequences that Dr. Levine and his colleague are trying now to accumulate. I think we very badly need a great deal more of just that kind of research.

Mr. GORDON. I notice on the chart on page 7 of your statement that tranquilizers are used at least 30.35 percent for placebo purposes.

Mr. BARBER. Excuse me. No. On that chart, placebo does not necessarily indicate tranquilizers. He might have used almost anything. He might have used some other kinds of things. That chart is intended—he does not specify what he used for placebos. There he might have used sugar pills.

Mr. GORDON. I see.

Mr. BARBER. It is intended to indicate that a considerable part of all prescribing is in a situation of lack of certainty and lack of control and the best the doctor can do is to avoid doing any harm.

Senator NELSON. Do you have any questions?

Mr. DUFFY. I have one or two.

I notice with some interest your comments here that we have a performance-oriented, striving, achievement-minded society. I was just wondering whether you might be suggesting that ultimately we are creating a society where it may be necessary, in order to function in that society, to rely on some of these psychotropic agents you are talking about; somewhat along the lines of perhaps "1984" or "Brave New World."

Mr. BARBER. No; I am not. I assume that the National Institute of Mental Health could also tell you about large research programs which they carry out which might be defined as prophylactic rather than in some way dealing with symptoms or hopefully curative. That is, I know they do a large part of their research on how to have a healthy childhood so that people can stand the kinds of tensions that come in a society of this kind. So that I think that is a kind of "dystopia," a kind of a excessively negative image that people have of 1984.

Our problems are much more real and immediate than that kind of horror. I do not think in the future we are going to have a drugged society, either.

Mr. DUFFY. You do not see that as a problem.

Mr. BARBER. No. I think the chances are that we will get better knowledge of social and psychological functioning which would be, as I say, prophylactic medicine, curative—preventive medicine, I guess is what I really want to say, rather than this later patching up our troubles.

Mr. DUFFY. In response to Mr. Gordon's question about regulation of promotional activities, you were not suggesting, I assume, that there be any regulation placed on promotional activities directly. You were just talking perhaps about over-the-counter drugs and advertising to the general public, is that correct?

Mr. BARBER. Well, as you know, and I have described some of this in some writing, there are among physicians themselves all kinds of charges that there is a great deal of high-pressure advertising, hard-selling Madison-Avenue-type advertising, of psychotropic drugs and other kinds of drugs, and again I have no specifics to recommend there, but that is recognized by many people and probably some in the drug industry itself as a problem.

Mr. DUFFY. One last thing, if I may.

It would appear you might conclude that there is perhaps over-prescribing of psychotropic drugs. However, you apparently can find a rationality for this. Perhaps, as you suggest here, this is a failing of the individual to cope with his own problems or of the doctor in his desire to help the individual to cope with his own problem. Do you see any other elements that might contribute to this?

Mr. BARBER. Well, I would like to put it the way Dr. Yolles did, in terms of cost-benefit ratio. I think the lesser cost would be if the patient and the physician were more able to cope with their lack of certainty and lack of control and if the patient then did not spend the money that is necessary for these placebos and unnecessary drugs. But what I am saying is that, given this situation—that is, inability to cope—it is not entirely disfunctional when people behave in this way. It probably does give some benefit for the cost, both the physician and to the patient.

There are a number of examples of this kind. There was a fad for appendectomies, tonsillectomies, and so on. The history of medicine is filled with these kinds of fads that I think in part come out of this same sort of situation.

Mr. DUFFY. Thank you, Professor.

Senator NELSON. Thank you very much, Professor, for your very valuable testimony. We appreciate your taking the time to come.

(Whereupon, at 12:30 p.m., the hearing was adjourned, subject to the call of the Chair.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, JULY 29, 1969

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 9:30 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Dole.

Also present: Benjamin Gordon, staff economist; Elaine C. Dye, clerical assistant; and James P. Duffy III, minority counsel.

Senator NELSON. Our witnesses this morning are Dr. Henry Brill, director of Pilgrim State Hospital, and Dr. F. A. Freyhan, director of research, Department of Psychiatry, St. Vincent's Hospital, N.Y.

We are very pleased that you took the time to appear here this morning. We will hear from Dr. Brill first.

Your prepared statement will be printed in the record. The committee would be very pleased to have you depart from your text if you desire at any time to elaborate anything that you have in the text. And for any questions that we ask we would be happy to have comments from both of you if you wish.

STATEMENT OF DR. HENRY BRILL, DIRECTOR, PILGRIM STATE HOSPITAL, WEST BRENTWOOD, LONG ISLAND, NEW YORK, N.Y.

Dr. BRILL. Mr. Chairman, I am Dr. Henry Brill of West Brentwood, N.Y. And I would be very glad to dispense with the reading of the qualifications and go right on with the statement, if you would like.

Senator NELSON. It will be printed in the record.[1]

Dr. BRILL. I do not speak for any of the groups—I quoted a number of groups I am associated with—I do not speak for any of these groups here today, but I am here in purely a personal capacity. I appreciate the opportunity of appearing to speak about psychotropic drugs. The organizations and the experiences are listed as qualifying background for the statement, and you will note that none of these activities provides a special knowledge with respect to the economics of drug development and distribution nor with regard to merchandising or marketing practices such as advertising or promotion. Nevertheless, I have been active for many years in areas which are closely related to these issues and hope that some of the comments will cast additional light on the central questions which interest your committee.

[1] See p. 5321.

If we discuss psychiatric drugs in a narrow context, it is quickly apparent that we are indeed an over-medicated society. Even without statistics common experience is such that it is generally conceded that a vast amount of the psychotropic medication which is dispensed is uncalled for and a goodly proportion of it never gets beyond the family medicine cabinet. These data are often taken to mean that a large number of cases who gets drugs do not need treatment at all and are not sick and with this I cannot agree.

A drug may be of little or no value for the condition under treatment, but information from every available source agrees that there is a vast amount of untreated nervous and mental disorder which needs treatment in our general population. These disorders lie behind a great deal of alcoholism, illicit drug taking, and much of the disordered, disruptive, and dangerous behavior which fills so much space in the daily press. Psychiatric disorder is by no means confined to the more traditional psychoses, neuroses and psychosomatic illnesses. We are thus an over-medicated society relative to our capacity to treat and to cure, and not in relation to our need for treatment.

The problems of over-medication are probably as old as history. Drugs which affect the mental state are among the easiest to identify, and they were among the earliest medications.

Ancient Roman writers warned about the dangers of medications "which darken the mind;" and during the 19th century abuse of opiates was condemned in almost the same terms as was the abuse of alcohol. When the sedatives appeared, their abuse also quickly became a matter of medical criticism and in the course of time it began to rouse increasing public reaction. One of the great unsolved problems in this reaction has been the tendency to confuse the lump together two completely different classes of drug abuse. The first is the so-called medical drug abuse, the overuse of psychiatric drugs for treatment. This type has become somewhat more marked during recent years with the increasing availability of many kinds of drugs and has been strongly reinforced by the rising public expectations of freedom from all types of pain discomfort and unpleasant tension.

I may say that physicians that I have been in contact with agree that the tolerance for discomfort of the general population has been lowered visibly during our own professional experience.

Mr. GORDON. Doctor, may I interrupt you?

Dr. BRILL. Yes, sir.

Mr. GORDON. What is the effect on society of lower tolerance and also, that whenever we have some sort of a problem, we take tranquilizers?

Dr. BRILL. It is very difficult for me to give you a meaningful answer. Society always has taken drugs to reduce tension. Alcohol, of course, is a classical one. Many other drugs have been taken that are far more dangerous than some of the drugs we are talking about today. So that human beings have traditionally turned to drugs to reduce tension.

My own feeling is that there is no visible overall effect from taking drugs of this sort in the total picture. Now, it may be possible to find such effects by specific research. I don't know of such research.

Senator NELSON. What exactly do you mean by the statement that

during your own medical practice or the medical practice of your contemporaries there has been a reduced tolerance for the acceptance of tensions? This is, I assume, psychological?

Dr. BRILL. Yes. This is not limited to medicine, this is a general social phenomenon. It is particularly visible, however, in connection with mental disorder, and emotional disorder; people demand relief and expect relief to a greater extent and are willing to tolerate discomfort to a lesser extent than they were 35 years ago. They don't expect to be uncomfortable, they expect relief, and they want it now.

You see, the flood of new drugs has raised public expectations as to what can be expected from drugs. Now, a great deal more can be expected than was possible 35 years ago, but not quite as much as the public thinks.

Senator NELSON. If I understand it, you said the threshold for pain has been lowered?

Dr. BRILL. Physical and psychological, I would say so.

Senator NELSON. I suppose they are inextricably tied together, is that correct?

Dr. BRILL. They are.

Senator NELSON. And the capacity for tolerance of pain is associated with the mental attitude of the subject, is that what you are saying?

Dr. BRILL. Yes. It goes even further than that. If one can disassociate the emotional aspects of pain from the physical aspects of pain it no longer is so intolerable. This can be done by various procedures. And it is quite striking to see that even though the physical pain continues after the emotional aspects have been removed, the suffering is far less. So that it is the emotional aspects of pain that are really the intolerable aspects.

Senator NELSON. Please continue.

Dr. BRILL. To continue now with the description of medical drug abuse which must be distinguished from nonmedical for meaningful discussion, medical drug abuse involves persons of mature years, both men and women equally; it is a solitary problem and not a group activity; and it is scattered diffusely through the social structure. It has no tendency to social catagion or to antisocial behavior and the resulting damage is to the individual. This is the group created by overt medication.

The second group of drug abusing cases is nonmedical. They are young, predominantly male, and they seek drug intoxication as a source of pleasure. Theirs is a group activity, socially contagious, and thus a threat to others. Antisocial behavior is not infrequent and the drugs are largely illicit. Such cases have nothing to do with the problem of overmedication and little contact with medical practice except when they are brought for treatment of their dependence and its complications.

Opinions about the value of drugs in psychiatry has swung like a pendulum. When I entered medicine in 1932, the medical attitudes about all drug therapy was one of profound skepticism. The few drugs which had some influence in mental and emotional conditions were seen as relatively harmless but ineffective in small doses and dangerously toxic in larger amounts. Then came an era of spectacular advance in pharmacology and with the appearance of the "miracle drugs"

skepticism gave way to an unbounded optimism which in retrospect is easy to understand. I myself saw the new tranquilizers initiate a revolutionary advance in our own hospitals as they did in mental hospitals all over the world. A long-term relentless increase of population was suddenly halted and reversed, the atmopshere in the wards became quiet and relaxed, restraints disappeared, and the open ward finally became a reality for all psychiatric institutions. Some 60 percent or more of mental hospital cases were soon on drug therapy and this is the situation currently. In the meantime, penicillin had made paresis a thing of the past; the anticonvulsants phenobarbital and diphenylhydration were presenting the psychiatric complications of epilepsy so well that special hospitals for this condition were disappearing while other drugs lightened the burden of mental patients by spectacular control of many infections including tuberculosis which in our patients had produced a mortality 19 times as high as it did in the general population.

Senator NELSON. You are saying that patients in mental institutions had a tuberculosis mortality 19 times higher than others?

Dr. BRILL. To put it slightly differently, the mortality for the tuberculosis in mental hospitals was 19 times as high as the tuberculosis mortality in the general population at a specific point——

Senator NELSON. What is the explanation for that?

Dr. BRILL. Poor hygiene, poor nutrition, and close contact with contagion from one to the other. At that time, in the 1930's, and before, there was no repeated screening of the population with X-ray to screen out active cases, and contagion spread like wildfire from a single focus. This has changed dramatically.

Under such conditions the general public and the medical profession was ready to believe almost any claim made for a new drug and correspondingly the demand for relief of symptoms was increased.

Senator NELSON. You mentioned a moment ago that a census of mental hospitals showed that the number of patients had dropped drastically, and I think we have had some statistics here on that. Are there any good statistics to show how many patients, who would otherwise be confined to a hospital, are in fact able to be employed? We have statistics to show that the number in hospitals dropped from 750,000 to a half million in the past 15 years, but I don't believe we have had any statistics indicating the number of patients released from the hospitals who were able subsequently to make a living or support themselves.

Dr. BRILL. You asked how good are the results of these release statistics?

Senator NELSON. Well, we know they are able to be out of the hospital, I assume, even though they continue to receive medication. How many of them are employable?

Dr. BRILL. The only large scale study of this type that I am familiar with crossed my desk only the other day. It is my recollection that it is a minority of the total number. And I will be glad to give you the figure—my recollection is, some where in the neighborhood of 40 percent, but I will give you the figure that I have.

Certainly by no means all of them.

On the other hand, these people are far better off, far happier and for more comfortable living free than living under the restraints and constraints of the mental hospital environment.

Senator NELSON. Will you please submit those figures?

(The information was subsequently received and follows:)

PILGRIM STATE HOSPITAL,
West Bretwood, N.Y. August 3, 1969.

Hon. GAYLORD NELSON,
Chairman, Monopoly Subcommittee,
U.S. Senate,
Washington, D.C.

Attention Mr. Gordon.

DEAR MR GORDON: During my testimony before Senator Nelson I promised to send on a statement of the work capacity of ex-mental patients, and I enclose a statement herewith. You may be able to get a much better description of the case material, and this may help interpreting the statistics.

To me they seem slightly pessimistic, but my recollection was of the 40% from Utah rather than the 25% in Boston. Both may be low figures since a large proportion of the cases were not in the Labor market because they were housewives so the data needs some further explanation. With all this I would guess that between 40% and 60% of the eligible and available cases do go to work.

Sincerely.

HENRY BRILL, M.D., *Director.*

TIPS AND TRENDS IN THE EMPLOYMENT OF THE MENTALLY HANDICAPPED

HOW EX-MENTAL PATIENTS ADJUST TO WORK

It isn't always easy. That's the conclusion of several studies of the job adjustment of ex-mental patients, rounded up by Dr. Joan H. Criswell, assistant chief of research grants and demonstrations of Social and Rehabilitation Services of H.E.W., in an article in *Rehabilitation Literature.* What the studies show:

Boston, Mass.—Only 25 percent of ex-mental patients with more than 90 days of hospitalization entered the labor market. Of these, half found jobs without help; most of the others needed months and sometimes years to adjust fully to the world of work.

Utah.—The full-time employment rate for all rehabilitated handicapped persons is 87 percent; for former mental patients, 41 percent. Ex-mental patients researchers found, need not only more counseling but different kinds of counseling tailored to their needs.

Vermont.—Many patients leaving the State hospital found "live-in" jobs that gave them some haven from the hurly-burly of everyday life. Two-thirds of the ex-patients still keep contact with rehabilitation counselors by phone, letters or personal visits.

These studies point up questions that researchers in the future are going to grapple with, Dr. Criswell said:

> Are we setting our sights too high to think of rehabilitation of marginally-employed ex-patients as a *permanent* return to full-time employment? Why can't we accept that they may have to quit once in a while to go back to the hospital?
>
> Can patients really think of themselves as "well" when they mingle only with patients in halfway houses and institutions? Shouldn't they have a chance to mix with non-patients?
>
> If some patients have trouble adjusting to the community, shouldn't the community make an effort to adjust to them? Can't community resources (labor, management, etc.) band together to furnish fuller living conditions for ex-patients (recreation, rehabilitation, social living)?

Dr. BRILL. Additional drugs appeared for treatment of major mental disorder and such substances came to be classed as major tranquilizers. Later a group of antidepressants were added and neither they nor

the major tranquilizers lent themselves to abuse by patients although they caused many other types of adverse reactions.

Very early in this period another new class of drugs later known as minor tranquilizers was introduced particularly for outpatient work. It was soon obvious that the spectacular mental hospital results were not to be repeated with these drugs in outpatients.

It was also clear that these drugs belonged to the general class of barbiturate-like drugs although their effect on anxiety was more pronounced in relation to the degree of somnolence produced. They also shared another characteristic of the barbiturates; if used in high doses for prolonged period they were capable of creating addiction. While not attractive to street addicts or to nonmedical drug abusers they still posed a problem in medical drug dependence. Together with the stimulant drugs which are also used in outpatient practice they have become a matter of increasing concern, although other forms of toxicity are relatively mild in most cases. As early as 1957, many questions were being raised about the effects of all the new psychiatric drugs; but their use continued to increase rapidly. Accounts in the public press and promotion to the medical profession undoubtedly played a large role in the speed with which the minor tranquilizers were widely accepted, but it would be a serious mistake to assume that this was solely and simply an interest induced in an otherwise healthy population.

These drugs fell short of public expectations and there was doubt as to how well they met the needs of the patients but there could be no question about the existence of a need for treatment. This was only too apparent in simple clinical experience and repeated scientific surveys showed that between 15 percent and 25 percent of the total adult population suffer from a disabling degree of psychiatric disorder at any given time although such disability is only practical in most cases. The situation was further complicated by the fact that in ordinary medical practice major physical illness is regularly accompanied by anxieties and tensions which must be controlled if they are not to prolong the condition or even threaten life itself.

As a result the use of all these drugs was not limited to well defined indications but extended to the widest variety of conditions. They were often combined with other drugs and the treatment of emotional disorders often resolved itself into nothing more than a long term self-administration of these drugs. That this represents inadequate medical practice is beyond argument and it has been opposed by organized medicine and academic groups everywhere, but it was not until the thalidomide disaster that the general optimism about all drugs disappeared and the pendulum swung to skepticism. In the case of psychiatric drugs the negative trend was intensified by a wave of illicit nonmedical drug abuse which has now become a public health problem of epidemic proportions.

And I may say as an aside here that nonmedical drug abuse has virtually nothing to do with the medical type of drug abuse, which is an adverse reaction of over use of the type of drugs we are talking about. As already mentioned, nonmedical abuse of drugs as intoxicants rather than as medicines is a separate problem so that in effect

we have at present two drugs abuse problems which are relatively unrelated.

In spite of the swing to skepticism we continue to be an over-medicated society with respect to psychiatric drugs in that we are treating many persons who derive little or no benefit other than a suggestive effect and some suffer adverse effects from the medications.

It would be relatively easy to discuss this issue in the relatively narrow context of the statistics of psychotropic drug use, the proportion of adverse reactions, trends in these figures, and estimates as to the proportion of abuse, but such discussion constitutes more a statement of the problem than a contribution to a solution. It does not tell us how we may go about reducing the total drug intake without interfering with that part which is necessary. A widespread and urgent human need is involved and it would seem from all past experience in this field that the demand for relief of psychiatric symptoms will not abate until it is met more effectively. The problem is by no means new nor is it only the expression of the specific stresses of our own time. The irrational in human behavior is traced broadly throughout the entire history of mankind. Mental and emotional disorder was so prevalent among the illustrious associates of Aristotle that he declared genius and insanity to be closely related and a list of the mentally ill among the historical figures of the world shows that they had their full share of psychiatric disorder by our modern epidemiological standards and we can assume that this was true also of their less well observed contemporaries. If we include alcohol among the psychiatric drugs, we have further evidence of the nature of the problem and the broad context in which a solution will probably have to be sought.

I must confess that I have only a few simple, somewhat scattered, and by no means original thoughts as to solutions. It would seem that a purely negative program which seeks only to cut off a flow of misleading information to physicians and to the general public may have some effect, but it is likely to fail of its full purpose because of the firmly entrenched public and professional attitudes and practices with respect to substances of this type. Such practices long antedate the appearance of modern drugs and represent a type of folklore and tradition that has proved to be extraordinarily persistent. Seen in historical perspective, the modern sedatives and stimulants merely replaced an older series of tonics and sedatives which in turn had replaced a still older less effective and more dangerous pharmacopeia. To change this it would seem necessary to displace any biased flow of data by creating a program of better information for the public and for the profession. In so doing it would be well to study the way in which the commercial material is prepared, and to make full use of the educational techniques which have been developed there. Such a program would require a steady flow of continually updated drug information clearly written, brief and succinct, easily understood, well printed, and liberally illustrated.

Senator NELSON. Who would furnish this?

Dr. BRILL. I have left that open, but the implication is that it would have to have Government support.

Senator NELSON. And how would it be disseminated?

Dr. BRILL. I think that this will appear in the immediately following sentences, and perhaps to avoid repeating myself, I will say something about it after I have finished the paragraph.

The specific data on individual drugs would be presented in the context of the newest developments in the basic sciences such as physiology, pharmacology, and pharmacological chemistry, and it would be low in cost or free. A major start in this type of educational program applied to a variety of topics has already been made by a number of governmental and private agencies, but it has not as yet received sufficient support to comprise an overall and comprehensive operation.

To answer your question, Senator, I think that there are various mechanisms that could be set in motion. Perhaps the simplest would be some central agency which would have the responsibility to see that there is a comprehensive program and which could make use of voluntary agencies and Government agencies to increase the flow of the kind of information which I have in mind.

Now, it might seem unworthy to call attention to this, but I have seen some of the material available from the Communist countries. They have moved in this direction, of course, far less effectively than our commercial interests. But the trend for providing adequate and easily available information of this type I think is worldwide. It just hasn't gained a great deal of momentum. The British have done quite a bit along this line. But all advance is held back by a simple lack of funds.

I would particularly urge that good writing and good format are extremely important in this sort of thing.

Senator NELSON. What about the role of the medical journals and publications in the field?

Dr. BRILL. The medical journals present to a large extent materials and scientific papers that have been written on specific topics. I have in mind a type of review, a type of digest of the material appearing in the current medical journals. The New York Academy of Science publishes a little brochure every month which features articles of this type. And if you like, I can send that on to you so that you can have an idea. There are a number of publications. But there is no comprehensive program. And this is the sort of thing that I think might very well compete with any commercial flooding of the market.

Senator NELSON. Perhaps both of you may wish to comment on this. I have been looking at the medical publications, but I haven't made what might be called an exhaustive examination. I believe it is generally conceded that the most comprehensive survey ever done by a distinguished group of scientists is the National Academy of Science Council of Research's evaluation of drug efficacy of all the drugs in the marketplace.

I haven't looked at all medical publications, so I have to hedge a bit. However, except for the New England Journal of Medicine, those that I have looked at have not made a substantial, or at least what I would consider a substantial, presentation of the conclusions of the National Academy of Sciences-National Research Council, particularly with regard to their recommendation on the fixed combination antibiotics. The Journal of the American Medical Association and several other medical publications, which I have examined, have given sub-

stantial space to attacking the conclusions of the National Academy of Sciences without presenting them in full.

This astonished me, because in reading the history and background of the legislation, and in looking at the formulation of the panels by an independent body, and noting the great distinction of the clinicians who participated on these panels, I would have thought that the scientific publications would have made front page banner headlines in great detail about what the panels said about the fixed combination antibiotics. Yet as I look at the publications I find they are still carrying full-page ads of the fixed combinations which the National Academy says ought to be removed from the market. The FDA also says they should be removed from the market. In the editorial text of the Journal of the American Medical Association itself—10 years ago there was an article signed by Dr. Dowling, who was a former chairman of the AMA's Council of Drugs, that there is no rational reason for using fixed combinations. Can you, as physicians, give us an explanation? If the medical publications themselves aren't going to carry this distinguished material what makes you think they will carry what you are talking about—which incidentally I think would be a very important advance.

Dr. BRILL. I will try to answer first, and I think Dr. Freyhan might want to get into the discussion at this point.

I had in mind perhaps a Government subsidized operation which would make use of good science writers, and make use of the best and most authentic material in the field, which would be uninfluenced by any other consideration except about medical principles and practices. I don't think that we should try to abolish differences of opinion among medical writers or within the profession, even opinions that we might disagree with, like fixed combinations. I personally am quite doubtful about the value of these combinations. I share the more conservative view on this, but I wouldn't want to foreclose the right of other people to express a contrary opinion.

Senator NELSON. I am not qualified to have a viewpoint about this particular matter but I just want to point out that the five panels on antibiotics were composed of very distinguished people and their conclusions were unanimous. The point I raise is that a good many of the medical publications—and I don't say all because I haven't looked at all of them—except the New England Journal didn't bother to present the comprehensive viewpoint expressed and the conclusions reached by the National Academy of Sciences.

Those that I have looked at ran lengthy criticisms from independent practitioners around the country attacking the National Research Council's results. And in reading the attacks it was clear to me that the physicians who were attacking hadn't read the National Academy of Sciences' conclusion, because they were attacking things the Academy had not said.

This is the point I am making. The medical profession itself is not prepared to present in great detail conclusions reached by a distinguished panel, whether they agree or not, and I am sure if there is criticism of it that they ought to run that too. However, you are making the suggestion that the Government present papers evaluating these situations by objective scientists. How would you get a more ob-

jective group than the panels, and how would you get their views to the medical profession if their publications aren't going to give it a fair play? That is the question I am raising.

Dr. BRILL. Always such decisions are the decisions of a group of people in an editorial position. And I am sure it is done in good faith. But my suggestion would be that somehow the medical profession be put in the position to publish other material, making good use of science writers, making good use of the best forms of presentation, and that this be in the hands of the medical profession. I don't mean to suggest that the Government should do it, but it should make it possible for the medical profession to do it, not held back by any economic considerations.

Senator NELSON. I would agree that it should be made possible. But I just raise the point that it is a very significant development that has been downplayed in many of the medical publications—I haven't had a chance to look at all of them, but they were downplayed in many. And all of these publications are taking ads for the drugs which each panel of the National Academy of Science-National Research Council on Antibiotics unanimously recommended ought to be removed from the marketplace. I think it raises very serious questions.

Did you want to comment on it, Dr. Freyhan?

Dr. FREYHAN. I believe there is one small oasis in the desert, Senator, and that is the Medical Letter. I am sure that you are familiar with the unique position of the Medical Letter. At the recent 10th anniversary dinner in honor of the Medical Letter, one of the speakers suggested that the Medical Letter be supported by the Government to insure the widest possible circulation to all physicians. I don't know whether the Medical Letter actually wants this, but I thought that this was an interesting suggestion. I understand that the Medical Letter now appears in various languages because of the professional interest in objective drug evaluations. While some of the evaluations may be too severe, they do represent a consensus of many consultants whose opinions are ascertained prior to any publication. Moreover the Medical Letter has a sound policy of reevaluating drugs from time to time to add new information from clinical experience and published literature.

So this may be the answer to look for. I think this may be the only publication so far that is an objective appraisal of a nonprofit organization, not tied to the industry, and not accepting any advertisements.

Senator NELSON. I think that every witness who has commented on the Medical Letter in the past 2¼ years before this committee has spoken of it with the same respect that you have. And someone did make a suggestion that the Government subsidize it to which, according to my memory, the Medical Letter people reacted quite negatively. I suppose one of the questions that we are concerned with is that there are a good many people who are very biased against anything associated with the Government. You will note continuous attacks by certain members of the medical profession on the Food and Drug Administration or the HEW, and any funding tie might very well cause them to lose some of the regard that they now have. But certainly all of the witnesses who have commented—and there have been a number—have agreed that the Medical Letter is a very fine publication.

My recollection is that circulation is unfortunately somewhere in the 30,000 or 35,000 range, which is quite a limited distribution to a profession which has some 325,000 members.

But it still raises a tough question. When the publications that are professional publications treat this kind of a distinguished report in the skeptical way that a number of them have——

Dr. BRILL. I am familiar with the report. I had something to do with the activities of one of the associated groups in the National Research Council. And I would feel that a digest of what was developed by this group would be very valuable if well presented and made available to the profession. Now, I would not be in favor of a single party line on drugs. Science is too full of unpleasant surprises where the minority or the oddball opinion turns out to be correct, and the opinion of the authority turns out to be in error, so that one cannot take a single line on scientific matters. Yet a completely free and unbiased presentation of material which is guided by and built on good, general, basic principles in pharmacology and therapy, I think this is something that would be beyond controversy.

And I may say that with respect to all the details one can argue, but with respect to the general principles of therapy there is far more consensus of opinion, and it is possible to develop presentations of the type of the Medical Letter that look unbiased and really are unbiased.

Senator NELSON. Please continue.

Dr. BRILL. Finally, it would be a major mistake if we were to allow our concern about the drawbacks, limitations, and abuses of currently available psychiatric drugs to blind us to the potential which future drugs may have in psychiatry or if it were to cause to withhold support of research in this field or even actively to discourage such research. There is an urgent need for large-scale methods of treatment not only of pathological anxiety, and depression and of schizophrenia, but even more for pathological states of aggression and inertia. There is no theoretical reason why we should not expect to find part of the solution in new drugs and no method of therapy is more likely to permit large-scale application than is drug therapy. This does not mean that we shall in the future be able to depend on drugs alone any more than we can now depend on unaided drugs for other medical purposes. On the other hand new drugs combined with other methods have accomplished great advances in the last 20 years; advances which I believe could not have been achieved by other techniques alone; it would seem that a similar pattern of coordinated advance using new drugs and new psychiatric techniques can be expected to carry us further forward in the future.

Thank you very much.

Senator NELSON. Thank you, Dr. Brill, for a very fine statement.

(The complete prepared statement of Dr. Brill follows:)

STATEMENT BY HENRY BRILL, M.D.

Mr. Chairman and Members of the Subcommittee, I am Dr. Henry Brill of West Brentwood, New York. I am Director of Pilgrim State Hospital, President of the American College of Neuropsychopharmacology, Chairman of the American Medical Association Committee on Alcoholism and Drug Dependence, Chairman of the National Research Council Committee on Problems of Drug Depend-

ence and a member of the Expert Committee on Drug Dependence of the World Health Organization. I have also been First Deputy Commissioner of the New York State Department of Mental Hygiene, and Vice Chairman of the New York State Narcotic Addiction Control Commission. During the early 1950's, I was instrumental in the initiation and organization of the large scale program of tranquilizing drug therapy in the New York State mental hospitals and later on was charged with the development of the Department's program for treatment of narcotic addicts, and subsequently as Vice Chairman of the Commission was assigned for two years to assist in the development of the State's comprehensive program for control of drug dependence.

I do not speak for any of these groups today, but am here in a purely personal capacity and appreciate the opportunity of appearing before your committee to speak about psychotropic drugs. The organizations and the experiences are listed as qualifying background for the statement, and you will note that none of these activities provides a special knowledge with respect to the economics of drug development and distribution nor with regard to merchandising or marketing practices such as advertising or promotion. Nevertheless, I have been active for many years in areas which are closely related and hope that some of the comments will cast additional light on the central questions which interest your committee.

If we discuss these questions in a narrow context, it is quickly apparent that we are indeed an over-medicated society. Even without statistics common experience is such that it is generally conceded that a vast amount of the psychotropic medication which is dispensed is unnecessary, and even allowing for the fact that a goodly proportion of it never gets beyond the family medicine cabinet. These data are often taken to mean that a large number of cases do not need treatment at all and with this I cannot agree. To me the term over-medication means essentially that the drugs are of little or no value for the condition under treatment. Information from every available source agrees that there is a vast amount of untreated nervous and mental disorder in our general population. These disorders lie behind a great deal of alcoholism, taking of illicit drugs, and much of the disordered disruptive and dangerous behavior which fills so much space in the daily press. Psychiatric disorder is by no means confined to the more traditional neuroses and psychosomatic illnesses. We are thus an over-medicated society relative to our capacity to treat and to cure, but not in relation to our need for treatment.

The problems of over-medication are probably as old as history. Drugs which affect the mental state are among the easiest to identify, and they were among the earliest medications. Alcohol, which is a drug by all except legal definition, was known before bread was; or so it is thought, and the story of the first hypnotic and hallucination producing drugs is lost in antiquity. The sedatives as we know them today first began to appear after 1850 and each of them in turn was much over-used. This includes the bromides, chloral, and the barbiturates. Of course during all this time, alcohol continued to be the most widely used tranquilizer as it is today, leaving aside its even greater use for social pleasure. The over-use of all of these drugs has long been a matter of medical concern. Ancient Roman writers warned about the dangers of medications "which darken the mind"; and during the 19th century abuse of opiates was condemned in almost the same terms as was the abuse of alcohol. When the sedatives appeared, their abuse also quickly became a matter of medical concern and in the course of time it began to rouse increasing public reaction. During this period and since, there has been a continuing tendency to confuse two completely different classes of drug abuse. The first is the so-called medical drug abuse, the over-use of psychiatric drugs for treatment of various symptoms.

This has become more marked during recent years with the increasing availability of many kinds of drugs and has been strongly reinforced by the rising public expectations of freedom from all types of pain discomfort and unpleasant tension. Medical abuse involves persons of mature years who abuse drugs to relieve symptoms. It is a solitary problem and not a group activity, and it is scattered diffusely through the social structure. It has no tendency to social contagion or to antisocial behavior and the resulting damage is to the individual. These cases are often seen in clinical settings.

The second group of drug abusing cases is non-medical. They are young, predominantly male, and thus seek drug intoxication as a source of pleasure. Theirs is a group activity, a social contagion, and thus a threat to others. Antisocial

behavior is not infrequent and the drugs are largely illicit. Such cases have relatively little contact with medical practice except when they are brought for treatment of their dependence and its complications.

When I entered medicine in 1932, bromide over-use accounted for many admissions to psychiatric hospitals and barbiturate complications were already a common place in medical practice. Medical attitudes toward all drugs therapy was one of profound skepticism and the few drugs which had some influence in mental and emotional conditions were seen as relatively harmless, but ineffective if used in small doses and dangerously toxic in larger amounts. Then came an era of spectacular advance in pharmacology and with the appearance of the miracle drugs skepticism gave way to an unbounded optimism which in retrospect is easy to understand. I saw the new tranquilizers initiate a revolutionary advance in our own hospitals and in mental hospitals all over the world. A long-term relentless increase of population was suddenly halted and reversed, the atmosphere in the wards became quiet and relaxed, restraints disappeared, and the open mental hospital ward finally became a reality for all psychiatric institutions. Some 60% or more of mental hospital cases were soon on drug therapy and this is the situation currently. In the meantime, penicillin had made paresis a thing of the past; the anticonvulsants phenobarbtial and diphenylhydantoin were preventing the psychiatric complications of epilepsy so well that special hospitals for this condition began to disappear while other new drugs lightened the burden of mental patients by spectacular control of many infections including tuberculosis which in our patients had produced a mortality 19 times as high as it did in the general population. Under such conditions the general public and the medical profession was ready to believe almost any claim made for a new drug and correspondingly the demand for relief of symptoms was increased.

Additional drugs appeared for the treatment of major mental disorder and such substances came to be classed as major tranquilizers. Later a special group of anti-depressants were added and neither these nor the major tranquilizers created problems of abuse by patients although they caused many other types of adverse reactions.

Very early in this period a new class of drugs later known as minor tranquilizers was introduced particularly for out-patient work. From the very start it was obvious that the spectacular results of mental hospital practice were not to be repeated with these new drugs in out-patients with less serious forms of disorder. It was also clear that these drugs belonged to the general class of barbiturate-like drugs although their effect on anxiety was more pronounced in relation to the degree of somnolence produced. They also shared another characteristic of the barbiturates; if used in high doses for prolonged periods they were capable of creating an addiction. While not as attractive to "street addicts" or non-medical drug abusers they still posed a problem in medical drug dependence and together with the stimulant drugs which are also used in out-patient practices they have become a matter of serious concern, although other forms of toxicity are relatively mild in most cases.

As early as 1957, many questions were being raised about the effects of all the new psychiatric drugs; but their use continued to increase rapidly. Accounts in the public press and promotion to the medical profession undoubtedly played a large role in the rapidity with which the minor tranquilizers were widely accepted, but it would be a serious mistake to assume that this was solely and simply an interest induced in an otherwise healthy population. The effects of these drugs fell short of expectations and there was much concern as to how well they met the needs of the patients but there could be no doubt about the existence of a vast need. This was only too apparent in simple clinical experience and repeated scientific surveys showed that between 15% and 25% of the total adult population suffer from a disabling degree of psychiatric disorder at any given time although such disability is only partial in most cases. The situation was further complicated by the fact that in ordinary medical practice major physical illness is regularly accompanied by anxieties and tensions which must be controlled if they are not to prolong the condition or even threaten life itself.

As a result the use of all these drugs was not limited to well defined indications but came to be applied in the widest variety of conditions often combined with other drugs and the treatment of many emotional disorders resolved itself into nothing more than a long term self-administration of these drugs. That this represents inadequate medical practice is beyond argument and it has been opposed by organized medicine and academic groups everywhere, but it was not

until the thalidimide disaster that the general optimism about all drugs disappeared and was replace by a growing skepticism. In the case of psychiatric drugs the negative trend was intensified by a wave of illicit non-medical drug abuse which has become a public health problem of epidemic proportions. As already mentioned this constitutes abuse of drugs as intoxicants rather than as medicines so that in effect we have at present two drug abuse problems which are relatively unrelated.

In spite of all this we continue to be an over-medicated society with respect to psychiatric drugs in the sense that we are treating many persons who derive little or no benefit other than a suggestive effect and some suffer adverse effects from the medications. It would be relatively easy to discuss this issue in a relatively narrow context describing the statistics of psychotropic drug use, the proportion of adverse reactions and trends in these figures, and to make estimates as to the proportion of abuse, but such discussion constitutes more a statement of the problem than a contribution to a solution. It does not tell us how we may go about reducing the total of drug intake without interfering with that part which is necessary. A widespread and urgent human need is involved and it would seem from all past experience in this field that the demand for relief of psychiatric symptoms will not abate until it is met more effectively. The problem is by no means new nor is it only the expression of the specific stresses of our own time. The irrational in human behavior is traced broadly throughout the entire history of mankind. Mental and emotional disorder was so prevalent among the illustrious associates of Aristotle that he declared genius and insanity to be closely related and a list of the mentally ill among the historical figures of the world shows that they had their full share of psychiatric disorder by our modern standards and we can assume that this was true also of their less well observed contemporaries. If we include alcohol among the psychiatric drugs, we have further evidence of the nature of the problem and the broad context in which a solution will probably have to be sought.

I must confess that I have only a few simple somewhat scattered, and by no means original thoughts as to solutions. It would seem that a purely negative program which seeks only to cut off a flow of misleading information to physicians and to the general public may have some effect, but it is likely to fail of its full purpose because of the firmly entrenched public and professional attitudes and practices with respect to substances of this type. Such practices long antedate the appearance of modern drugs and represent a type of folklore and traditon that has proved to be extraordinarily persistent. Seen in historical perspective, the modern sedatives and stimulants merely replaced an older series of tonics and sedatives which in turn had replaced a still older less effective and more dangerous pharmacopeia. It would seem better to seek to replace this biased flow of data by providing better information to the public and to the profession. In so doing it would be well to study the way in which the commerical material is prepared, and to make full use of the educational techniques which have been developed there for the profession. This would require a continual flow of completely updated drug information which is clearly written, brief and succinct, easily understood, well printed and liberally illustrated. The specific data on individual drugs would be present in the context of the newest developments in the basic sciences such as physiology, pharmacology and pharmacological chemistry, and it should be low in cost or free. A major start in this type of professional educational program applied to a variety of topics has already been made by a number of governmental and private agencies, but it has not as yet received sufficient support to comprise an over-all and comprehensive operation.

Finally it would be a major mistake if we were to allow our concern about the drawbacks, limitations, and abuses of currently available psychiatric drugs to blind us to the potential which future drugs may have in psychiatry and to lose interest in support of research in this field or even to discourage such research. There is an urgent need for large scale methods of treatment not only of pathological anxiety, and depression and of schizophrenia, but even more for pathological states of aggression and intertia. There is no theoretical reason why we should not expect to find part of the solution in new drugh and no method of therapy is more likely to permit large scale application than is drug therapy. This does not mean that we shall in the future be able to depend on drugs alone any more than we can now depend on unaided drugs for other medical purposes.

On the other hand new drugs combined with other methods have accomplished great advances in the last 20 years. Advances which I believe could not have been achieved by other techniques alone. It would seem that a similar pattern of coordinated advance using new drugs and new psychiatric techniques can be expected to carry us further forward in the future.

Senator NELSON. Mr. Gordon.

Mr. GORDON. Concerning the drugs you are talking about, are you referring here also to the minor tranquilizers that are used for such symptoms as anxiety, pain, and so forth, by the general population.

Dr. BRILL. I am not sure that I understand your question.

Mr. GORDON. You talk about having more abuses of currently available psychiatric drugs, and also about more research—I suppose you are thinking in terms of perhaps Government sponsored research——

Dr. BRILL. Yes, indeed.

Mr. GORDON. Are you including the minor tranquilizers, especially those that are used for nonpsychiatric disorders?

Dr. BRILL. On the tranquilizers, I think we are troubled by a matter of definition. If one defines psychiatric disorders as psychoses, then of course they would be used for nonpsychiatric disorders. But I think that for the most part they are used in people who have psychiatric disorders. The problem is that they are not as effective as we would like to have them be by a long measure. They are used particularly for the control of anxiety, but they do not control anxiety very effectively, although they have certain values.

I certainly would feel that continued research for better antianxiety drugs is of tremendous importance, because anxiety is a part of most psychiatric disorders, and anxiety is also a component of physical illness that kills and disables people. It is impossible to treat many physical conditions unless one can control anxiety.

Take the case of a coronary attack. It is impossible to treat coronary thrombosis unless you can control the fear that goes with it—there is a specific fear that goes with a coronary attack, and unless you can control it the patient is likly to die.

Mr. GORDON. Doctor, would you advocate the type of research where there would be testing for relative efficacy and safety as well as the relative merits of the various drugs.

Dr. BRILL. Yes, sir. I think this is an important part of research.

Mr. GORDON. And you would make this available to the physicians so the medical community would know about the results?

Dr. BRILL. That is the kind of information that I think should be continually updated and easily seen.

Mr. GORDON. Do you know if there is much research conducted along these lines where one drug is tested against the other in an objective, scientific manner?

Dr. BRILL. The National Institutes of Health have been conducting studies of this type for a long time and supporting studies of this type. I think that this needs to be continued and expanded.

Senator NELSON. I take it we are talking about duplicative drugs, so to speak—that is, a drug is in the marketplace and another one that will perform the same function for the same problem is introduced into the marketplace, and frequently, as you know better than I, sometimes the new drugs are more toxic than the old ones, and are no more

efficacious. Are you discussing the case in which you would compare the drugs, which have the same function, for relative efficacy?

Dr. BRILL. That would be included. But I think there is a pitfall here, because relative statistical efficacy is not the same as relative individual efficacy. And unfortunately all of these issues are complicated by the fact that in many cases a given drug will be tolerated by one individual and not tolerated by another one, but a closely related drug will be tolerated by a second individual. So the evaluation is not merely a simple statistical evaluation as to how many people are benefited by drug A as compared with how many people are benefited by drug B.

Senator NELSON. Recognizing that to be true, I would assume, though, that in controlled studies you may develop very clear cases in which the statistical results demonstrate that one drug is more toxic than the other—in other words, over a period of time you can with controlled studies develop some distinctions, can you not?

Dr. BRILL. Very much so; and particularly the identification of long term toxicity is one of the more reliable results of such studies—and of course of acute toxicity.

Senator NELSON. Thank you very much, Dr. Brill.

Our next witness is Dr. F. A. Freyhan.

Dr. Freyhan, we are very pleased to have you come here today and present your statement to the committee.

STATEMENT OF DR. FRITZ A. FREYHAN, DIRECTOR OF RESEARCH, DEPARTMENT OF PSYCHIATRY, ST. VINCENT'S HOSPITAL, NEW YORK, N.Y.

Dr. FREYHAN. Thank you, Senator. I appreciate the opportunity of participating in this hearing.

In preparing my statement for this hearing I reviewed my previous testimony before Senator Kefauver and subsequently Senator Humphrey at committee hearings concerned with the vexing problems of the use and abuse of modern psychiatric drugs. In attempting to outline the problems as I see them today I must say at the outset that psychiatry could not have progressed to its present standards of therapeutic achievement without the discovery of not only new drugs, but unique methods of drug treatment for the benefit of a great multitude of patients with minor and major psychiatric disorders. After 15 years of drug treatment in psychiatry, one cannot seriously question that the merits and accomplishments greatly outweigh the combined disadvantages of toxicity and misuse.

But in spite of this record of excellence there are developments which are less assuring and potentially ominous. It is of course no secret that overuse of drugs, not just psychoactive drugs, represents a perplexing problem in contemporary medicine. Depending on orientation, bias and vested interests, the blame tends to be ascribed to our culture, to professional attitudes, and to the promotional influence of the commercial interests of the pharmaceutical industry. Since I want to avoid redundant generalizations which would be of little value for the work of this committee, I shall limit my comments to those matters which I regard as highly important yet rarely mentioned in public discussions.

To prescribe a drug presupposes competent judgment of a qualified

physician. He must be knowledgeable and experienced in various aspects of clinical pharmacology and therapeutic techniques. The rapid development of new drugs poses serious problems in terms of dissemination of knowledge and acquisition of therapeutic experience for physicians practicing medicine. But the therapeutic experience for psychiatry in this regard are unparalleled in any other medical specialty. When the modern drugs were first introduced 15 years ago, psychiatric orientation was at a stage furthest removed from the mainstream of medicine. One would therefore expect that the evolution of major pharmaco-therapy in psychiatry was accompanied by major changes in psychiatric training and education. But for reasons which are deeply anchored in the history and organization of psychiatry, pharmacopsychiatry, that is, the science of drugs relating to nature and treatment of psychiatric disorders, gained only minimal representation in academic curricula and post graduate training programs. Rather paradoxically then we now find that drugs have become the most widely used psychiatric treatment while psychiatric education still reveals a striking neglect in regard to theory and practice of drug treatment.

I should like to take the liberty to place in the record the briefest of my publications on this topic which is titled: "Drug Treatment and Psychiatric Education" and was published in the December 12, 1968, issue of Medical Tribune and Medical News.

Senator NELSON. It will be printed in the record.

(The document follows:)

[From Medical Tribune and Medical News, Thursday, December 12, 1968]

CURRENT OPINION—DRUG TREATMENT AND PSYCHIATRIC EDUCATION

(By F. A. Freyhan, M.D.[1])

The modern era of pharmacopsychiatry began in this country with the introduction of chlorpromazine and reserpine in 1954. It is estimated that today between 70 and 90 per cent of all psychiatric patients are treated with psychoactive drugs, whether alone or in combination with psychotherapy and other treatments. Moreover, a large segment of nonpsychiatric patients receive psychoactive drugs for complaints of anxiety, tension, or mood disturbances. What are so widely used today are not conventional medications, but ever more potent compounds with both highly complex therapeutic and adverse reactions. The latter are not limited to somatic reactions, but include psychotoxic complications and social side effects.

One would expect that the evolution of major pharmacotherapy in psychiatry led to significant changes in psychiatric training and education. That this is not the case has been shown by several official surveys of representative psychiatric training centers. Only a few training programs have placed appropriate emphasis on new knowledge derived from biological and social sciences. According to reported evidence, psychiatric residents during their three-year training period tend to lose their sense of identity as physicians and become isolated in their field of interest. A recent study by a joint committee of the American Psychiatric Association and the American College of Neuropsychopharmacology confirmed the virtual absence of systematic training in psychiatric pharmacotherapy. A few special lectures on psychopharmacology and bits of informal clinical instruction seem to be all the residents can expect. In general, drug treatment is neither taught nor supervised. This stands in stark contrast to

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psychotherapy, where intensive individual supervision—rightfully—considered of primary importance for teaching psychotherapy. But for lack of training, drugs may, and actually are, prescribed for the wrong reason, administered with faulty techniques, and evaluated without sufficient knowledge of action and complications.

Seen in historical perspective, this situation reflects an unresolved conflict in the relationship of psychiatry to medicine. When modern pharmacotherapy arrived on the therapeutic scene, psychiatric theory and practice were farthest removed from the mainstream of medicine. Lacking viable biological theories of mental disorders, professional interest focused primarily on psychodynamic theory and intensive psychotherapeutic methods. The rapid expansion of psychopharmacology into a new science with not only therapeutic but major theoretical significance for clinical psychiatry created serious controversies regarding changes in the conceptual frame of reference for treatment and training.

At present, pharmacopsychiatry appears to be in the paradoxical state of rapidly advancing theoretical knowledge, on one hand, and only hesitating progress in the quality of clinical treatment, on the other. There are, of course, many reasons for this disparity. The role of clinical pharmacology in medicine is today generally a matter of critical concern for professional and governmental authorities. Neither undergraduate teaching of pharmacology nor postgraduate education prepares physicians for their therapeutic responsibilities in the use of drugs. Furthermore, the rapidly growing number of new drugs overtaxes medical practitioners in all specialties.

But so far as psychiatry is concerned, the situation is still more complicated by the fact that drug treatment is regarded very ambivalently. Psychiatric theory has not been brought sufficiently up to date to bridge the gap between psychodynamic and psychobiological aspects of etiology and treatment. Psychotherapy is still widely taught to be the treatment of choice. Yet drugs have proved their value and are prescribed on an enormous scale by psychiatrists of all orientations. In the absence of valid differential evaluations of therapeutic methods, drug treatment is popularly rationalized as either a substitute for or adjunct to psychotherapy. While it is true that drug treatment can make patients accessible for psychotherapy, it is equally important to acknowledge that there are specific indications for only one, or only the other. A recent study evaluated the attitude of psychiatric residents on drug treatment of patients hospitalized in a prominent training center. Medication, it was found, was begun with equal promptness by physicians with psychoanalytic and eclectic orientation. This seemed to confirm the nonexistence of bias regarding drug treatment. Special tests were developed to evaluate these physicians' competence in the area of drug treatment. It turned out that both groups knew most about psychosocial, least about medical, aspects of drug treatment. But the psychotherapeutically oriented physicians scored worst on questions pertaining to adverse effects and pharmacological typology of drugs. The fact that physicians use drugs in spite of their biases, but without adequate knowledge in clinical pharmacology, may, therefore, seem more disturbing than if bias were to keep them from treating with drugs at all.

What amounts to a disturbing schism between psychiatric pharmacotherapy and medicine can not be viewed with complacency. A recent congress of ophthalmologists was reported to have brought to light an increasing incidence of glaucoma and other serious eye disorders due to antidepressants with anticholinergic effects. The opthalmologists were critical of the seemingly injudicious use of antidepressants by general practitioners, internists, and psychiatrists, since many patients had repeated episodes of glaucoma prior to the prescription of these drugs and because, in some instances, there had been repeated prescriptions despite the recurrence of serious ocular symptoms. An editor's comment on this report was to the effect that any physician who prescribes an antidepressant should be aware of the potential hazards to which he exposes a patient. But while nobody would disagree with this editorial opinion, it nevertheless fails to come to grips with the issue. As a matter of cold fact, neither evaluations of medical histories nor systematic physicial examinations are taught to be preliminary procedures for the prescription of antidepressants or, for that matter, other psychoactive drugs. Nor have standards for monitoring drug effects been developed, let alone implemented, to guard effectively against multitudes of adverse reactions.

The achievements of modern pharmacotherapy have yet to be matched with corresponding revisions of psychiatric theory, practice, and education. The implications for training can not be underestimated. Inevitably, new training programs should be brought closer to the mainstream of modern medicine.

Dr. FREYHAN. What seems to me discouraging, if not alarming, is the widening of a gap between advances in experimental and basic pharmacological research on the one hand, and the actual quality of clinical treatment on the other hand. One should not, as often seems to be the case, take it for granted that medical research and resulting clinical application could be regarded as two sides of the same coin. Insofar as psychopharmacology is concerned, it seems to me that interest and support given to laboratory research has not been matched by concern and funds for the development of high standards of clinical practice.

Although it is a matter of professional faith to support the cause of basic research, I am persuaded to take a different position at this time. Basic research today is relatively affluent whereas clinical research may be looked upon as a poor cousin. To obtain funds for expensive laboratory hardware seems easier to obtain than to convince granting agencies that high-quality clinical services represent, in fact, clinical laboratories for clinical therapuetic research.

In my testmony before the subcommittee in 1963, I suggested the development of an NIMH teaching and training center for clinical psychopharmacology. As Director of Clinical Studies at the Clinical Neuropharmacology Research Center of the NIMH at that time, I thought that the unique resources of the NIMH could turn the tide in establishing a model center of clinical training in psychopharmacology. This seemed even more desirable in view of the NIMH initiated development of nationwide community mental health centers in which drugs would be a major form of treatment. Whether this suggestion was premature, impractical, or too idealistic, is a matter of no concern today. Only today I am even more disturbed by the evidence of separation between high-caliber research in psychopharmacology, and the mediocre if not inadequate quality of drug treatment as practiced all too frequently.

Senator NELSON. Aren't there centers for the teaching of clinical psychopharmacology in any of the medical schools?

Dr. FREYHAN. Basic pharmacology is of course taught. Clinical pharmacology is a very neglected subject. Very few medical schools have a formal course in it. When it comes to postgraduate training—I am now talking about psychiatric training—the surveys which I mentioned, and my own experience in various university hospitals and other training centers, clearly confirm the lack of formally established programs for teaching clinical psychopharmacology.

Senator NELSON. Thank you.

Dr. FREYHAN. An interim appraisal of community mental health center services, published earlier this year by the Joint Information Service of the American Psychiatric Association and the National Association for Mental Health—Washington, D.C., 1969—disclose that up to 90 percent of the patients in the facilities under study received psychotropic drug treatment. I believe that this information adds to the compelling logic of the indivisibility of treatment, education and research.

Thus if we concern ourselves with the effects of the so-called tranquilizing, antidepressant, and anxiety-reducing drugs on the individual and our society, we must first of all be certain about the quality of treatment with these drugs as practiced. Undoubtedly the burden of the quality of treatment is in our medical schools, training centers, and on the medical profession. I am glad to report that there is greater awareness of the need for change which hopefully may bring about an improvement in training. I have the privilege of serving on various committees of national and international organizations which are exclusively concerned with the implementation of better training and higher standards of treatment.

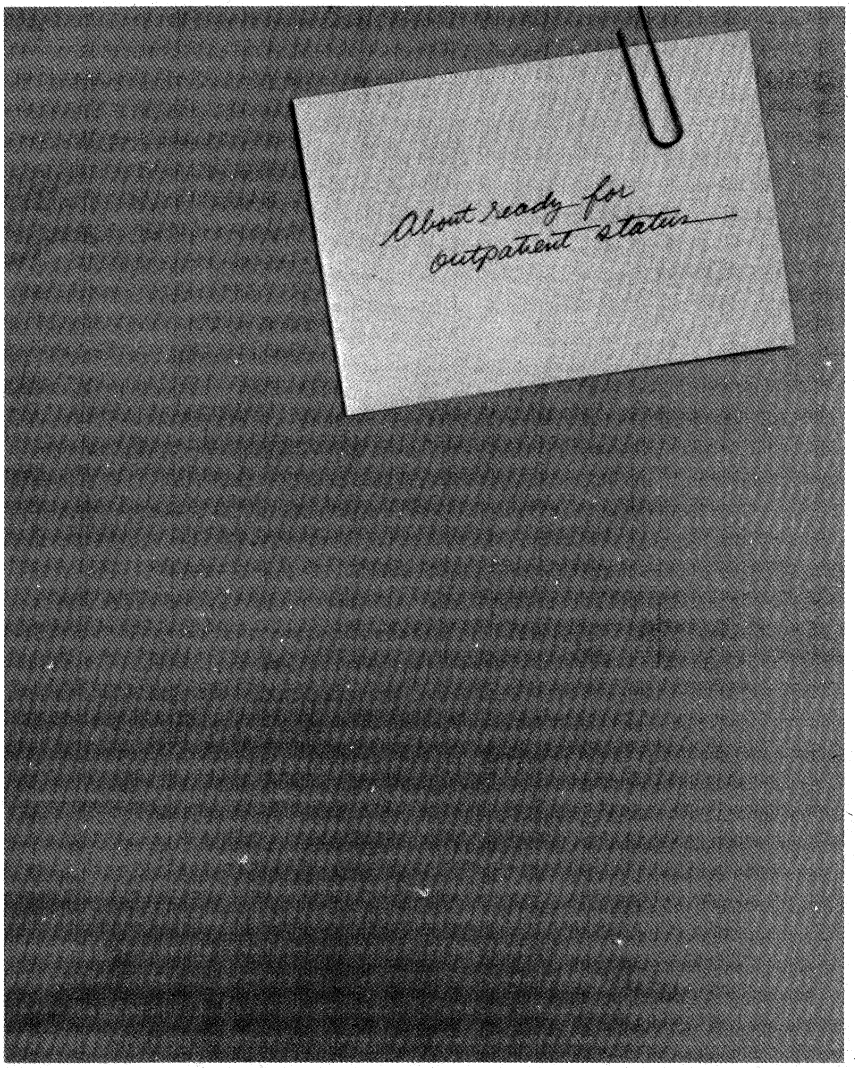
Yet stronger measures are needed to attach the persisting educational deficiencies on all fronts.

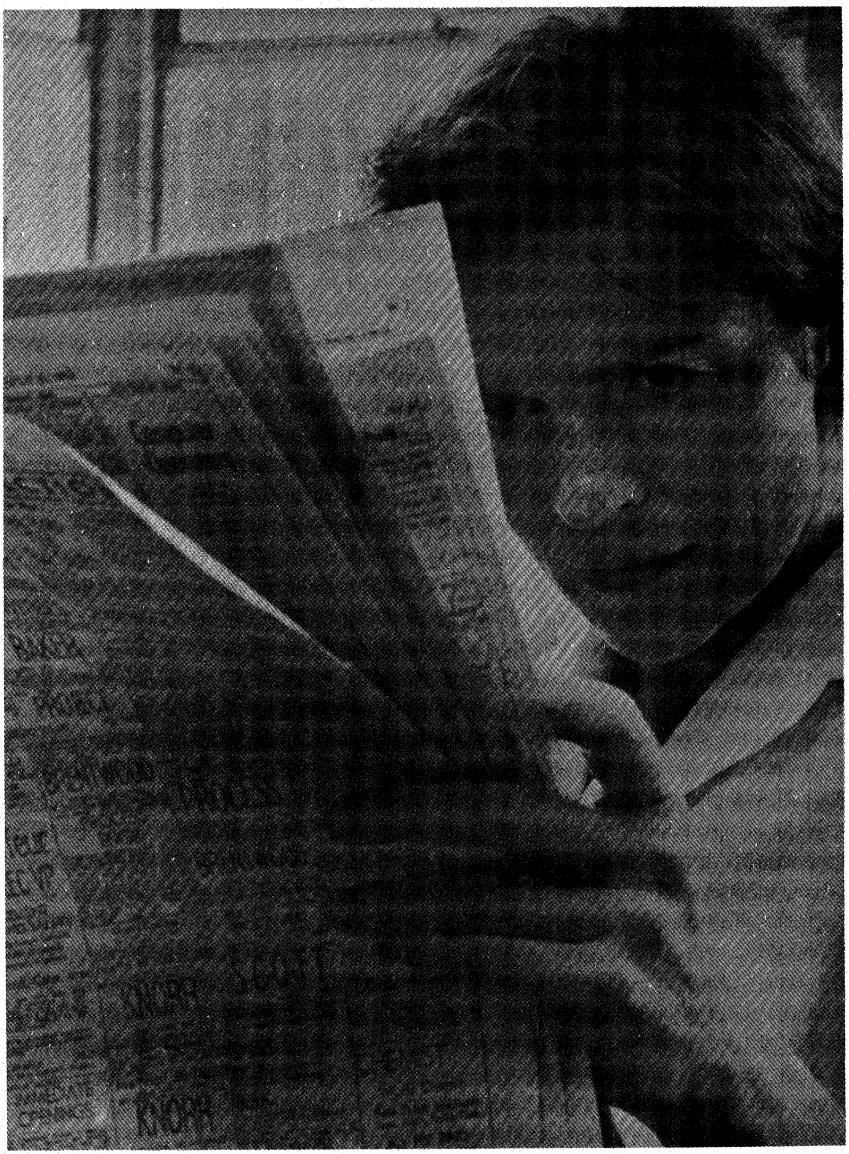
Turning to the influence of advertising on promotion of drugs I want to demonstrate the problem on the basis of a current advertisement for the drug, Valium, by Roche Laboratories.

I have a copy here if I may pass this to you.

Senator NELSON. The ad will be printed in the record at this point.

(The document follows:)


About ready for
outpatient status



Preparing the apprehensive patient for release...

-consider Valium®(diazepam) -before and after

As the big day approaches, her apprehension increases. Your encouragement may be all she needs; but during the hours you don't see her, extra help with Valium® (diazepam) may ease the transition.

As you discuss her plans and prepare the patient for outpatient status, you may be aware of increasing psychic tension underlying her natural excitement about release. In such cases, Valium (diazepam)—in addition to psychotherapeutic support—has often proved valuable in helping the patient through this crucial period of tension-arousing adjustments. More assured and less tense, she may be able to look ahead with confidence.

At the time of release, you are satisfied with her potential for growth, and she seems ready, but you may be concerned about the emotional demands of her new life. Here, again, if psychic tension can threaten a crisis when she's on her own, Valium—in concert with professional therapy—may help her stay calm through difficult situations or encounters.

For full prescribing information, please see page 6.

3

and as the newer patient progresses in psychotherapy—

to help allay psychic tension... Valium®(diazepam)

By helping to reduce the psychoneurotic patient's tension to more manageable levels, Valium (diazepam) may improve her ability to explore new experiences and verbalize them with you more freely. Under its calming influence, she often is less inclined to "tune out" whenever scheduled sessions touch upon sensitive issues, and she usually is also better able to communicate her own feelings and opinions. Because she is less distracted by physical and psychic stress, she tends to be more attentive and cooperative, more willing to interact with those about her. Thus, therapeutic sessions can become fruitful more rapidly; the patient's sense of well-being may improve.

Useful, too, for acute anxiety-tension states

For acutely agitated patients who require prompt calming, Valium (diazepam) is also available in ready-to-use ampuls for I.M. or I.V. administration. With Injectable Valium (diazepam), severe psychic tension is usually relieved within minutes. This parenteral dosage form has also proved effective for symptomatic relief in the treatment of acute alcohol withdrawal.

For full prescribing information, please see page 6.

Valium® (diazepam)

Tablets 2 mg, 5 mg, 10 mg

Ampuls 2 cc

By relieving psychic tension, it can help

- □ ease patients into therapy
- □ lessen reaction to crisis situations
- □ improve communication
- □ reduce tension-induced insomnia and fatigue
- □ relieve stress-induced psychosomatic symptoms
- □ support the patient between therapeutic sessions

Complete Prescribing Information

Description: (Oral and Injectable) Valium (diazepam) is a benzodiazepine derivative developed through original Roche research. Chemically, diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. It is a colorless crystalline compound, insoluble in water and has a molecular weight of 284.74.

Pharmacology: (Oral and Injectable) In animals Valium (diazepam) appears to act on parts of the limbic system, the thalamus and hypothalamus, and induces calming effects. Valium (diazepam), unlike chlorpromazine and reserpine, has no demonstrable peripheral autonomic blocking action, nor does it produce extrapyramidal side effects; however, animals treated with Valium (diazepam) do have a transient ataxia at higher doses. Valium (diazepam) was found to have transient cardiovascular depressor effects in dogs. Long-term experiments in rats revealed no disturbances of endocrine function. Injections into animals have produced localized irritation of tissue surrounding injection sites and some thickening of veins after intravenous use.

Oral LD_{50} of diazepam is 720 mg/kg in mice and 1240 mg/kg in rats. Intraperitoneal administration of 400 mg/kg to a monkey resulted in death on the sixth day.

Reproduction Studies: A series of rat reproduction studies was performed with diazepam in oral doses of 1, 10, 80 and 100 mg/kg. At 100 mg/kg there was a decrease in the number of pregnancies and surviving offspring in these rats. Neonatal survival of rats at doses lower than 100 mg/kg was within normal limits. Several neonates in these rat reproduction studies showed skeletal or other defects. Further studies in rats at doses up to and including 80 mg/kg/day did not reveal teratological effects on the offspring.

In humans, measurable blood levels of Valium (diazepam) were obtained in maternal and cord blood, indicating placental transfer of the drug.

Indications: ORAL AND INJECTABLE: Valium (diazepam) is useful in the symptomatic relief of tension and anxiety states resulting from stressful circumstances or whenever somatic complaints are concomitants of emotional factors. It is useful in psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation.

In acute alcohol withdrawal, Valium (diazepam) may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.

Valium (diazepam) is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma); spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia); athetosis; stiff-man syndrome.

ORAL: Oral Valium (diazepam) may be used adjunctively in convulsive disorders, although it has not proved useful as the sole therapy.

INJECTABLE: Tetanus. If apprehension, anxiety and acute stress reactions are present prior to gastroscopy and esophagoscopy, Injectable Valium (diazepam) may be a valuable adjunct. (See **Precautions.**)

Injectable Valium (diazepam) is a useful adjunct in status epilepticus and severe recurrent convulsive seizures.

Valium (diazepam) is a useful premedication (the I.M. route is preferred) for relief of anxiety and tension in patients who are to undergo surgical procedures. Intravenously, it is also useful prior to cardioversion. In either instance, the patient's recall of the procedure is markedly diminished.

Contraindications: ORAL: Valium (diazepam) is contraindicated in patients with a known hypersensitivity to this drug and, because of lack of sufficient clinical experience, in children under 6 months of age. It may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in acute narrow angle glaucoma.

INJECTABLE: Injectable Valium (diazepam) is contraindicated in infants and in patients with a known hypersensitivity to this drug. It may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in acute narrow angle glaucoma.

Warnings: ORAL AND INJECTABLE: As is true of most CNS-acting drugs, patients receiving Valium (diazepam) should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.

Since Valium (diazepam) has a central nervous system depressant effect, patients should be advised against the simultaneous ingestion of alcohol and other CNS-depressant drugs during Valium (diazepam) therapy.

ORAL: Valium (diazepam) is not of value in the treatment of psychotic patients and should not be employed in lieu of appropriate treatment. As with other agents which have anticonvulsant activity, when Valium (diazepam) is used as an adjunct in treating convulsive disorders, the possibility of an increase in the frequency and/or severity of grand mal seizures may require an increase in the dosage of standard anticonvulsant medication. Abrupt withdrawal of Valium (diazepam) in such cases may also be associated with a temporary increase in the frequency and/or severity of seizures.

INJECTABLE: When used intravenously the solution should be injected slowly, directly into the vein, taking at least one minute for each 5 mg (1 cc) given. Do not mix or dilute Injectable Valium (diazepam) with other solutions or drugs. Do not add to I.V. fluids. Injectable Valium (diazepam) is not recommended as the sole

treatment for psychotic or severely depressed patients. Injectable Valium (diazepam) should not be administered to patients in shock, coma, or in acute alcoholic intoxication with depression of vital signs.

Physical and Psychological Dependence: Withdrawal symptoms (similar in character to those noted with barbiturates and alcohol) have occurred following abrupt discontinuance of diazepam (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). These were usually limited to those patients who had received excessive doses over an extended period of time. Particularly addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving diazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

Use in Pregnancy: Use of any drug in pregnancy, lactation or in women of childbearing age requires that the potential benefit of the drug be weighed against its possible hazard to mother and child. (See *Reproduction Studies.*)

Management of Overdosage: Manifestations of Valium (diazepam) overdosage include somnolence, confusion, coma and diminished reflexes. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdosage, although, in general, these effects have been minimal following overdosage. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of Levophed® (levarterenol) or Aramine (metaraminol). Ritalin (methylphenidate) or caffeine and sodium benzoate may be given to combat CNS-depressive effects. Dialysis is of limited value. As with the management of intentional overdosage with any drug, it should be borne in mind that multiple agents may have been ingested.

Precautions: ORAL AND INJECTABLE: If Valium (diazepam) is to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed—particularly with known compounds which may potentiate the action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. The usual precautions are indicated for severely depressed patients or those in whom there is any evidence of latent depression; particularly the recognition that suicidal tendencies may be present and protective measures may be necessary. The usual precautions in treating patients with impaired renal or hepatic function should be observed.

ORAL: In elderly and debilitated patients, it is recommended that the dosage be limited to the smallest effective amount to preclude the development of ataxia or oversedation (2 mg to 2½ mg once or twice daily, initially, to be increased gradually as needed and tolerated).

INJECTABLE: Valium (diazepam) is not recommended for bronchoscopy and laryngoscopy, because increased cough reflex and laryngospasm have been reported. Furthermore, during gastroscopy the operator must be aware of this possible reaction and necessary countermeasures should be available. Until additional information on its safety and efficacy is available, injectable diazepam is not recommended for obstetrical use or in diagnostic procedures other than gastroscopy and esophagoscopy.

Injectable Valium (diazepam) has produced hypotension, respiratory depression or muscular weakness in some patients, particularly when used with narcotics, barbiturates or alcohol. Since Valium (diazepam) may have an additive effect with narcotics, appropriate reduction in narcotic dosage is possible.
Lower doses (usually 2 mg to 5 mg) should be used for elderly and debilitated patients.

The safety and efficacy of Injectable Valium (diazepam) in children under age 12 have not been established.

Adverse Reactions: ORAL AND INJECTABLE: Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium (diazepam) therapy and are of no known significance.

ORAL: Side effects most commonly reported were drowsiness, fatigue and ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued.

INJECTABLE: Side effects most commonly reported were drowsiness, fatigue and ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hiccups, hypoactivity, hypotension, incontinence, jaundice, changes in libido, nausea, phlebitis at injection site, changes in salivation, skin rash, slurred speech, syncope, tremor, urinary retention, urticaria, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued.

Dosage and Administration: ORAL: Dosage should be individualized for maximum beneficial effect. While the usual daily dosages given below will meet the needs of most patients, there will be some who may require higher doses. In such cases dosage should be increased cautiously to avoid adverse effects.

Adults:	**Usual daily dose**
Symptomatic Relief of Tension and Anxiety States and Psychoneurotic States.	Depending upon severity of symptoms—2 mg to 10 mg, 2 to 4 times daily
Symptomatic Relief in Acute Alcohol Withdrawal.	10 mg, 3 or 4 times during the first 24 hours, reducing to 5 mg, 3 or 4 times daily as needed
Adjunctively for Relief of Skeletal Muscle Spasm.	2 mg to 10 mg, 3 or 4 times daily
Adjunctively in Convulsive Disorders.	2 mg to 10 mg, 2 to 4 times daily
Geriatric Patients, or in the presence of debilitating disease.	2 mg to 2½ mg, 1 or 2 times daily initially; increase gradually as needed and tolerated
Children: Because of varied responses to CNS-acting drugs, initiate therapy with lowest dose and increase as required. Not for use in children under 6 months.	1 mg to 2½ mg, 3 or 4 times daily initially; increase gradually as needed and tolerated

Dosage and Administration: INJECTABLE: Dosage should be individualized for maximum beneficial effect. In acute conditions the injection may be repeated within one hour although an interval of 3 to 4 hours is usually satisfactory. Generally not more than 30 mg should be given within an 8-hour period.
Intramuscular: Injectable Valium (diazepam) should be injected deeply into the muscle.
Intravenous use: The solution should be injected slowly, directly into the vein, taking at least one minute for each 5 mg (1 cc) given. Do not mix or dilute Injectable Valium (diazepam) with other solutions or drugs. Do not add to I.V. fluids.

	Usual dosage*
Moderate Psychoneurotic Reactions: Manifested by tension-anxiety alone or with depressive symptomatology, agitation, restlessness and psychophysiological disturbances.	2 mg to 5 mg, I.M. or I.V. Repeat in 3 to 4 hours, if necessary.
Severe Psychoneurotic Reactions: Where severe anxiety, apprehension or agitation exist alone or associated with depressive symptoms.	5 mg to 10 mg, I.M. or I.V. Repeat in 3 to 4 hours, if necessary.
Acute Alcohol Withdrawal: As an aid in symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.	10 mg, I.M. or I.V. initially, then 5 mg to 10 mg in 3 to 4 hours, if necessary.
Acute Stress Reactions: Adjunctively, when apprehension, anxiety and acute stress reactions are present prior to gastroscopy and esophagoscopy. (See **Precautions.**)	5 mg to 10 mg, I.M. or I.V., approximately 30 minutes prior to the procedure.
Muscle Spasm: Associated with local pathology, cerebral palsy, athetosis, stiff-man syndrome or tetanus.	5 mg to 10 mg, I.M. or I.V. initially, then 5 mg to 10 mg in 3 to 4 hours, if necessary. For tetanus, larger doses may be required.
Status Epilepticus and Severe Recurrent Convulsive Seizures: In the convulsing patient, it is recommended the drug be given intramuscularly if there is difficulty in administering it slowly intravenously over the required period of time.	5 mg to 10 mg, I.M. or I.V. initially. Repeat in 2 to 4 hours, if necessary.
Preoperative Medication: To relieve anxiety and tension. *(If atropine, scopolamine or other premedication are desired, they must be administered in separate syringes.)*	10 mg, I.M. (preferred route), 1 to 2 hours before surgery.
Cardioversion: To relieve anxiety and tension.	5 mg to 15 mg, I.V., within 5 to 10 minutes prior to the procedure.

*Lower doses (usually 2 mg to 5 mg) and slow increase in dosage should be used for elderly or debilitated patients and when other sedative drugs are administered. (See **Precautions** and **Adverse Reactions.**)

Once the acute symptomatology has been properly controlled with Injectable Valium (diazepam), the patient may be placed on oral therapy with Valium (diazepam) if further treatment is required.

How Supplied: ORAL: Valium (diazepam) scored tablets—2 mg, white; 5 mg, yellow; and 10 mg, blue—bottles of 100 and 500.

INJECTABLE: Ampuls, 2 cc, boxes of 10. Each cc contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

Dr. FREYHAN. This is circulated through the mail. It is an 7-page brochure entitled "About Ready for Outpatient Status." The text is carefully worded and does not contain specific misstatements—at least, I was unable to find them. Yet, as is so often the case in cleverly worded advertisements, it grossly misleads by implication. The fact that a patient is ready for outpatient status may be an indication of improvement, but hardly for the prescription of Valium. Most hospitalized patients today are apt to receive one or several psychotropic drugs which, more often than not, are continued after discharge. The advertisement therefore implies a specific fact of value described as "an extra help" to ease the transition. The text abounds with seductive allusions to preventing crises, coping with life, and helping psychotherapy to rapid success. If we compare these assertions with objective appraisals as published in the scientific literature, we find little evidence that Valium possesses an exceptional value in the relief of anxiety. Thus, while Valium is an effective agent for various clinical purposes, the cited advertisement is a flagrant example of transgressing from truth to fiction. Valium is known to be one of the biggest moneymakers. If my information is correct, the so-called antianxiety drugs, including meprobamate, Librium, and Valium, are by far the most overprescribed psychoactive drugs. It should be the responsibility of editors of medical journals and, in the last analysis, of every practicing physician, to develop greater resistance to seductive promotion of these agents.

I would add here, when it comes to a seduction, it takes a seductor and a seductee. And I feel that myself and my colleagues—or it seems to be evident from the sales statistics—are so easily seduced by the clever advertisement. I have covered only a few focal issues, but I hope I can amplify on these matters in response to questions. Thank you.

Senator NELSON. Thank you very much for your excellent statement. Both of you could address yourselves to this, if you wish. I don't think, in the testimony that we have taken previously, that we have had any explanation in the record of what is the physiological effect of the use of various minor and major tranquilizers. I don't mean necessarily the side effects, but what occurs physiologically, within the system, which results in reducing the anxiety of the patient. Either one, or both of you.

Dr. BRILL. That is an easy one. I would like to answer that. The mechanism of action of drugs generally is highly mysterious. We don't even know how aspirin helps a headache. So that a good explanation of the action that we are talking about is still lacking, and is something that needs research; because, when the action is elucidated, we will be in a much better position to develop new drugs that can do this more effectively.

Senator NELSON. Do you want to add to that?

Dr. FREYHAN. I agree that more sophisticated formulations, as found in the scientific literature, may add up to the same thing that Dr. Brill just outlined. I might just add that, for all practical purposes, the antianxiety drug is closely related to what used to be called sedatives.

Senator NELSON. Do you know in what way a sedative acts on the system?

Dr. FREYHAN. In addition to that, there is the effect of relaxation of muscle tone. Taken together, mild sedation and a lessening of muscular tension produce, subjectively, feelings of relaxation.

Senator NELSON. Dr. Freyhan, you referred to an ad that you considered misleading. If you were the editor of a medical journal, would you accept an ad like that?

Dr. FREYHAN. I would not. As a matter of fact, I am editor-in-chief of a psychiatric journal, and my contract provides that I can accept or reject specific commercial advertisments. I suspect, however, that this particular ad was sent through the mail, since it might not find acceptance by editors of some of the journals. Be that as it may, I think that this ad is rather typical for a long series of advertisements on Librium and Valium by Roche Laboratories.

Senator NELSON. I would like to ask what strikes me as a very basic question, and that is whether there is any value in fact in medical ads at all for drugs. I don't remember who said it, but I was reading a piece recently by a physician who was critical of the idea that drugs are advertised at all in medical journals. The comparison he made was that, if the physicist discovered a new particle or element of some kind, then his method of informing other physicists wouldn't be to buy ads in scientific publications, and those who are interested in the field would read the scientific literature.

But, in any event, is there a really, genuinely important function performed by advertising and promotion from a medical standpoint when a good percentage of it looks like this "behavioral drift" ad that counsel showed you?

Dr. FREYHAN. I think that there is a justification for drug advertisements. Speaking for myself, and perhaps for most of my colleagues, advertisements have the advantage of providing easy available information on dosage pertaining to tablets and ampules, and various other technical items of administration. While one could get this information from other sources, advertisements have the advantage of easy access as one looks through the pages of a journal. The promotional aspect of the advertisement which deals with clinical indications may be of less value, and should under no circumstances be the only information on which the physician bases his choice of medication. But I do think that advertisements have a place in providing needed information in an easy accessible manner.

Dr. BRILL. I might add to that that in countries where the commercial aspects are presumably far less important, such as behind the Iron Curtain, there is still a form of drug advertisement which is not too dissimilar in principle from our own. And I would agree with what Dr. Freyhan said; namely, that it is convenient and it is important that the busy physician have changes in the Pharmacopeia called to his attention in a way that sticks.

Senator NELSON. You referred in your testimony to Valium. You are critical of that ad, and you wouldn't find it acceptable. I think I can produce for you 100 or 200 or 500 ads of other drugs presented with precisely the same objective and the same technique imprinted in every medical journal in this country.

Let me give you one. We had extensive testimony, a whole volume here, on the use of chloramphenicol. The ads there ran for a long,

long time with a bronchoscope, and just a simple heading, "Chloromycetin when it counts." It is not indicated for any upper respiratory illness, so why the bronchoscope? The Journal of the AMA accepted the ad. And so did all the rest of them. And then we had testimony from a group of distinguished experts about the use of chloramphenicol, including Dr. Dameshek from Mount Sinai and Dr. Mark Lepper, and Dr. Best, in which their guess was, from their experience, that anywhere from 90 to 98 percent of those that prescribe chloramphenicol tend to prescribe it in nonindicated cases. In fact, in one test that I read recently in 406 cases of chloramphenicol induced aplastic anemia, half of whom as of this test died, only 6 percent were given for indicated cases, and 12 percent were given for the common cold. Now, where did the physician who prescribed it get his information about the use of chloramphenicol except from the promotional advertising? Certainly no place in the literature. In the Journal of the AMA Dr. Dameshek himself, plus others, I think, over the years, wrote distinguished pieces criticizing the misuse of chloramphenicol. But in the pages of the Journal they accepted promotional advertising.

And it is quite obvious that the promotion was much more persuasive to the physician, the promotion in the advertising, than the scientific literature, all of which has been cautioning for a good many years about the misuse of chloramphenicol.

Dr. FREYHAN. I think we have two different psychological sets. It does not require much sophistication to understand that the pharmaceutical industry must sell products in a competitive market. The psychological set is one of promoting the quality of a product. The other set is that of the academically trained mind of the physician. In this frame of reference one must distinguish between what is scientific presentation and what commercially motivated advertisement. As much as I agree on the fact of abuse and distortion in some advertisements, I find it difficult to see the physician as a victim. We do, after all, have a choice, we have other sources of information available. I think that it is a task for the medical schools and for training centers to develop a physician's ability of discriminating between scientific and promotional aspects as reflected in literature and advertisements.

Senator NELSON. But I gave you what I think is a well-documented case of chloramphenicol where the distinction was not made, physically not made, so to speak. Not that this was true of all physicians. I received all kinds of mail from physicians quite critical of the use of chloramphenicol. And, in fact, after our hearings the use of chloramphenicol in the country dropped by over 50 percent. There was great publicity, and then the FDA finally sent a letter to every physician in this country.

If we had no advertising at all of the kind we have now, under what circumstances would any physician in this country prescribe chloramphenicol? He would have to go to Goodman and Gilman, he would have to go to the Medical Letter, he would have to go to the scientific literature. Otherwise he wouldn't know what it was for.

Dr. BRILL. Senator, may I comment on that?

Physicians have been making mistakes in pharmaceuticals for a long, long time, long before the advent of drug advertising of this type. And

I think we have here the problem of the baby in the bath. And this, I think is what Dr. Freyhan has been trying to say. The problem is how to get positive information across to the physician, authoritative and clear and in a form that will register under the conditions of active medical practice. And it resolves itself into a problem of education of the physician. And I think also it resolves itself into a problem of education of the public, because pressure from the public has a great deal to do with what goes on. In England, for example, where they have a different situation about medical practice, the public exerts even greater pressure on the physician. And it results in problems of medication of the type we are speaking about.

Senator NELSON. Do you wish to comment, Dr. Freyhan.

Dr. FREYHAN. Not long ago I attended a clinical conference in which a very talented and competent psychiatric resident presented a case and his choice of drug for treating the patient. As I was a bit surprised about his particular choice, I asked him how he had reached his decision. He referred to a very popular advertisement recommending this drug, an advertisement found in the pages of our most prestigious psychiatric journals.

The truth of the matter is, and I tried to point this out in my introductory statement, that we now prescribe drugs on an astronomical basis, yet do not train physicians in either the science of clinical pharmacotherapy nor even in the techniques of drug treatment. Nor do we have developed drug therapeutic facilities and services which transcend conventional setups in outpatient departments, clinics, and so forth.

At a recent international congress on psychoactive drugs, I was asked to evaluate the influence of modern drugs on the longterm outcome of schizophrenia. After surveying the literature, and adding my own observations, I had to state that no conclusions could be drawn because of lack of authoritative studies. This was not so much due to lack of scientific effort as to the absence of innovations in clinical facilities which could have provided a setting for longitudinal studies.

You asked a little while back how many drug-treated patients go home and how many are actually able to go to work. I have done research in this area for quite a few years. I generally agree with Dr. Brill's estimate but I believe that the results may be better if one includes housewives who in response to drug treatment function adequately. From a statistical point of view it is always easier to judge results in terms of jobs obtained by patients previously unable to work, but there is a large group of housewives whose improvement must be measured not in terms of jobs, but in regard to their capacity for being well-functioning housewives.

Treatment does not only depend on giving drugs, but on an understanding of the influence of drugs not only on illness, but on change in social functions as well. And there are not really yet the kind of clinical facilities that have conceptually caught up with more sophisticated treatment and evaluation of therapeutic results. On one hand, comprehensive mental health centers lean on drug treatment involving up to 90 percent of all patients treated. But the treatment often merely amounts to a visit lasting a few minutes in which the patient is given a prescription. He is asked to come back in a few weeks or a month, and

his prescription may be refilled. This is a far cry from comprehensive psychiatric treatment. If we are concerned about physicians' dependence on drug advertisements, it really represents an educational neglect because the scientifically fascinating aspects of drug treatment have not been appropriately presented to resident physicians. Drugs are given but with little conviction of their actual value and often in the absence of knowledge of drug action. The psychiatric trainee remains confused in regard to what can be achieved by drugs and what by psychotherapy. It may take 5, perhaps 10 years before comprehensive treatment reflects comprehensive knowledge.

Senator NELSON. You referred to it being the responsibility of the physician to make a distinction. That of course is true. But physicians aren't any different from anybody else in terms of being susceptible to advertising. Everybody is. The drug firms hire the ablest, subtlest writers in the world. And they pay them some of the highest salaries in the country. I have read all kinds of ads and thought the product must be great, and it turned out it didn't do anything the ad said. Everybody has had that experience. But here you have a special case in which the consumer of the product has no qualification whatsoever to decide whether it is to his benefit, where the physician who prescribes is being influenced by ads and where the medical journals that carry the ads have the high respect of the physician. The contraindication and side effects are in such very fine print that I have very great difficulty reading them myself.

But the drug advertisement is carried by the AMA journal which claims in its principles of advertising that it will not accept an ad for a fixed combination unless efficacy has been proved. And according to the National Academy of Science-National Research Council no efficacy has been proved in any fixed antibiotic combination.

Many of these medical publications have some very fine principles. If I were a physician and knew about this I would trust the publication that I take, the journal that I read which is in my specialty. So I read the ad, such as the one you have seen on "behavioral drift." It recites what the patient says, and tells you what drug to prescribe. I might very well prescribe it based upon my respect for the publication it appeared in.

In fact, I think that is what happens; doesn't it? I would like to make it quite clear that I totally agree with you.

There has to be a better way of advertising drugs. Only I think sometimes the blame is too one sided. Something must be done also about physicians' critical ability to understand what kind of information they are depending on. Somehow I feel the blame tends to be somewhat one sidedly on the ad without enough criticism directed at the physician who, for lack of training on the one hand, and for reasons of simplicity or gullibility on the other hand, depends for his prescribing information, to a large extent, on clever advertising.

Dr. BRILL. I think you are asking a question that we don't really have an answer for. And that is, what would the physician do in the absence of advertising. It really is a scientific question. And we are trying to answer on the basis of projections of our experience. My own feeling is that it would not improve practice. It might even be more unfortunate than it is now with respect to errors in prescribing. It would be a rather—I would prefer to see a positive form of education introduced rather than to rely on merely a withdrawal of this type of information.

Senator NELSON I suppose each publication has a different standard, and I have looked at a great many of them. Now, Dr. Freyhan would not have accepted this ad because he thinks it is misleading. But as I look at it I can show you a large number of such ads in distinguished medical publications which are every bit as misleading as this one, if not more so. Each publication seems to have some standard. But in some publications, quite obviously, the advertising department decides what goes in the publication, and not a group of qualified physicians.

But supposing we had a good, tough standard—your ads can't be misleading. Any group of physicians who know the field can read these ads and tell you whether they are misleading or not. And in every medical publication in every edition there are ads that would be strongly criticized by those members of the profession who are familiar with the use of the drug being advertised.

Why are they there?

Dr. FREYHAN. I think that medical publications may, to some extent, take the same attitude that, let us say, the New York Times takes. The New York Times is a highly respected paper which, while judicious in the acceptance of advertisements, would not want to be identified with message or content of the advertisements it publishes. How to react to an advertisement is left to the reader who may be a potential buyer. And I think that many editors of medical journals may take somewhat the same attitude. While responsible editors would not want to accept an ad which is misleading in the sense of factual misstatements, they leave the message of the advertisement to the judgment of the reader since the advertisement section is clearly not part of the journal's scientific content. There is something in the very nature of any advertisement which demands critical evaluation from the reader.

Senator NELSON. Isn't there a very sharp distinction between the New York Times responsibility and the responsibility of the medical publications?

Dr. FREYHAN. Yes.

Senator NELSON. People are qualified to make judgments about the value of automobiles and sewing machines and lawnmowers and whatever that may be advertised in the New York Times. But in the field of drugs the consumer of the product isn't qualified at all, and,

of course, he doesn't even see the advertising. Isn't there a very special responsibility of the medical profession to the public? After all, there is no one else who is qualified to judge the quality of the advertising, the quality of the product other than the medical profession.

So when the Journal of the American Medical Association or any of the other professional journals accepts advertising, don't they have a special, very special, responsibility for that advertising and as custodians of the health of the public a special responsibility to that public?

This is what the profession says all the time. And that is why it seems to me that this kind of "behavioral drift" ad, or all the rest of these, are shocking misrepresentations.

I would like to see the profession do something about it before it becomes necessary for the Government to step in.

But we have to take a case as dramatic as chloramphenicol and have a congressional committee, on which there isn't a single member of the medical profession, expose it to the public by calling in experts about the vast misuse of chloramphenicol. Why weren't the journals that were taking the ads for chloramphenicol which says, "Chloromycetin when it counts," with a bronchoscope on it, why weren't they throwing those ads out? They knew the statistics, and why weren't the medical societies calling conventions and everything else? They knew exactly what was happening. But it took a congressional committee to do it. This is the shocking thing to me.

Dr. BRILL. Senator, in principle I think that the medical profession thoroughly recognizes what you have just said; that is, that medical publications have a very special responsibility with respect to the advertisements that they carry. Now, with regard to the psychiatric drugs, the situation is not nearly as clear cut as it is in the case of chloramphenicol.

I wish it were, then we could be more clear cut in our statements here. Unforutnately, if we take the "behavioral drift" ad that you have there, this could be a symptomatic description of depression. This includes the symptoms of a relatively mild, but still quite disabling, depression. On the other hand, it could be something far less serious. And this is where we have difficulty in defining what is or what is not misleading, because of the poorly defined parameters of our practice.

Now, perhaps the simplest way to head off this thing is, you must make a diagnosis first, and then after having made the diagnosis, these are the kinds of symptoms that you would be trying to treat.

And perhaps the real criticism is that it appeals to poor diagnostic practices.

Dr. FREYHAN. I would say that this Aventyl advertisement [1] is first of all in poor taste. It also is misleading in a number of statements. There is the statement "an immediate effect and a rapid overall response." There are various potent antidepressant drugs, and this is surely a competitive field. But there is no conclusive evidence that Aventyl acts faster than other antidepressants. While there is some

[1] See p. 5350.

basis for this belief, it has never been satisfactorily proven. Furthermore, while the drug may influence, directly or indirectly, a number of symptoms which may be part and parcel of depression, they are singled out here dramatically in a misleading manner. I am referring to what is described here as fear of cancer, and can't sleep. Certainly, the symptoms given here are extremely broad. They would only be therapeutically influenced if they were part of clinical depression and not just vague complaints in the absence of real depression. There is another misstatement implying that tranquilization occurs, while it also refers to an immediate stimulatory effect. This looks to me as though the ad wants to please everybody, in the sense that if you want to tranquilize your patient a little bit, this drug is good; if on the other hand you want to stimulate, this drug is good too. Actually, the term "tranquilization" should not be used in connection with this type of antidepressant. In classifying drugs, a sharp line of division is made between agents which tranquilize and those which act as antidepressants. This advertisement could particularly mislead the nonpsychiatrist who, in response to his patients' complaints, might think that Aventyl promptly tranquilizes one and promptly stimulates another.

Mr. GORDON. According to the National Institute of Mental Health, 70 percent of the drugs are prescribed by nonpsychiatrists, that is, GP's, internists, and surgeons. So I think we have to consider those and the effect on that type of person rather than on the psychiatrist.

Dr. FREYHAN. Yes.

Mr. DUFFY. Doctor, when you as a physician are confronted with apparently inconsistent claims within the same document; namely, the advertising that you have been reading to us, do you feel that you have fulfilled your professional responsibility to your patient by taking action solely on the basis of what you have read in that advertisement, or would you feel that you should investigate further?

Dr. FREYHAN. I don't believe I would ever prescribe a drug solely on the basis of an advertisement.

Mr. DUFFY. Do you feel that any physician should?

Dr. FREYHAN. No.

Mr. DUFFY. One other thing that comes to my mind, is anybody forced to read an advertisement like this, or can you thumb over it and ignore it?

Dr. FREYHAN. Of course nobody is forced to read an advertisement although I will say that it may be difficult to overlook them since most medical journals have the scientific pages sandwiched between dozens of pages of advertisements in front and in the back. But certainly the advertisement is optional reading.

Mr. GORDON. Doctor, on that same specific advertisement, would you look under the side effects, probably on the fifth page, I think it is a five-page advertisement. You notice the first sentence.

Dr. FREYHAN. Yes.

Mr. GORDON. Would it be reasonable to assume that the first sentence would discourage the physician from reading any further, the warnings on side effects? There are a good many listed there.

Dr. FREYHAN. Generally it is true that serious side effects are rarely observed with this group of drugs. On the other hand given a patient with pathology of the eye, this drug could seriously aggravate the existing ocular disorder. The present arrangement of listing adverse effect defeats its own purpose. By listing all adverse effects ever observed, as now required by law, attention is diverted from those adverse reactions only significant for patients of certain ages or having other specified diseases. Merely cataloging all effects does not realistically represent what complications to look for in a given patient. If you have an elderly patient and you do not check his ocular status, and he gets glaucoma, then he has certainly lost by far more than he has gained under the antidepressant therapy.

Mr. GORDON. Doctor, I am going to submit to you a group of advertisements, specific advertisements. And I am wondering if you could comment on some of them.[1]

Here is one for Triavil. Would you read it so that the people in the room will know what it is about,

Dr. BRILL. "Am I old" in blue print. "In the face of obvious decline, anxiety is often seen in reactive depression. Triavil treats both."

I presume that refers to anxiety as well as reactive depression.

And then the text follows. And it ends in capital letters "For moderate to severe anxiety with coexisting depression, Triavil containing perphenazine and amitryptiline hydrochloride."

Mr. GORDON. What do you think of that?

Dr. BRILL. It ends up in all fairness, "for additional prescribing information please see the following page," in smaller letters.

Dr. FREYHAN. My comment would be again that it is promising far more than this particular combination of compounds can achieve. There are no gross misstatements. The cleverness of "Am I old" obviously appeals to anyone who, with or without justification, feels that he has reached whatever he thinks is a critical age.

Senator NELSON. Which ad is that?

Dr. FREYHAN. This is Triavil. It has the skull and the two ladies sitting in there apparently preparing for the end. There now comes the salvation with Triavil.

If one overlooks the gimmicks in here and reads the text, there is not, I would think, as much distortion in it as in the headline "Am I old."

Dr. BRILL. I personally don't like the ad. It doesn't attract my favorable reaction. It may be that many physicians are turned off by the kind of ad which is not medically attractive. And to me this is not medically attractive. "Am I old" is really not a medical question. In

[1] See pp. 5350–5368.

other words, one cannot treat old age as such. And I don't see it as a good lead. So it may be that a good many of these ads defeat their own purpose, because of the lack of scientific attractiveness, which to my mind would be the real lead in for most medical men.

Mr. DUFFY. Excuse me, Doctor. But it just occurs to me that we are perhaps analyzing this ad, or at least part of it, in the way that I might approach poetry or modern art or something like that. And if I understand Dr. Freyhan correctly, you would not be making a proper medical judgment as a physician based on simply reading the content of that ad, you should go read something else. And it just seems to me that I might look at that and get a totally different impression, a highly subjective artistic approach.

I guess I am merely pointing this out as my reaction to what you are saying. But I am just wondering what your reaction might have been had I asked you that question that I asked Dr. Freyhan, what do you think a physician's responsibility in prescribing a drug is, how far must he go into it before he is qualified in your opinion to make the judgment that he will prescribe the drug?

Dr. BRILL. I will answer exactly as he did. And so would any physician have to answer. That is standard practice. I was referring only to the practice that some of the ads which we like least, perhaps, may actually be the least harmful, because they are the least attractive. And I was making another point that I had made previously before you came in, and that is that a program of positive education—and Dr. Freyhan said very much the same thing—a program of positive education would be very much in order, and that such a program could very well use the skills that have been developed in connection with the commercial presentation of medical material. And I refer of course to a subsidized program, not one that has any commercial contact at all.

Mr. GORDON. Would you turn to that green book there, page 4508. There are two advertisements, one on the "Always Weary" and the other one on the "Torschlusspanik." Dr. Console, in answering one of Senator Nelson's questions, says that "exhibit 2"—this is the "Always Weary" ad—"is in extremely poor taste not only because the woman depicted in the photograph can be suffering from anything from simple exhaustion, to anemia, through chronic schizophrenia, and on to any chronic debilitating diseases, but also because it is only slightly, if at all, removed from the crass television commercials that say she has "tired blood" and needs Geritol, or those that say she has the "blahs," and needs Alka Seltzer. She needs careful diagnostic workup and not a prescription for Valium t.i.d. or g.i.d. four times a day.

The advertisement is a total composition deliberately intended to convey the impression that the "Always Weary (a diagnostic category unknown to me) can be treated by writing a prescription for Valium."

What did you think of that particular testimony? [1]

Dr. FREYHAN. Looking at the picture one is led to believe that it may be an advertisement for a good cup of coffee. The woman in the picture is stirring a cup of coffee and if she is very tired as she appears to be, caffein may be far more effective than Valium with its sedative action. Thus while the picture raises the question of what is better for fatigue, caffein as a stimulant, or Valium as a sedative, I would agree that the advertisement is absurd whether you look at the picture or read the text.

Mr. GORDON. On the next one, on Torschlusspanik, Dr. Console said:

> This is even worse and probably represents the best in advertising and the very worst in drug advertising. Advertising becomes more effective as it makes a stronger appeal to the irrational unconscious need of the reader. To imply that the extremely variable and complex psychodynamics that may lead to symptom formation or psychopathology in this critical period of any man's life can conveniently be dropped into a waste basket labeled "Torschlusspanik" and treated with Librium approaches criminal neglect. I know of no scientific evidence that supports this oversimplified diagnosis and recommendation for therapy.

Would you comment on that.

Dr. BRILL. I think that we come back to the principle, diagnosis first, treatment afterward, in both this and the preceding advertisement the principle is the same; namely, that a single symptom has been picked out. And this symptom may well be and not infrequently is the presenting symptom of the depression, but we must in all cases have a diagnosis first and a treatment afterward. And if there is any justification for such advertising, it is to call to the attention of the practicing physician that such a symptom may call for a differential diagnosis of depression.

Mr. DUFFY. Excuse me, Doctor. I took a look at that picture—and of course I am not a doctor, so I really don't know—I am referring to the first picture there of the housewife, who looks like actually she needs 2 weeks of vacation. That is my nonmedical judgment, after taking a look at that picture.

But again, I am just curious as to how you evaluate this, or how you would expect the average physician to evaluate this. Of course, if offends your artistic sense, it is somewhat poor taste, that was a comment that you used. But what about the medical judgment?

Dr. BRILL. You mean to evaluate a patient of this type? It calls for a physicial examination, a mental examination, a history, laboratory work, and standard practices of differential diagnosis. It cannot be

[1] See testimony of Dr. A. Dale Console, pt. 11, pp. 4478–4514.

done by looking at a picture, nor can it be done by looking directly at a patient and paying attention to the single presenting system.

Dr. FREYHAN. These pictures remind me of the kind of advertisements which are frequently used to promote sex hormones. There is an appeal to the fear of aging symbolized by loss of potency and energy. The emphasis on pictorial material is aimed at self-comparison. This advertisement, for example, uses the term "Torschlusspanik." In the German language this term is used in connection with men or women, and particularly women, who fear that the door to marriage is closing forever. The overemphasis on portraying panic stricken faces may, if at all, appeal to an intellectually anemic physician who reacts by means of prescribing this medicine in this frame of reference.

Mr. DUFFY. Would it be better to ban the intellectually anemic physician, then.

Dr. FREYHAN. Yes.

Dr. BRILL. I might add, it might be better to give him an intellectual transfusion in the form of education.

Senator NELSON. Very well.

Thank you very much, Dr. Brill and Dr. Freyhan, for your very fine testimony. We appreciate your taking time from your busy practices to come here and testify today. It is very helpful.

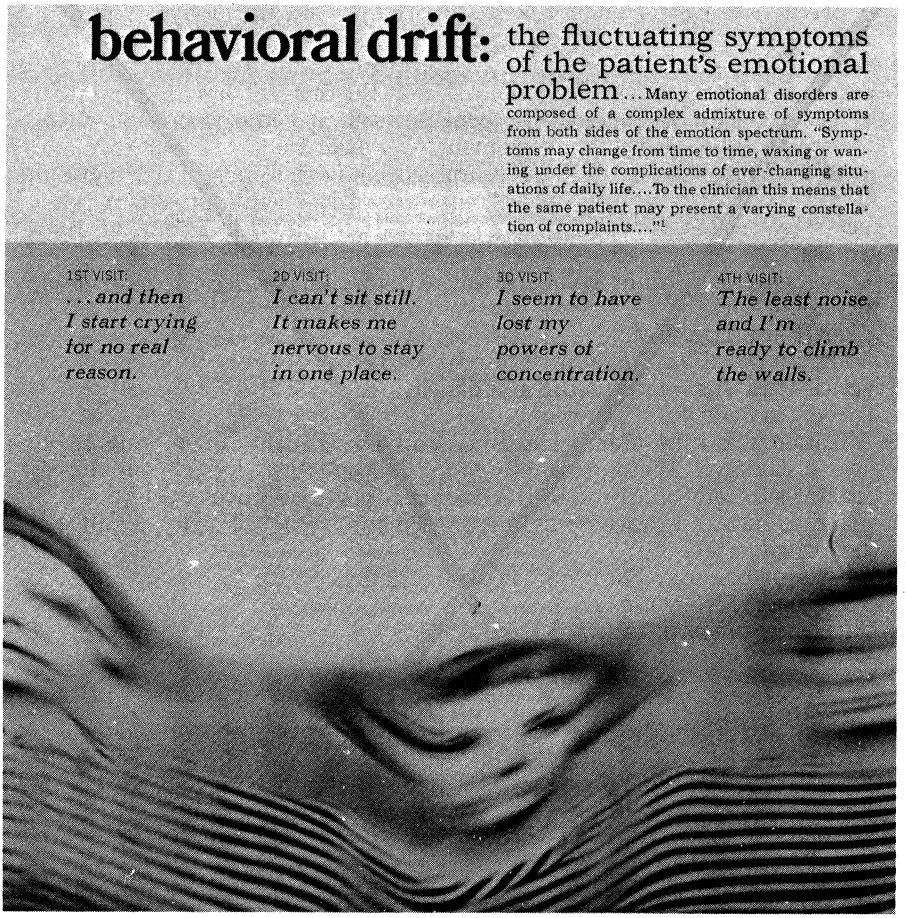
Mr. GORDON. I have some advertisements which I ask be put in the record.

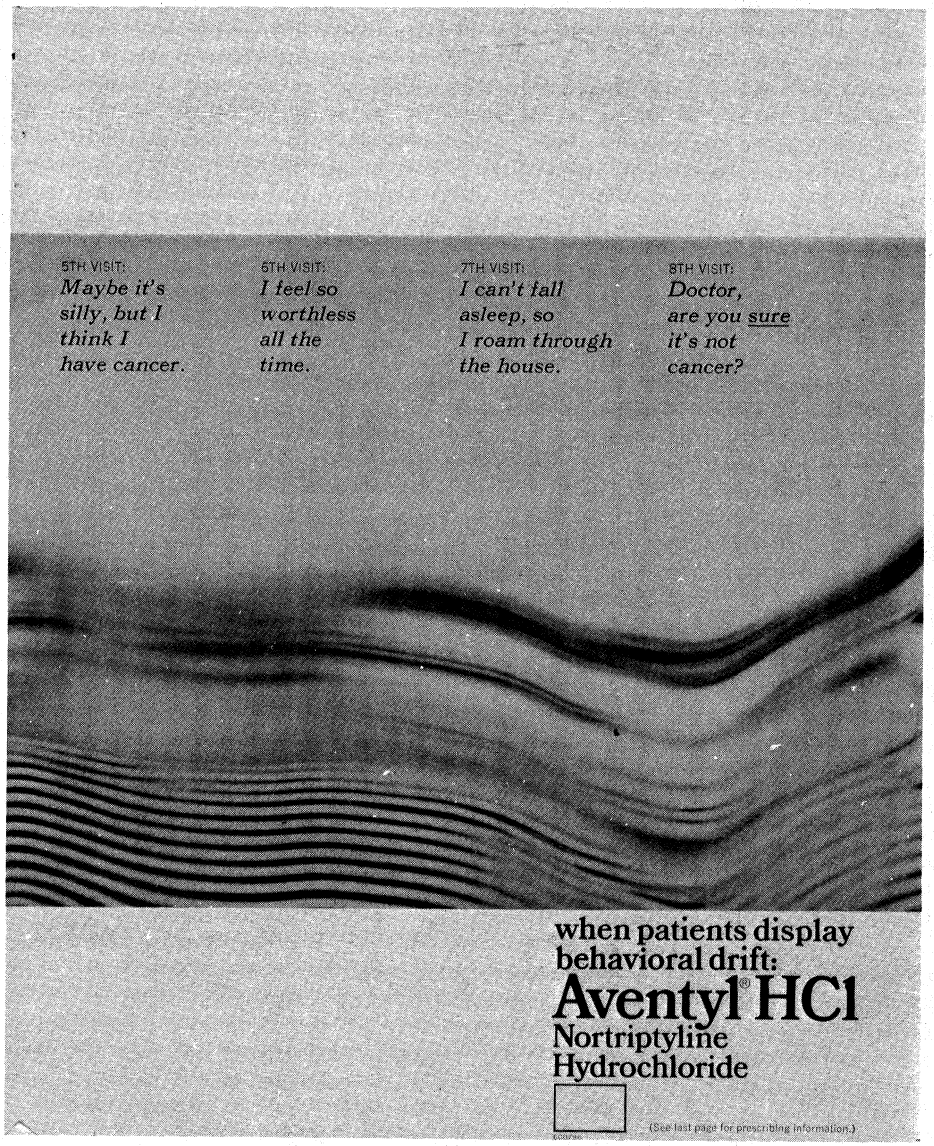
Senator NELSON. They may be placed in the record.

Thank you very much.

(The documents follow:)

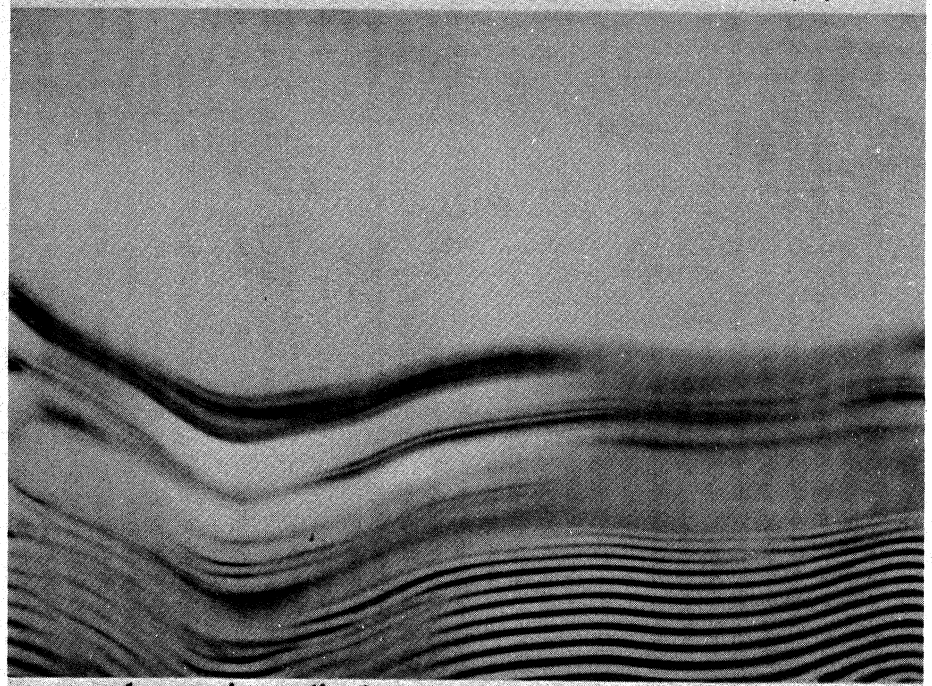
[From Medical World News, September 2, 1966]




5TH VISIT:
Maybe it's silly, but I think I have cancer.
6TH VISIT:
I feel so worthless all the time.
7TH VISIT:
I can't fall asleep, so I roam through the house.
8TH VISIT:
Doctor, are you sure it's not cancer?
when patients display behavioral drift:
Aventyl® HCl
Nortriptyline Hydrochloride
(See last page for prescribing information.)

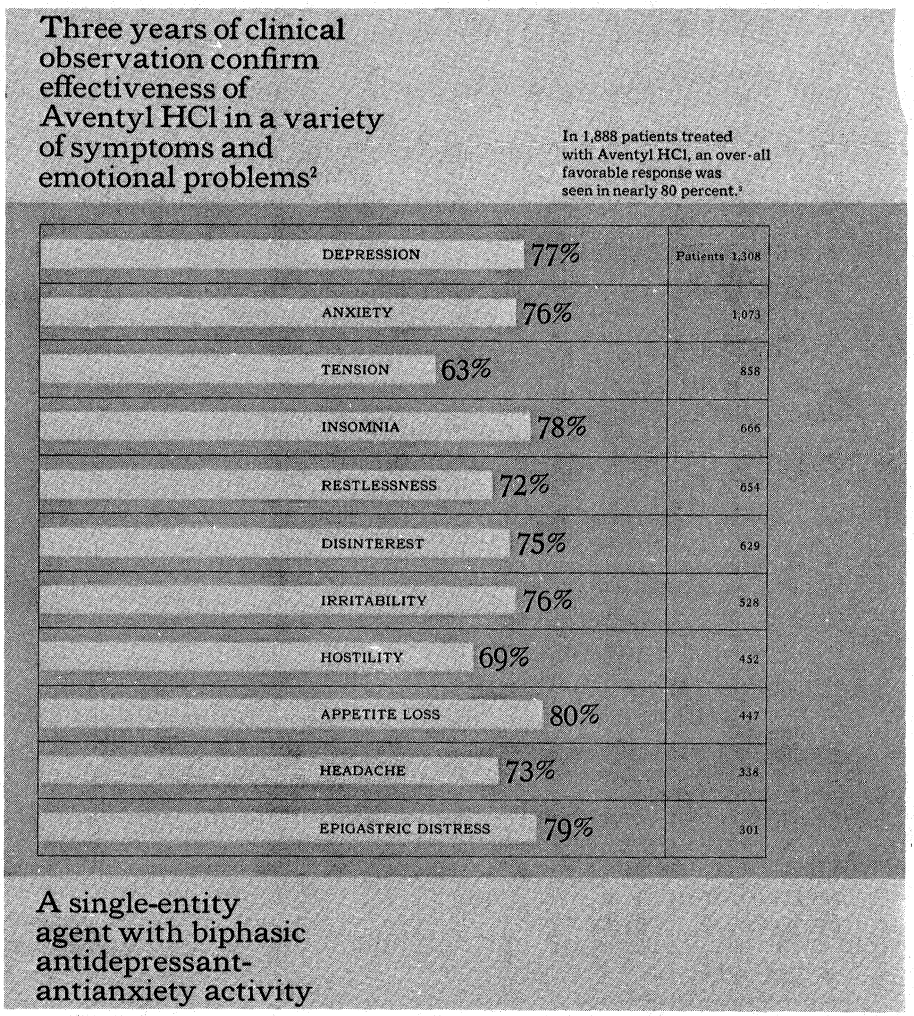
behavioral drift:

When the true range of usefulness of Aventyl HCl was evaluated, common presenting complaints were used as a measure of therapeutic effectiveness. As the bar graph shows, regardless of the side of the norm from which these symptoms originated, Aventyl HCl produced a high degree of satisfactory response.

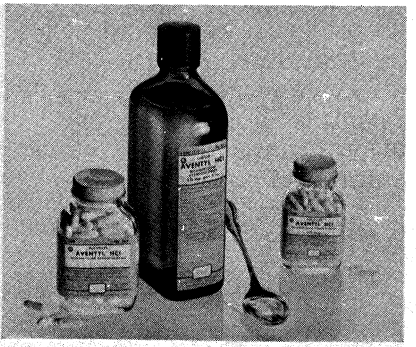


when patients display
behavioral drift:
Aventyl® HCl
Nortriptyline
Hydrochloride

600796



81-280 O—69—pt. 13——7



An immediate effect and a rapid over-all response

Prompt tranquilization occurs and provides evidence of initial improvement in some patients. In others, an immediate stimulatory effect is observed. Generally, a peak is rapidly reached and is soon followed by lasting over-all improvement.

Of those patients who responded to Aventyl HCl, 50 percent improved within one week, 79 percent by the second week, and 94 percent within one month.[2]

Well-tolerated therapy

Unwanted effects appear to be milder and less frequent than those produced by certain other antidepressants. Studies indicate Aventyl HCl has considerably less anticholinergic activity than certain of its predecessors.

In contrast to some tranquilizers, Aventyl HCl has not been reported to cause either habituation or withdrawal symptoms.

1. Cahn, B.: Guidelines for Understanding Emotional Disorders, M. Times, 93:1082, 1965.
2. From data available through the Lilly Research Laboratories.

when patients display behavioral drift:

Aventyl® HCl
Nortriptyline Hydrochloride

Additional information available to physicians upon request.
Eli Lilly and Company
Indianapolis, Indiana 46206

050796

Actions and Indications: Aventyl HCl is a notably safe and effective agent for the treatment of mental depression, anxiety-tension states, and psychosomatic disorders and for use as an adjunct to psychotherapy.

Contraindications: Concomitant use with a monoamineoxidase inhibitor is contraindicated, since potentiation of adverse effects can be serious—even fatal. The monoamineoxidase inhibitor should be discontinued for at least ten to twenty-one days before treatment with Aventyl HCl is started.

Warnings: Use in convulsive or hypotensive states should be closely followed. At present, data are insufficient to recommend use of Aventyl HCl during pregnancy. The possibility of a suicidal attempt in a depressed patient should always be considered. Although there have been no reports of bone-marrow damage or other serious effects, careful observation of the patient and periodic laboratory studies are recommended as with all new medications.

Precautions: Because of its anticholinergic activity, Aventyl HCl should be used cautiously in patients with glaucoma or in those having a propensity for urinary retention. Care should be employed when Aventyl HCl is given in conjunction with sympathomimetic drugs. Its use in hypnonarcosis along with intravenous hexobarbital-methamphetamine for severe anxiety has resulted in a higher-than-usual incidence of stimulatory side-effects. As with similar drugs, it is advisable to observe for epileptiform seizures during the initial phase of treatment.

Side-Effects: No single side-effect can be considered as occurring frequently, and most are mild and transitory. Dry mouth was noted in 26 percent of patients; drowsiness in 11 percent. The following were seen occasionally (in 6 to 10 percent): constipation, dizziness, tremulousness, confusional state, restlessness, weakness, and blurred vision. Side-effects rarely noted (in 1 to 5 percent) were epigastric distress, sweating, peculiar taste, fatigue, weight gain, weight loss, insomnia, headache, paresthesia, nausea and vomiting, rash and itching, and delayed micturition. Miscellaneous side-effects were reported in less than 0.5 percent. There have been no reports of habituation or of withdrawal symptoms. No potentiation or increased incidence of side-effects was observed when Aventyl HCl was used together with tranquilizers, other antidepressants (except MAO inhibitors), oral stimulants, sedative-hypnotic preparations, and standard drugs given for primary medical disorders.

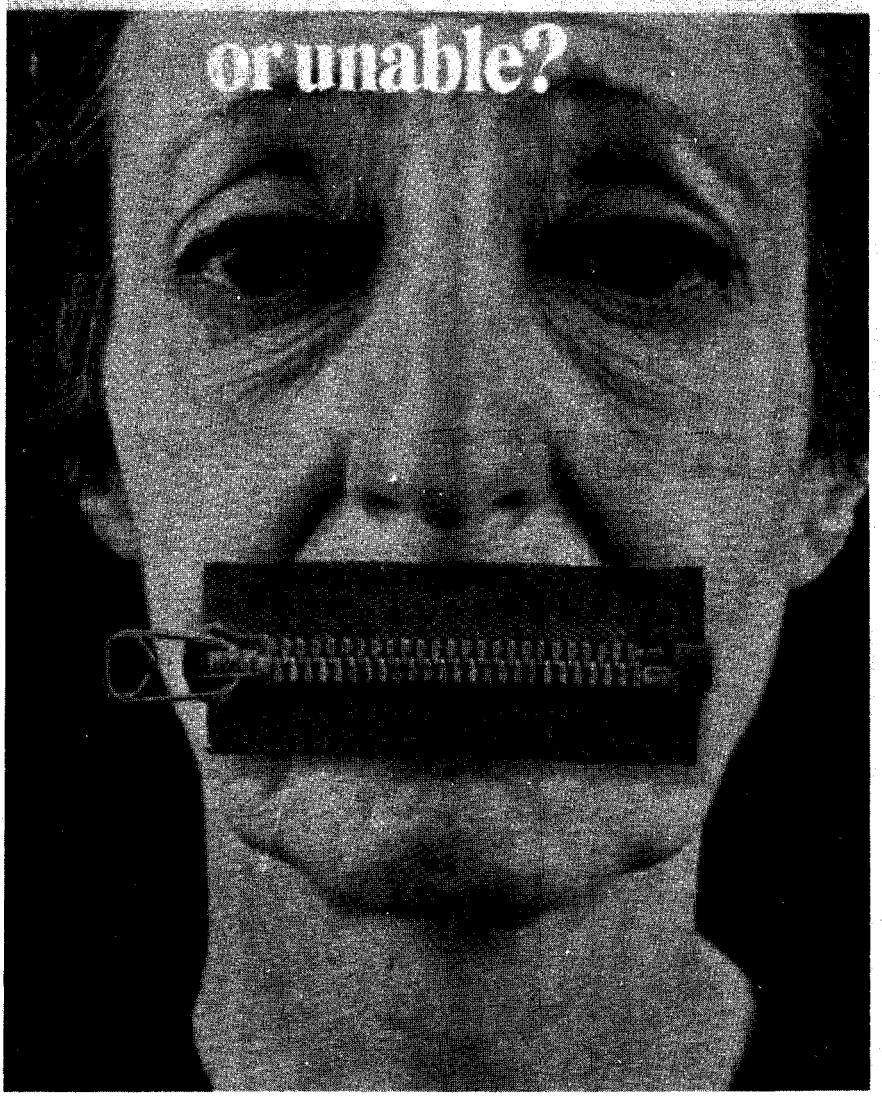
Dosage: Most adults respond well to 25 mg. three times daily, but the dose should be adjusted to the needs of the patient.
Usual dosage range (in divided doses):
Adults—20 to 100 mg. daily.
Children—10 to 75 mg. daily (1 to 2 mg. per Kg. of body weight).

(See package literature for complete dosage information.)

[Arch. Gen. Psychiat., Vol. 20, April 1969]

The psychoneurotic patient:

Unwilling to communicate or unable?



Librium® (chlordiazepoxide HCl) Valium® (diazepam)

When communication barriers make the psychoneurotic patient inaccessible... ETRAFON helps establish a meaningful dialogue

In emotional illness, inability of the patient to communicate effectively with the counseling physician is a common finding. Many patients stubbornly refuse to reveal their true feelings, deny the presence of emotional distress, and focus persistently on vague somatic complaints as the cause of their illness.

In such patients, adjunctive therapy with dual-purpose ETRAFON may break the communication barrier and thereby help to establish the rapport so essential to successful psychotherapy. And ETRAFON often provides relief of such distressing symptoms as fatigue, anorexia, insomnia, depressed mood, and functional gastrointestinal complaints.

- treats *both* components of moderate to severe anxiety/depression states
- provides symptomatic relief often not achieved with tranquilizer or antidepressant component alone
- reportedly reduces (or may eliminate) need for electroshock therapy in severe anxiety and depression
- has shown a relatively low incidence of major side effects, including extrapyramidal reactions*
- helps control the emotionally distressed patient until time and psychotherapy restore his zest for life

*See clinical considerations

ETRAFON®

brand of tranquilizer-antidepressant • perphenazine 2 mg. and amitriptyline hydrochloride 25 mg.

ETRAFON offers the flexibility and convenience of four dosage strengths: (1) For emotionally distressed patients with moderate to severe anxiety/depression states—ETRAFON 2-25 (perphenazine 2 mg. and amitriptyline HCl 25 mg.); (2) In severe anxiety/depression states and for more severely ill patients with schizophrenia—ETRAFON-FORTE 4-25 (perphenazine 4 mg. and amitriptyline HCl 25 mg.); (3) For the elderly or adolescent patient—ETRAFON-A 4-10 (perphenazine 4 mg. and amitriptyline HCl 10 mg.); (4) For flexibility in adjusting maintenance dosage to the lowest amount consistent with the relief of symptoms—ETRAFON 2-10 (perphenazine 2 mg. and amitriptyline HCl 10 mg.).

Clinical Considerations

Indications: Coexisting anxiety, agitation and depression of moderate to severe degree, of emotional origin or associated with chronic physical disease; also useful in schizophrenia with associated depression.

Contraindications: Drug-associated central nervous system depression from barbiturates, alcohol, narcotics, analgesics, or antihistamines; pregnancy; bone marrow depression, glaucoma, or urinary retention. Not to be used with MAOI drugs. Allow at least two weeks between therapies.

Precautions: Same as for components, perphenazine and amitriptyline. Use carefully in patients with histories of convulsive disorders or adverse reactions to phenothiazines. ETRAFON potentiates effects of antidepressants, CNS depressants, atropine, phosphorus insecticides, and heat. The antiemetic effect of the perphenazine component may conceal existence of brain tumor, intestinal obstruction, or toxicity due to overdosage of other drugs. Not recommended for use in children. The possibility of suicide is inherent in depression and may remain until significant remission occurs. Therefore, patients receiving ETRAFON should be carefully observed in the event that they require hospitalization and additional therapy. Tranquilizing effects of ETRAFON appear to reduce tendency to mania or hypomania in manic-depressive patients. If hypotension develops, levarterenol (norepinephrine) can be used, but not epinephrine, as its action is blocked and partially reversed by perphenazine.

Warning: Patients on ETRAFON should be cautioned against driving a car or operating machines requiring alert attention. Response to alcohol may be potentiated.

Side Effects: Similar to those reported with either component alone. Phenothiazines have produced blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia) and liver damage (jaundice, biliary stasis), and extrapyramidal symptoms such as dyskinesia, akathisia, parkinsonism, hyper-reflexia and ataxia. Dystonic reactions such as opisthotonic and oculogyric crises have also been reported, as has severe, acute hypotension; the latter is of particular concern in patients with mitral insufficiency or pheochromocytoma. A significant unexplained rise in body temperature can indicate intolerance to perphenazine; discontinue therapy.

Occasionally, allergic reactions to perphenazine have included erythema, itching, urticaria, laryngeal and glossal edema, facial edema (primarily periorbital edema), angioneurotic edema, peripheral edema, anaphylactoid reactions, reversed epinephrine effect, photosensitization, asthma, and exfoliative dermatitis.

Other side effects reported include endocrine disturbances (galactorrhea, disturbances in the menstrual cycle), grand mal convulsions, cerebral edema, altered cerebrospinal fluid proteins, polyphagia, paradoxical excitement, photophobia, skin pigmentation, failure of ejaculation, and EKG abnormalities (quinidine-like effect). Reactivation of psychotic processes and catatonic-like reactions have been seen with phenothiazines.

Autonomic reactions such as blurred vision, dryness of the mouth, nasal congestion, salivation, headache, nausea and vomiting, and change in pulse rate have been observed occasionally with perphenazine, as have urinary frequency or incontinence, constipation, polyphagia or anorexia, and motor restlessness. Significant autonomic side effects, however, have been infrequent in patients receiving less than 24 mg. perphenazine per day.

Pigmentary retinopathy and pigmentation of cornea and lens have been associated with the use of certain phenothiazines and, although not reported with perphenazine, might occur. Some patients have reported hypnotic effects (minimal in active patients), lassitude, muscle weakness, and, paradoxically, mild insomnia.

With amitriptyline alone, agranulocytosis and jaundice have occurred rarely. Anticholinergic effects include blurred vision, dry mouth, tachycardia, urinary retention, constipation and, more rarely, paralytic ileus; occasionally, numbness and tingling of the limbs, including possible peripheral neuropathy.

Rarely, allergic-type reactions have occurred, manifested by skin rash or swelling of the face and tongue, and itching. Other side effects of amitriptyline include increased perspiration, skin rash, drowsiness, nausea, fainting, dizziness, jitteriness, excitement, headache, heartburn, anorexia, hypotension, fine tremor, and incoordination; also temporary confusion or disturbed concentration, or rarely, transient visual hallucinations. Epileptiform seizures have been reported rarely in chronic schizophrenia during treatment with amitriptyline.

Consider the possibility of potentiation with combined use of antidepressants. Patients should be cautioned against errors in judgment due to mood changes. *For more complete details, consult package insert or Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Union, New Jersey 07083.* 9-696

[From MD, April 1969]

Chronic fatigue can make almost anyone blue. But...

Ritalin®
(methylphenidate)
Sparks Energy in Minutes

relieves chronic fatigue and mild depression

Even a snappy new outfit may fail to put the starch back in drooping spirits, especially when mild depression goes hand in glove with chronic fatigue. But Ritalin is tailor-made for your patients who fit this pattern. With Ritalin, enthusiasm will be their long suit as they fashion more energetic lives for themselves. And this effective stimulant...

acts in minutes

Unlike other antidepressants, Ritalin usually brings relief with the very first dose. Your patient need not wait days or even weeks to begin feeling better. Ritalin also...

offers safety

In treating chronic fatigue and mild depression: Unlike amphetamines, Ritalin rarely affects blood pressure or heart rate; it has not been associated with muscle tremors or urinary retention as have the potent MAO inhibitors or tricyclic compounds. And toxic or adverse effects on blood, urine, liver or kidney function are not to be anticipated. For these reasons, Ritalin...

proves especially valuable for the elderly

This time-tested agent is well tolerated, even by older patients. It rarely affects appetite or causes rebound depression.

ORAL RITALIN

CONTRAINDICATIONS: Marked anxiety, tension, agitation. Contraindicated in patients known to be hypersensitive to the drug; in patients with glaucoma and with epilepsy, except to combat lethargy induced by anticonvulsant drugs.

WARNINGS: Should not be used for severe depression (exogenous or endogenous) except in the hospital under careful supervision. Should not be used to increase mental or physical capacities beyond physiological limits.

Use in Pregnancy

Safe use in pregnant women, or during lactation, has not been established. Therefore, benefits must be weighed against potential hazards.

PRECAUTIONS: Patients with an element of agitation may react adversely; discontinue therapy if necessary. Use cautiously with vasopressors and MAO inhibitors and in patients with hypertension. Ritalin may decrease the hypotensive effect of guanethidine.

In chronic overdosage, careful withdrawal is required because of patient's underlying emotional disturbance. Periodic CBC and platelet count are advised during prolonged therapy.

ADVERSE REACTIONS: Hypersensitivity reactions, nervousness, insomnia, anorexia, nausea, dizziness, palpitation, headache, dyskinesia, drowsiness, skin rash. Rarely blood pressure and pulse changes both up and down occur. A few instances of angina and cardiac arrhythmias have occurred.

Overt psychotic behavior and psychic dependence in emotionally unstable persons have occurred rarely with chronic overdosage.

DOSAGE: Administer orally in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Dosage will depend upon indication and individual response, the average range being 20 to 60 mg daily.

SUPPLIED: Ritalin® hydrochloride (methylphenidate hydrochloride) *Tablets*, 20 mg (peach), 10 mg (pale green) and 5 mg (pale yellow).

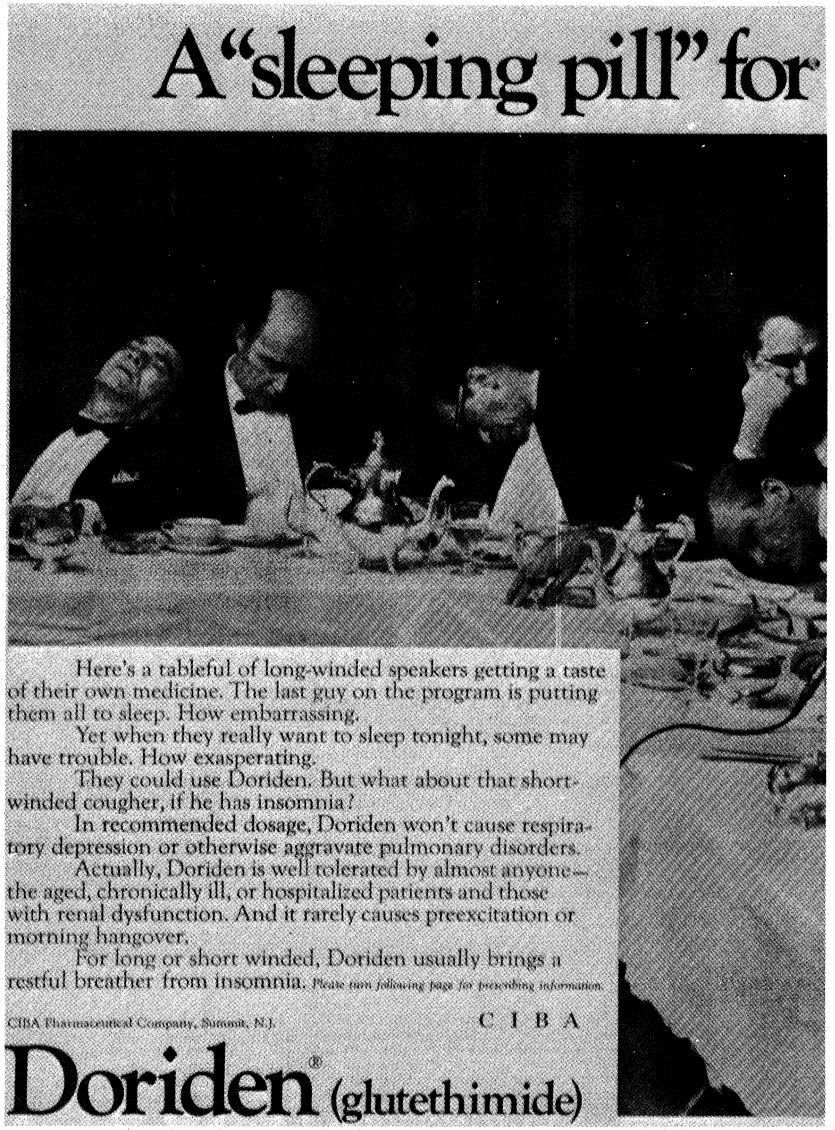
Consult complete product literature before prescribing.

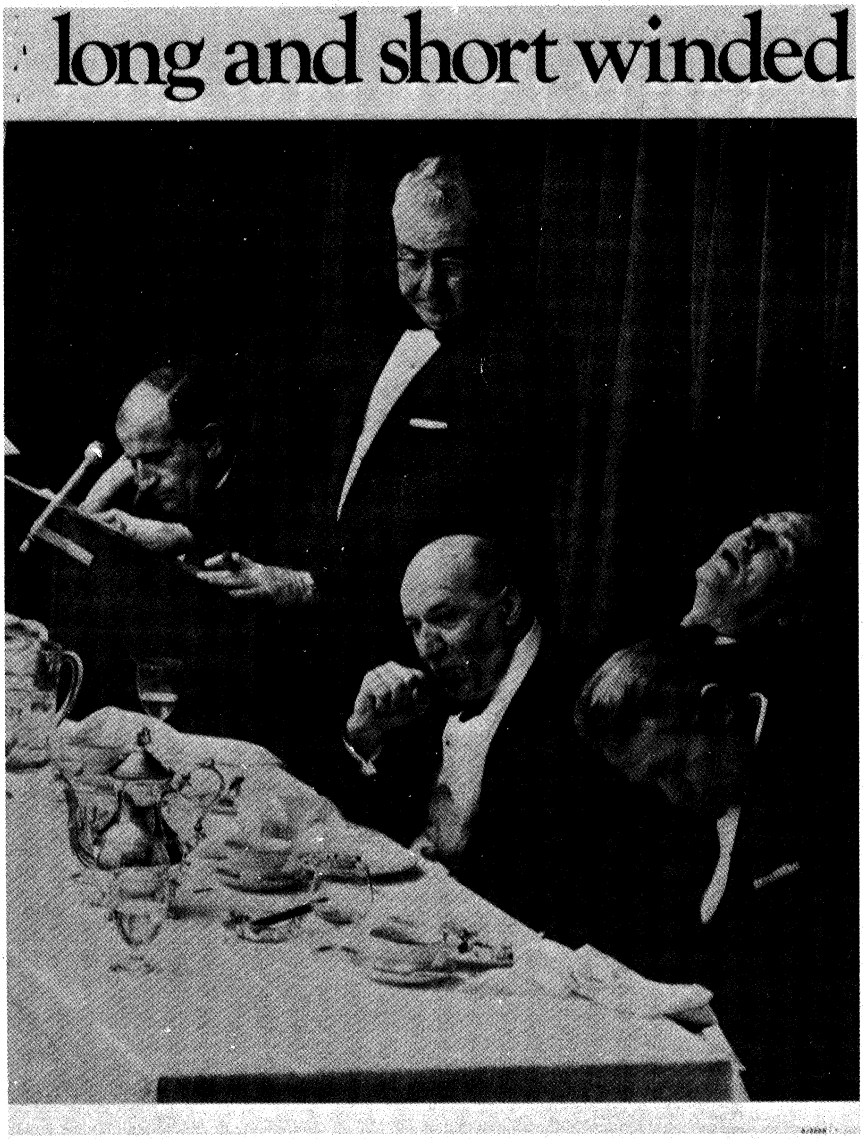
CIBA Pharmaceutical Company, Summit, N.J. 07901

C I B A

2/3979 MK

[From Medical Economics, June 9, 1969]




long and short winded

Doriden® (glutethimide)

INDICATIONS: For night-time, daytime, and preoperative sedation, as well as during first stage of labor.

CONTRAINDICATIONS: Known hypersensitivity to glutethimide.

WARNINGS: Caution patients about possible combined effects with alcohol and other CNS depressants. Do not operate machinery, drive motor vehicle, or engage in activities requiring complete alertness shortly after ingesting drug.

Dosage of coumarin anticoagulants may require adjustments during and on cessation of glutethimide therapy.

Physical and Psychological Dependence: Physical and psychological dependence have occurred. Prescribe cautiously for patients known to take excessive quantities of drugs. Limit repeated prescriptions without adequate medical supervision. Withdrawal symptoms include nausea, abdominal discomfort, tremors, convulsions, and delirium. Newborn infants of mothers dependent on glutethimide may also exhibit withdrawal symptoms. In the presence of dependence, dosage should be reduced gradually.

Pregnancy: Use of any drug in pregnancy or lactation requires weighing potential benefits against hazards.

PRECAUTIONS: Total daily dosage above 1 Gm is not recommended for continued administration. In presence of pain, an analgesic should also be prescribed.

ADVERSE REACTIONS: Withdraw glutethimide if a generalized skin rash occurs. Rash usually clears spontaneously 2 or 3 days after withdrawal. Occasionally, hemorrhagic or urticarial rash may occur. In recommended doses, there have been rare reports of nausea, hangover, paradoxical excitation, and blurring of vision. Rarely, acute hypersensitivity reactions, porphyria, and blood dyscrasias (thrombocytopenic purpura, aplastic anemia, leukopenia) have been reported.

DOSAGE: Individualize dosage. Not recommended for children under 12.

Night-time sedation: 0.25 to 0.5 Gm at bedtime. Repeat dose if necessary, but not less than 4 hours before arising.

Daytime sedation: 0.125 to 0.25 Gm t.i.d. after meals.

Preoperative sedation: 0.5 Gm the night before surgery; 0.5 to 1 Gm 1 hour before anesthesia.

First stage of labor: 0.5 Gm at onset of labor. Repeat if necessary.

SUPPLIED: *Tablets,* 0.5 Gm (white, scored); bottles of 100, 500, 1000 and Strip Dispensers of 100.

Tablets, 0.25 Gm (white, scored); bottles of 100 and 1000.

Tablets, 0.125 Gm (white); bottles of 100.

Capsules, 0.5 Gm (blue and white); bottles of 100.

Consult complete literature before prescribing.

C I B A

CIBA Pharmaceutical Company
Summit, N.J.

2/3926

[From Medical Economics, June 9, 1969]

What makes a woman cry?

A man?
Another woman?
Three kids?
No kids at all?
Wrinkles?
You name it.

Is she truly depressed?

Is that why she lets go in your office?

You comfort her.
Talk to her.
And, if she is depressed, consider Pertofrane.
Because
in 3 to 5 days
she can often begin
to cope,
work,
maybe play,
even enjoy.

Pertofrane®
desipramine hydrochloride
In depression...
when words are not enough

But before you prescribe Pertofrane, please see the full prescribing information and especially note Contraindications, Precautions, Warning, Adverse Reactions and Dosage. A brief summary of that information is included here.

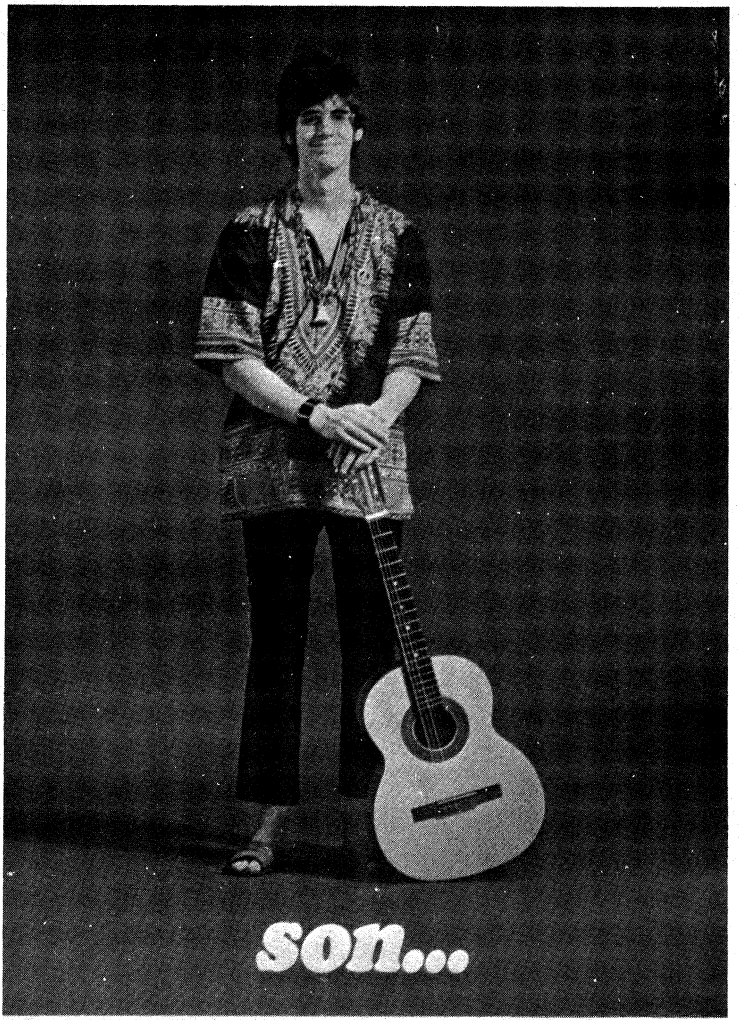
Pertofrane® desipramine hydrochloride

Indications: For relief of depression.
Contraindications: Do not use drugs of the M.A.O.I. class with Pertofrane. Hyperpyretic crises or severe convulsive seizures may occur; potentiation of adverse effects can be serious or even fatal. When substituting this drug in patients receiving an M.A.O.I., allow an interval of at least 7 days. Initial dosage in such patients should be low and increases should be gradual and cautiously prescribed.
Warning: Activation of psychosis may occasionally be observed in schizophrenic patients. Do not use in patients under 12 years old, and do not use in women who are or may become pregnant unless the clinical situation warrants the potential risk.
Precautions: Careful supervision and protective measures for potentially suicidal patients are necessary. Discontinuation of therapy or adjunctive use of a sedative or tranquilizer may be necessary in the presence of increased anxiety or agitation, hypomania or manic excitement. However, phenothiazines may aggravate the condition. Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those receiving anticholinergic drugs (including antiparkinsonism agents). Carefully observe patients with increased intraocular pressure. Prescribe cautiously in hyperthyroid patients and in those receiving thyroid medications. Cardiovascular complications (myocardial infarction and arrhythmias) are potential risks since they have occasionally occurred with imipramine, the parent compound. Desipramine may block the pharmacologic activity of guanethidine and related adrenergic neuron-blocking agents. Hypertensive episodes have been observed during surgery in patients on desipramine therapy.
Before prescribing the drug, the physician should be thoroughly familiar with prescribing information, with the literature, with all adverse reactions, with the diagnosis and management of depression, and with the relative merits of all measures for treating the condition.
Adverse Reactions: Dry mouth, constipation, disturbed visual accommodation, anorexia, perspiration, insomnia, drowsiness, dizziness, headache, nausea, epigastric distress, and skin rash (including photosensitization) may appear. Since orthostatic hypotension has occurred, carefully observe patients requiring concomitant vasodilating therapy, particularly during the initial phases. Other adverse reactions include tachycardia, changes in EEG patterns, tremor, falling, mild extrapyramidal activity, neuromuscular incoordination, epileptiform seizures. A confusional state (with such symptoms as hallucinations and disorientation) occurs occasionally and may require reduced dosage or discontinuance of therapy. Rarely, transient eosinophilia, slight elevation in transaminase levels, transient jaundice, or liver damage have occurred. If abnormalities occur in liver function tests, discontinue drug and investigate. Occasional hormonal effects, particularly decreased libido or impotence and instances of gynecomastia, galactorrhea and female breast enlargement have been observed. Urinary frequency or retention may occur. The drug should be discontinued if agranulocytosis, bone marrow depression, jaundice, thrombocytopenia, or purpura occur.
Dosage: 25 to 50 mg. t.i.d. The maximum daily dose is 200 mg. Continue maintenance dosage for at least 2 months after obtaining satisfactory response. Generally, elderly and adolescent patients should be given low doses.
Availability: Pink capsules of 25 mg. in bottles of 100 and 1000. (B) 46-530-E

For complete details, please see the prescribing information.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York 10502

[From Medical Economics, June 9, 1969]



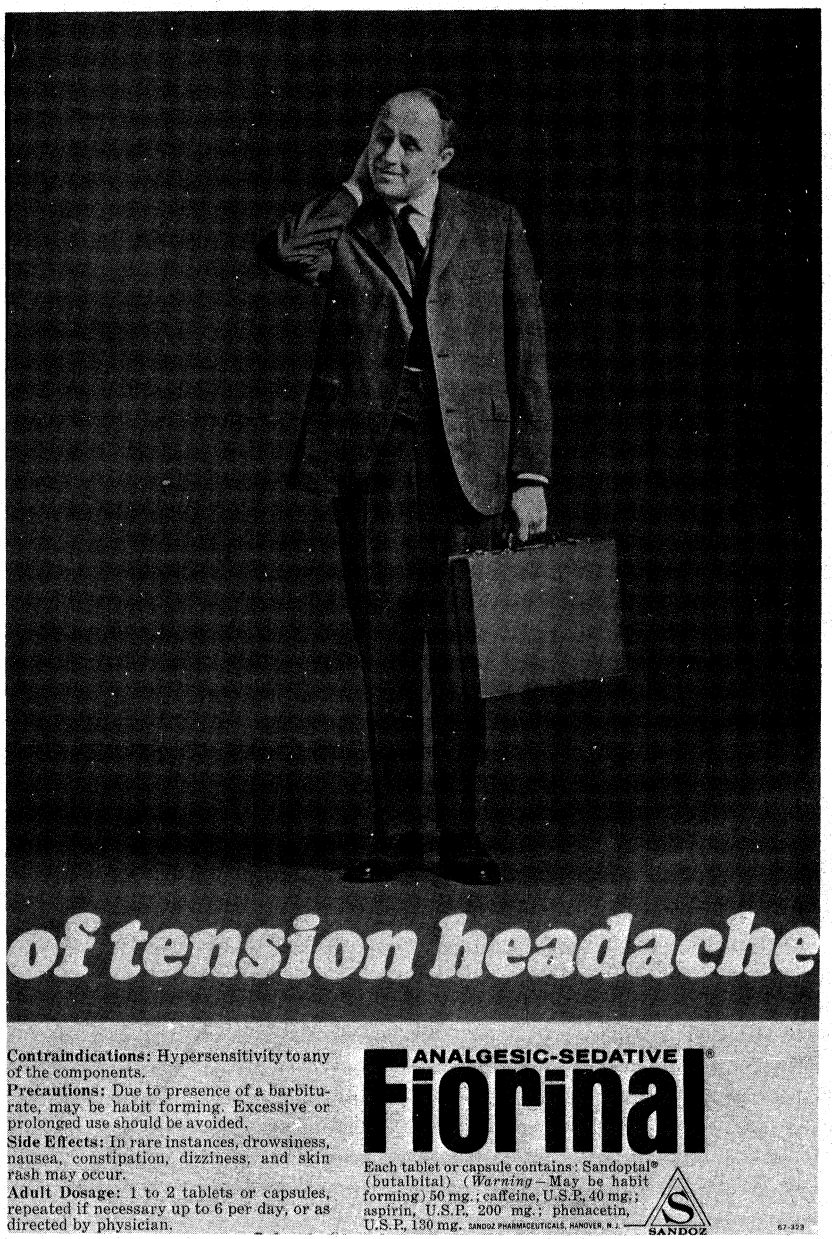
When nothing (including his son) goes the way he wants, tension headache frequently will clamp its grip on an already harried man.

When that happens, the patient usually can derive some comfort and considerable relief from both the pain and the accompanying tension of a tension headache by taking Fiorinal.

Fiorinal works fast and effectively as an analgesic, while it is also working as a sedative. In exerting this dual action, Fiorinal helps break the pain-tension interaction so characteristic of tension headache.

Specifically formulated for tension headache, Fiorinal is the most widely prescribed analgesic-sedative in the treatment of tension headache. It is non-narcotic and it leaves the patient capable of functioning in his environment.

Suggested adult dosage: 1 to 2 tablets to start, repeated as needed up to 6 tablets daily. Patients usually find a prescription for 50 Fiorinal tablets economical and convenient.



Contraindications: Hypersensitivity to any of the components.
Precautions: Due to presence of a barbiturate, may be habit forming. Excessive or prolonged use should be avoided.
Side Effects: In rare instances, drowsiness, nausea, constipation, dizziness, and skin rash may occur.
Adult Dosage: 1 to 2 tablets or capsules, repeated if necessary up to 6 per day, or as directed by physician.

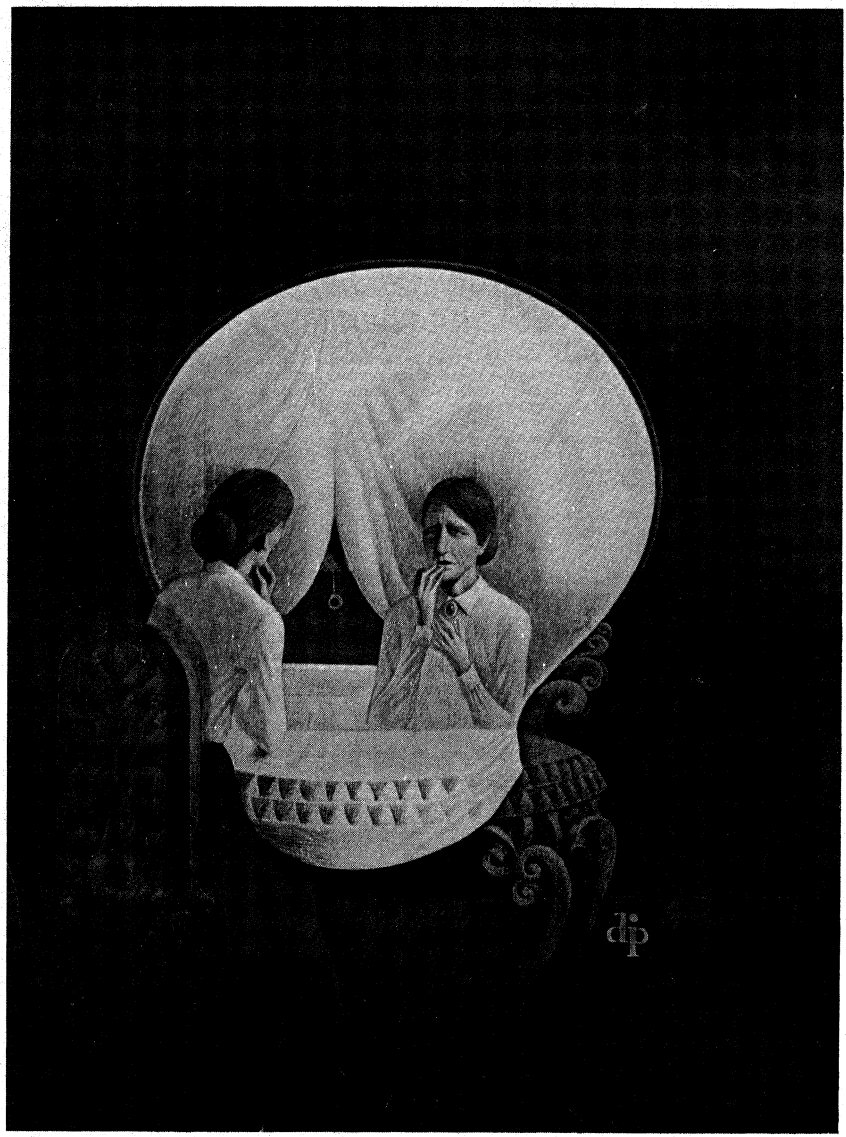
ANALGESIC-SEDATIVE®
Fiorinal®

Each tablet or capsule contains: Sandoptal® (butalbital) (*Warning*—May be habit forming) 50 mg.; caffeine, U.S.P., 40 mg.; aspirin, U.S.P., 200 mg.; phenacetin, U.S.P., 150 mg. SANDOZ PHARMACEUTICALS, HANOVER, N.J.

SANDOZ

67-323

[From Journal of the American Medical Association,
Vol. 208, No. 11, June 16, 1969]



Am I old?

In the face of obvious decline, anxiety is often seen in reactive depression

Triavil® treats both

To adapt successfully to alterations in appearance and the loss of functional capacity, the aging person must maintain a sense of worth and the belief that there is still much to do and enjoy in life. Without such resources, the individual may become emotionally bankrupt. Reactive feelings of anxiety and despair then often provoke physical-emotional symptoms which are, in effect, a call for help.

For the patient with moderate to severe anxiety *and* coexisting depression, TRIAVIL offers effective tranquilizer-antidepressant therapy. TRIAVIL contains perphenazine and amitriptyline HCl—to help allay anxiety, lift depressive mood, and relieve the functional somatic complaints so frequent in the older age group.

It should be borne in mind that the possibility of self-destruction is inherent in any serious depressive illness. During the early phases of psychopharmacologic therapy, therefore, close supervision of such patients is essential until you are satisfied that significant remission has taken place.

Patients who have received MAO inhibitors within two weeks should not receive TRIAVIL. Those on TRIAVIL should be warned that response to alcohol may be potentiated. The drug may impair alertness in some patients. Operation of automobiles and other activities made hazardous by diminished alertness should be avoided. Contraindicated in glaucoma, in patients expected to experience problems of urinary retention, in CNS depression from drugs, and in bone marrow depression. Not recommended in pregnancy.

For simplicity of administration and convenience, TRIAVIL is provided in four dosage strengths for flexibility of adjustment to the patient's changing needs.

FOR MODERATE TO SEVERE ANXIETY WITH COEXISTING DEPRESSION

TRIAVIL®

containing perphenazine and amitriptyline HCl

For additional prescribing information, please see following page.

for moderate to severe anxiety with coexisting depression

TRIAVIL®

containing perphenazine and amitriptyline HCl
TRANQUILIZER-ANTIDEPRESSANT

TRIAVIL®2-10: Each tablet contains 2 mg. of perphenazine and 10 mg. of amitriptyline hydrochloride.

TRIAVIL®2-25: Each tablet contains 2 mg. of perphenazine and 25 mg. of amitriptyline hydrochloride.

TRIAVIL®4-10: Each tablet contains 4 mg. of perphenazine and 10 mg. of amitriptyline hydrochloride.

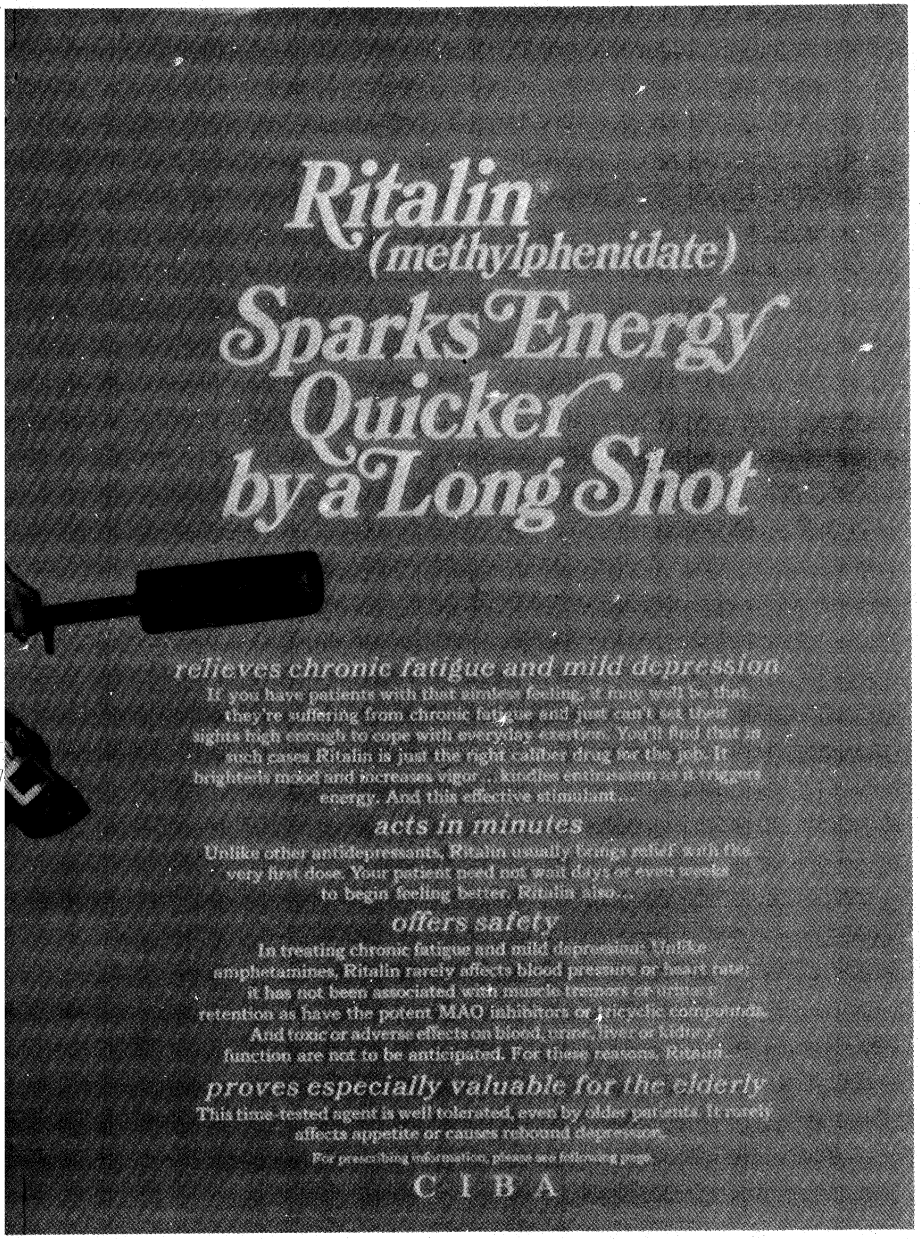
TRIAVIL®4-25: Each tablet contains 4 mg. of perphenazine and 25 mg. of amitriptyline hydrochloride.

INDICATIONS: Patients with moderate to severe anxiety and/or agitation and depressed mood; patients with depression in whom anxiety and/or agitation are severe; patients with depression and anxiety in association with chronic physical disease; schizophrenics with associated depressive symptoms.
CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; urinary retention; pregnancy; glaucoma. Do not give in combination with MAOI drugs because of possible potentiation that may even cause death. Allow at least 2 weeks between therapies. In such patients therapy with TRIAVIL should be initiated cautiously, with gradual increase in the dosage required to obtain a satisfactory response.
WARNINGS: Patients should be warned against driving a car or operating machinery or apparatus requiring alert attention, and that response to alcohol may be potentiated.
PRECAUTIONS: Suicide is always a possibility in mental depression and may remain until significant remission occurs. Supervise patients closely in case they may require hospitalization or concomitant electroshock therapy. Untoward reactions have been reported after the combined use of antidepressant agents having various modes of activity. Accordingly, consider possibility of potentiation in combined use of antidepressants. Not recommended for use in children. Mania or hypomania may be precipitated in manic-depressives (perphenazine in TRIAVIL seems to reduce likelihood of this effect). If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Caution patients about errors of judgment due to change in mood.
SIDE EFFECTS: Similar to those reported with either constituent alone. **Perphenazine:** Should not be used indiscriminately. Use caution in patients with history of convulsive disorders or severe reactions to other phenothiazines. Likelihood of untoward actions greater with high doses. Closely supervise with any dosage. Side effects may be any of those reported with phenothiazine drugs: blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); extrapyramidal symptoms (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, akathisia, dyskinesia, parkinsonism) usually controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine; severe acute hypotension (of particular concern in patients with mitral insufficiency or pheochromocytoma); skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; endocrine disturbances (lactation, galactorrhea, disturbances of menstrual cycle); grand mal convulsions; cerebral edema; altered cerebrospinal fluid proteins, polyphagia; paradoxical excitement; photophobia; skin pigmentation; failure of ejaculation; EKG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states; autonomic reactions such as dryness of the mouth, headache, nausea, vomiting, constipation, obstipation, urinary frequency, blurred vision, nasal congestion, and a change in the pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude; muscle weakness; mild insomnia; significant unexplained rise in body temperature may suggest intolerance to perphenazine, in which case discontinue. Antiemetic effect may obscure signs of toxicity due to overdosage of other drugs or make diagnosis of other disorders such as brain tumors or intestinal obstruction difficult. May potentiate central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol), atropine, heat, and phosphorous insecticides. **Amitriptyline:** Careful observation of all patients recommended. Side effects include drowsiness (may occur within the first few days of therapy); dizziness; nausea; excitement; hypotension; fainting; fine tremor; jitteriness; weakness; headache; heartburn; anorexia; increased perspiration; incoordination; allergic-type reactions manifested by skin rash, swelling of face and tongue, itching; numbness and tingling of limbs, including peripheral neuropathy; activation of latent schizophrenia (however, the perphenazine content may prevent this reaction in some cases); epileptiform seizures in chronic schizophrenics; temporary confusion, disturbed concentration, or transient visual hallucinations on high doses; evidence of anticholinergic activity, such as tachycardia, dryness of mouth, blurring of vision, urinary retention, constipation, paralytic ileus; agranulocytosis; jaundice. The antidepressant activity may be evident within 3 or 4 days or may take as long as 30 days to develop adequately, and lack of response sometimes occurs. Response to medication will vary according to severity as well as type of depression present. Elderly patients and adolescents can often be managed on lower dosage levels.

For more detailed information consult your Merck Sharp and Dohme representative or see the package circular.

MERCK SHARP & DOHME
Division of Merck & Co. Inc. West Point Pa 19486
where today's theory is tomorrow's therapy

[From Modern Medicine, June 30, 1969]



Ritalin®
(methylphenidate)
Sparks Energy Quicker by a Long Shot



ORAL RITALIN
CONTRAINDICATIONS: Marked anxiety, tension, agitation. Contraindicated in patients known to be hypersensitive to the drug; in patients with glaucoma and with epilepsy, except to combat lethargy induced by anticonvulsant drugs.
WARNINGS: Should not be used for severe depression (exogenous or endogenous) except in the hospital under careful supervision. Should not be used to increase mental or physical capacities beyond physiological limits.
Use in Pregnancy
Safe use in pregnant women, or during lactation, has not been established. Therefore, benefits must be weighed against potential hazards.
PRECAUTIONS: Patients with an element of agitation may react adversely; discontinue therapy if necessary. Use cautiously with vasopressors and MAO inhibitors and in patients with hypertension. Ritalin may decrease the hypotensive effect of guanethidine. In chronic overdosage, careful withdrawal is required because of patient's underlying emotional disturbance. Periodic CBC and platelet count are advised during prolonged therapy.
ADVERSE REACTIONS: Hypersensitivity reactions, nervousness, insomnia, anorexia, nausea, dizziness, palpitation, headache, dyskinesia, drowsiness, skin rash. Rarely, blood pressure and pulse changes, both up and down, occur. A few instances of angina and cardiac arrhythmia have occurred. Overt psychotic behavior and psychic dependence in emotionally unstable persons have occurred rarely with chronic overdosage.
DOSAGE: Administer orally in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. Dosage will depend upon indication and individual response, the average range being 20 to 60 mg daily.
SUPPLIED: Ritalin® hydrochloride (methylphenidate hydrochloride) *Tablets*, 20 mg (peach), 10 mg (pale green) and 5 mg (pale yellow).
Consult complete product literature before prescribing.
CIBA Pharmaceutical Company
Summit, New Jersey

C I B A

2/3897MK-1

THE STATE OF THE LAW AND COMPLIANCE*

(Address of William W. Goodrich, Assistant General Counsel, Department of Health, Education, and Welfare, Washington, D.C.)

Three years have passed since FDA first entered the world of prescription drug advertising.

We are more intrigued with what we see today, than we were by our first viewing. To borrow a quote: "We are reading more now and enjoying it less." And we are more convinced than ever that there is much room for needed improvement.

Getting to know you is a refreshing experience. It has been said of you that you have a unique ability to make a virtue out of a serious side effect.

The Kefauver investigations highlighted many excesses in drug promotion. But they suggested no remedies. The Executive Branch's first reaction was to strengthen the Federal Trade Commission Act. But the Congressional response was to require stronger control under the Federal Food, Drug, and Cosmetic Act. Instead of orders to cease and desist, new sanctions of seizure, injunction and criminal penalties were provided to do this job.

While the legislative developments were fast moving—and the legislative history is relatively thin—the message was loud and clear that there had to be some basic changes in this phase of drug promotion.

President Kennedy recommended—and the Congress enacted—provisions intended to "help assure the American people . . . that the promotional material [for Rx drugs] tells the full story . . . [the] possible bad effects as well as the good—and the whole truth about therapeutic usefulness."

This is the guideline that controls our operations.

The only concession made for the special needs of advertising was that the essential information might be presented "in brief summary." This requires the presentation of information in your ads which will fairly show the effectiveness of any drug, along with any side-effects, contraindications, precautions and warnings, in a form that is brief but neither false nor misleading. The central idea is to be sure that the message that comes through to the profession strikes a proper balance in telling what the drug is for, what the limitations are upon its usefulness, and what hazards may attend its use.

Lest there be any question as to precisely what is required—the law provides that every prescription drug advertisement and any other descriptive matter issued to promote sales shall contain a true statement of—

The formula;

The established name of the drug along with the trade name;

And "such other information in brief summary relating to side effects, contraindications and effectiveness as shall be required in regulations" issued by the Secretary.

Preclearance of ads is not required except in extraordinary circumstances. The Department was authorized to specify which promotional material is labeling (requiring full disclosure) and which is advertising (requiring the brief summary).

The regulations applicable to ad content were promptly issued—but only after a confrontation with both the pharmaceutical industry and the medical profession. Both professed to believe that advertising was not educational—that it served only a reminder role—and played no part in the physician's choice of drugs when he began to write on his prescription form.

We took the more realistic view that if advertising does not sell drugs it will not continue to run.

Therefore, the major issue requiring resolution was whether the regulatory controls would extend to the entire ad—or just to the little part that the advertiser might designate as the "brief summary."

Resolution of that issue was accomplished by final regulations, supplemented by a memorandum of understanding about their intent. The whole ad was controlled.

The regulations themselves are simple indeed. They were offered as the first step in public supervision of this very vital means of communication between

*Presented at "A Morning With FDA," Pharmaceutical Advertising Club, Roosevelt Hotel, New York City, Oct. 20, 1966.

the drug producer and the medical profession. The controls were not set in concrete; they can and will be improved as the need appears. To that end, we are announcing new proposals that would require that all new promotions—both advertising and labeling—to be submitted as soon as they are developed for use.

In essence, our current regulations require—insofar as the selling part of the ad is concerned—four things:

A fair summary of the effectiveness of the drug in the conditions for which it is offered, along with all of the side effects, contraindications, precautions, and warnings applicable both to the conditions for which the drug is advertised and for which it is commonly prescribed;

A fair balance in presenting the information on effectiveness and the related information on side effects, etc.;

A reasonably close association of the information on effectiveness and the information on side-effects, contraindications, etc., together with a discussion of the adverse data in the same degree of prominence that is achieved for the claims of effectiveness;

And the use of only those promotional claims which have been approved in advance upon the clearance of the drug for the market as a "new drug" or as a certified antibiotic, or, for drugs that required no preclearance, claims of effectiveness that are generally recognized as true or which are supported by substantial evidence, consisting of adequate and well-controlled investigations or adequate clinical experience on the basis of which it can fairly and responsibly be concluded that the drug will have the effectiveness claimed.

This is not a very big order.

Simply stated, drugs may be promoted only on the basis of proven effectiveness.

The total advertising message must be fair and frank in discussing both the usefulness and the hazards that may attend the administration of the drug.

And the layout of the ad must deal fairly with the scientific data that underlies the message.

As Dr. Goddard said in his Chicago speech to the Midwest PA Club, we have difficulty in understanding how a group of creative people with the talents you so regularly display should have any difficulty at all in understanding the advertising restrictions of our regulations.

"Fair balance", "resasonably close association", and the "same relative degree of prominence" are words of ordinary English.

No more inflexible words were used because the Agency wanted to move with the drug industry and the creative people in correcting what was an indefensible state of drug promotion.

If these concepts in the present regulations seem perplexing—we offer the memoranda of understanding which passed between us and the industry back in October, 1963. And we offer also a statement we made public in 1964 calling attention to the most common failings in drug promotion. More recently, at the medical section meeting of the Pharmaceutical Manufacturers Association on March 30, 1966, we described in great detail the basic premises underlying our evaluation of advertising and promotional labeling.

Bearing in mind Ben Franklin's comment that "Laws too gentle are seldom obeyed; too severe, seldom executed", we are preparing to move the informal comments in the memo of understanding and in the policy announcement into the positive provisions of regulations. And we will continue to examine the performance of all advertisers under our rules, so that misunderstanding and noncompliance can be promptly corrected.

With this background as to the state of the law, let's turn to the state of compliance by examining a few cases of actual performance.

Remembering that "all things that hurt, instruct", I apologize in advance for any injured feelings that may flow from a critical examination of some examples of your most recent work.

We would like to view with you the ads for the "big eight"—all of the eight new 1965 model drugs that entered the list of the 200 most prescribed during the first years of their introduction.

They are:

Aventyl—Eli Lilly
C-Quens—Eli Lilly
Indocin—Merck Sharpe Dohme
Lincocin—Upjohn

Oracon—Mead Johnson
Pediamycin—Ross
Pre-Sate—Warner Chilcott
Tegopen—Bristol Laboratories

Without implying that there has been a complete medical work-up as to the validity of all of the advertised claims for these drugs, I can say that I asked our medical staff—including some of the physicians who were primarily responsible for the clearance of the drugs for market—to comment on some current ads for these important new offerings of the pharmaceutical industry.

Here are the results.

"No doubt, this ad will sell huge amounts of Aventyl. It is pretty, impressive, and seems to pack quite an emotional wallop. However, the term 'behavioral drift' doesn't appear to be more than a Madison Avenue description. It certainly is not a bona fide psychiatric diagnosis.

"It is, from the ad, difficult to tell in the first 4 pages, whether Aventyl is primarily an anti-depressant, primarily a tranquilizer or what.

* * * * * * *

"The first sentence under side effects in both the ad and the package insert states that 'No single side effect can be considered as occurring frequently * * *.' This could lure the unsuspecting physician into not looking much further. While the incidence is mentioned later of the common side effects, it's a bit too late.

* * * * * * *

"All in all, the sins in this ad are those both of omission and commission. They include poor arithmetic, poor terminology, invention of psychiatric terms, and an overwhelming intent to 'snow' the practicing physician."

As the medical officer's comment shows, we share the responsibility for some of the defects in this ad, because we approved the package insert. That does not make the ad any better.

Aventyl was offered for a new psychiatric disorder, discovered right here on Madison Avenue. While this makes excellent ad copy, it does not promote the drug for the conditions for which it has been approved. Instead, it uses a new catch phrase to cover a host of "target" symptoms, so that the drug is indicated and prescribed for the ordinary frustrations of daily living to reach a much larger patient population than the scientific data will support.

C–Quens and Oracon were approved as new sequential oral contraceptives.

The central theme of the ad for Oracon is that it is safer than and superior to other oral contraceptives because it is so close to nature—that it is physiological, natural, and normal.

These claims are unsupported by scientific facts. Thus far, there is no substantial evidence that any oral contraceptive is either more effective or safer than any other that has been approved for the market.

This ad also makes a point that Oracon was "the first sequential oral contraceptive". It fails to inform the physician that it was approved only 13 days before C–Quens. The apparent purpose of the claim is to bolster the asserted, but unsupported, superiority.

The theme of the ad for C–Quens is directed to a single side effect of the oral contraceptives—weight gain.

The claim that women using sequential oral contraceptives experience less significant weight gain is ungrounded in scientific fact, and the ad is thus misleading in its major implication. Yet, it may serve its purpose of influencing the physician to shift a patient to this product on the basis of this illusory promise.

This ad, like the one for Oracon, claims "other advantages of therapy"—presumably less side effects, and this is bolstered by a claim that it contains "the smallest amount of hormone substance". The latter claim is literally false, and the claim of lower incidence of side effects has no scientific support.

The truth about the oral contraceptives is reported in an FDA publication, available from the Government Printing Office. It is that there is no adequate scientific data, at this time, proving these compounds unsafe for human use. There are nonetheless some very infrequent but serious side effects and some possible theoretic risks suggested by the experimental data. The physician must decide for his patient whether to accept the risk—small though it may be. And

the Committee which advised us said: The physician "can do this wisely only when there is presented to him dispassionate scientific knowledge of the available data."

We leave with you the question whether these two ads present the physician with "dispassionate scientific knowledge".

Indocin has been marketed for slightly more than one year. Like most new drugs offered to replace established products, this one was offered as safer and more effective. As new experience with the drug has been gained, more side-effects have been noted and more warning information has been required. Only a few days ago, the sponsor mailed a new revised brochure to the profession, with new cautionary information in heavy print. Yet the current ad continues the headline "extends the margin of safety in long term management of arthritic disorders".

There is not yet enough experience to support the claim for greater long-term safety. To the contrary, the longer the drug is used the more side-effect information appears.

This ad quotes authoritative sources, without the full impact of the actual articles. And it uses one reference which is from a 2-inch abstract, apparently of a 1964 speech. This latter reference is used to support a claim for "ankylosing spondylitis", but the ad does not inform the reader that this same abstract also states "Excellent results have also been obtained in some cases of rheumatoid arthritis . . . there have been striking failures as well."

The claim for gout is not supported by the package insert or by the scientific data.

And, finally, the "Brief Summary" omits some very important warning information that is required in the package insert—and thus in the ad.

As a side-light on this drug, it was featured in the July issue of "Pageant" magazine for "bursitis", "trick knee", "tennis elbow" and "a host of other less common disorders characterized by pain and swelling in and around the joints". The only support for these claims was user testimonials which, according to the article, were made available to the writers by the sponsor of the drug.

Lincocin is a new antibiotic entry among the 1965 models.

The ad to promote the drug is highly competitive in comparing the ease of use and the absence of some side effects expected from the established antibiotics. It is "practically painless on injection", unlike older intramuscular tetracyclines; it "does not share antigenicity with pencillin"; it has "no serious renal or neurologic abnormalities" and "no ototoxicity", unlike streptomycin or kanamycin.

Yet after such elaboration on what side effects the drug does not have, the ad obscures the most important information that the physician needs in using this drug—that hematologic toxicity can occur, and that the frequency of severe diarrhea is a unique feaure of Lincocin therapy.

Pediamycin was another 1965 model antibiotic. It was featured as being especially safe for infants, but no substantial evidence existed to support the claim. And the range of its usefulness were exaggerated.

Tegopen was the final entry on the 1965 list of antibiotic drugs. The headline was "This is a new every-day penicillin for common bacterial respiratory infections".

Plainly this was to encourage indiscriminate and routine use of a drug that was approved for use primarily against penicillin resistant staph infections.

The brief summary failed to communicate the real message that it is important to identify the infectious organism and to shift to regular penicillin when the organism is later found to be sensitive to penicillin G or V.

The artwork, layout, and design of the ad was to impress the reader with the frequency with which Tegopen can be used, and not to carry the real message which the approval of the drug intended.

Pre-Sate is a new drug for the treatment of an impossible condition to treat—overeating and overweight. It is, we believe, the consensus of medical opinion that there are no true anorexiants, and that dieting is the only answer to obesity.

This attractive ad is an admirable effort to crack this attractive market. While page 6 emphasizes the essential need for concurrent diet control, the total message is that Pre-Sate is a drug of superior efficacy in reducing body weight.

Statistical data is offered to prove the superiority of this drug over its established competitors. Animal data are used to support the claim that the mechanism of its action has been established.

But the claims of superiority and that it acts on the human satiety center of the hypothalmus are not scientifically established.

It is generally assumed that the 1962 Amendment did not control "relative efficacy", but ads which make claims of that kind are subject to critical review and proof that the Company's claims of superior effectiveness are well founded.

This ad appeared about the time of the Peritrate seizure. We are pleased to note improvements in later presentations.

Advertising prescription drugs should be a very special operation—wholly unlike advertising the 1967 model automobiles or the tars and nicotine of cigarettes. It should be based on the scientific data that allowed the drug to enter the market—you need look and can look no further than the official brochure for the allowable claims and the required warnings. As tempted as you may be by a new piece of investigative work that may be whispered to you to mount a new campaign to capture an entire market, you must remember that the approved claims are the limits beyond which promotion cannot go.

And in promoting newly developed and approved drugs, claims of greater safety and comparatively greater effectiveness can be made only on proven data—and then only with complete awareness that the limited experience with the drug accumulated during its investigational clinical practice; that clinical experience must be followed very closely and that ad campaigns will have to change as rapidly as clinical experience may require.

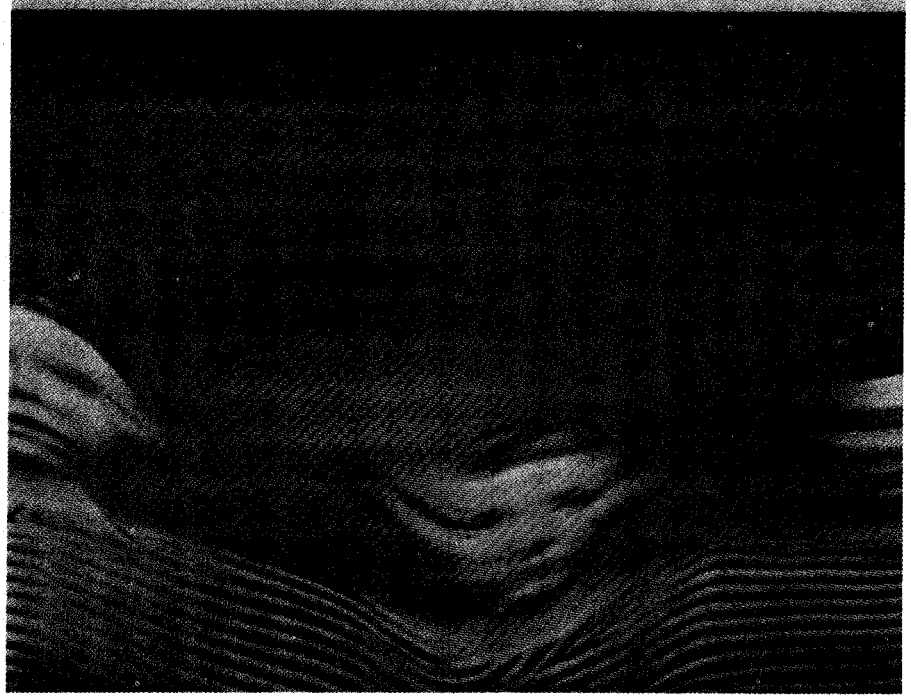
Please remember the thoughts that prescription drug advertising can go no further than the scientific support which sustains its approval for marketing; that you have an obligation in developing ad copy to tell the whole truth—good and bad; and that the entire advertising message must be designed around these basic ideas.

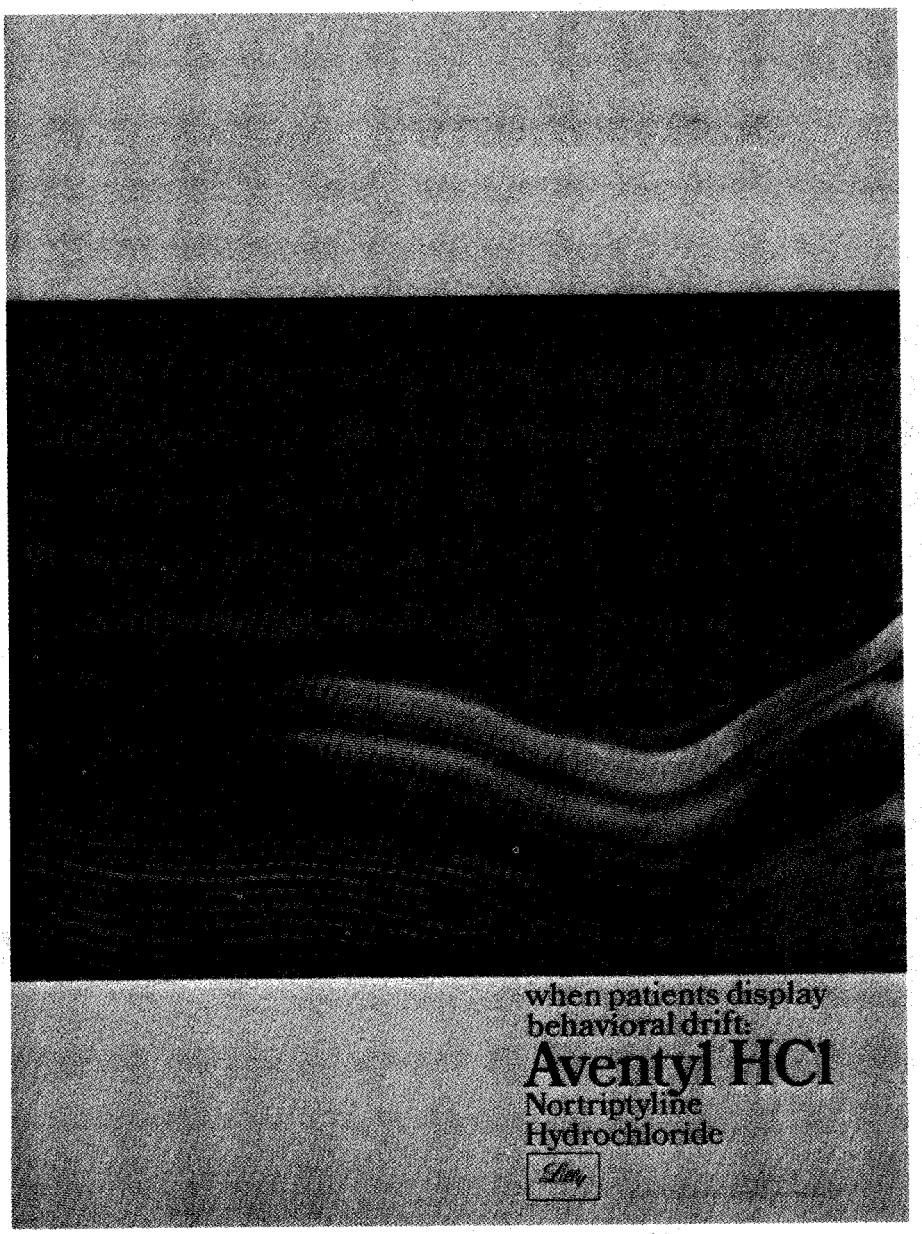
If the advertising copy for the "big eight" is typical of what is going on, Madison Avenue's new disease of "Behavioral Drift" is out of hand. Perhaps it can be cured by the placebo of talk, but more likely some stronger medicine will be necessary.

[From Journal of American Medical Association, Sept. 19, 1966, pp. 52–56]

behavioral drift: the fluctuating symptoms of the patient's emotional problem

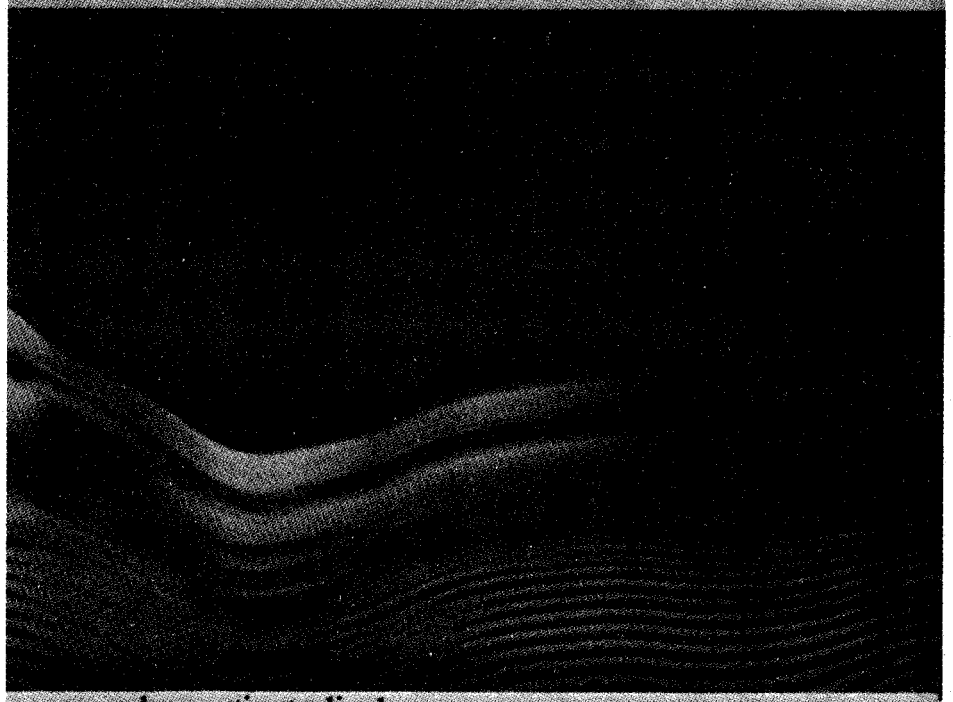
...Many emotional disorders are composed of a complex admixture of symptoms from both sides of the emotion spectrum. Symptoms may change from time to time, waxing or waning under the complications of ever changing situations of daily life. ... To the clinician this means that the same patient may present a varying constellation of complaints. ...[1]




when patients display
behavioral drift:
Aventyl HCl
Nortriptyline
Hydrochloride
Lilly

behavioral drift:

When the true range of usefulness of Aventyl HCl was evaluated, common presenting complaints were used as a measure of therapeutic effectiveness. As the bar graph shows, regardless of the side of the norm from which these symptoms originated, Aventyl HCl produced a high degree of satisfactory response.

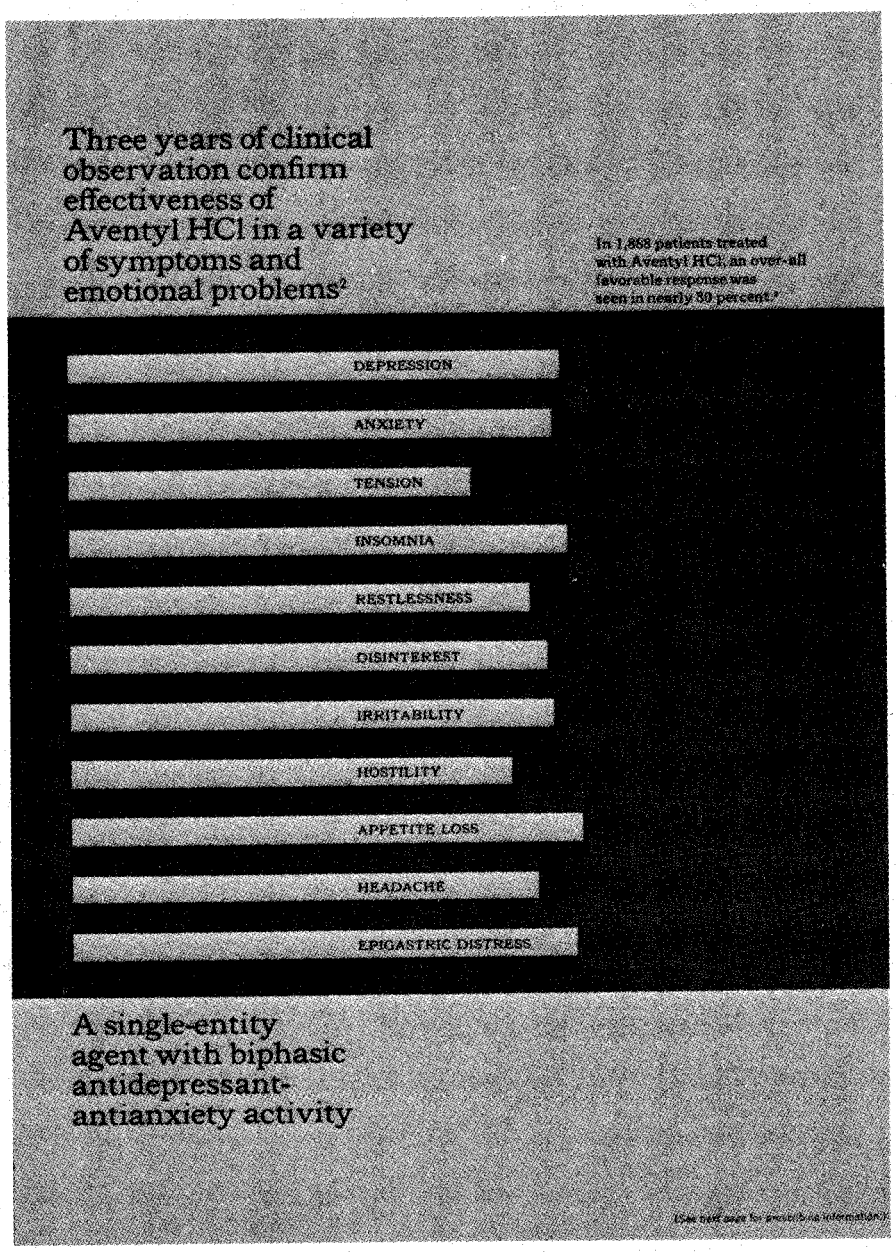


when patients display behavioral drift:

Aventyl® HCl

Nortriptyline Hydrochloride

Lilly


Three years of clinical observation confirm effectiveness of Aventyl HCl in a variety of symptoms and emotional problems[2]
In 1,868 patients treated with Aventyl HCl, an over-all favorable response was seen in nearly 80 percent.[2]
DEPRESSION
ANXIETY
TENSION
INSOMNIA
RESTLESSNESS
DISINTEREST
IRRITABILITY
HOSTILITY
APPETITE LOSS
HEADACHE
EPIGASTRIC DISTRESS
A single-entity agent with biphasic antidepressant-antianxiety activity



An immediate effect and a rapid over-all response

Prompt tranquilization occurs and provides evidence of initial improvement in some patients. In others, an immediate stimulatory effect is observed. Generally, a peak is rapidly reached and is soon followed by lasting over-all improvement.

Of those patients who responded to Aventyl HCl, 50 percent improved within one week, 79 percent by the second week, and 94 percent within one month.[1]

Well-tolerated therapy

Unwanted effects appear to be milder and less frequent than those produced by certain other antidepressants. Studies indicate Aventyl HCl has considerably less anticholinergic activity than certain of its predecessors.

In contrast to some tranquilizers, Aventyl HCl has not been reported to cause either habituation or withdrawal symptoms.

1. Gram, B.: Guidelines to Psychiatric Emotional Disorders, M. Times, 93:1483, 1965.
2. Free unit available through the Lilly Research Laboratories.

when patients display behavioral drift:

Aventyl HCl

Nortriptyline Hydrochloride

Lilly

Additional information available to physicians upon request.
Eli Lilly and Company
Indianapolis, Indiana 46206

Actions and Indications: Aventyl HCl is a potently well-tolerated and effective agent for the treatment of mental depressive disorders. Onset of action and therapeutic effects and tolerance are as efficient in geriatric as in younger patients.

Contraindications: Concomitant use with a monoamine oxidase inhibitor is contraindicated since potentiation of adverse effects can be serious or even fatal. The nonpsychotic patient receiving Aventyl HCl should be discontinued for at least ten days before treatment with Aventyl HCl is started.

Warnings: Use in myocardial infarction and in hypotensive states should be closely followed. At present, data are insufficient to recommend use of Aventyl HCl during pregnancy. The possibility of a suicidal attempt in a depressed patient should always be considered. Although there have been no reports of bone marrow damage or other serious effects, careful observations of the patient and periodic laboratory studies are recommended as with all new medications.

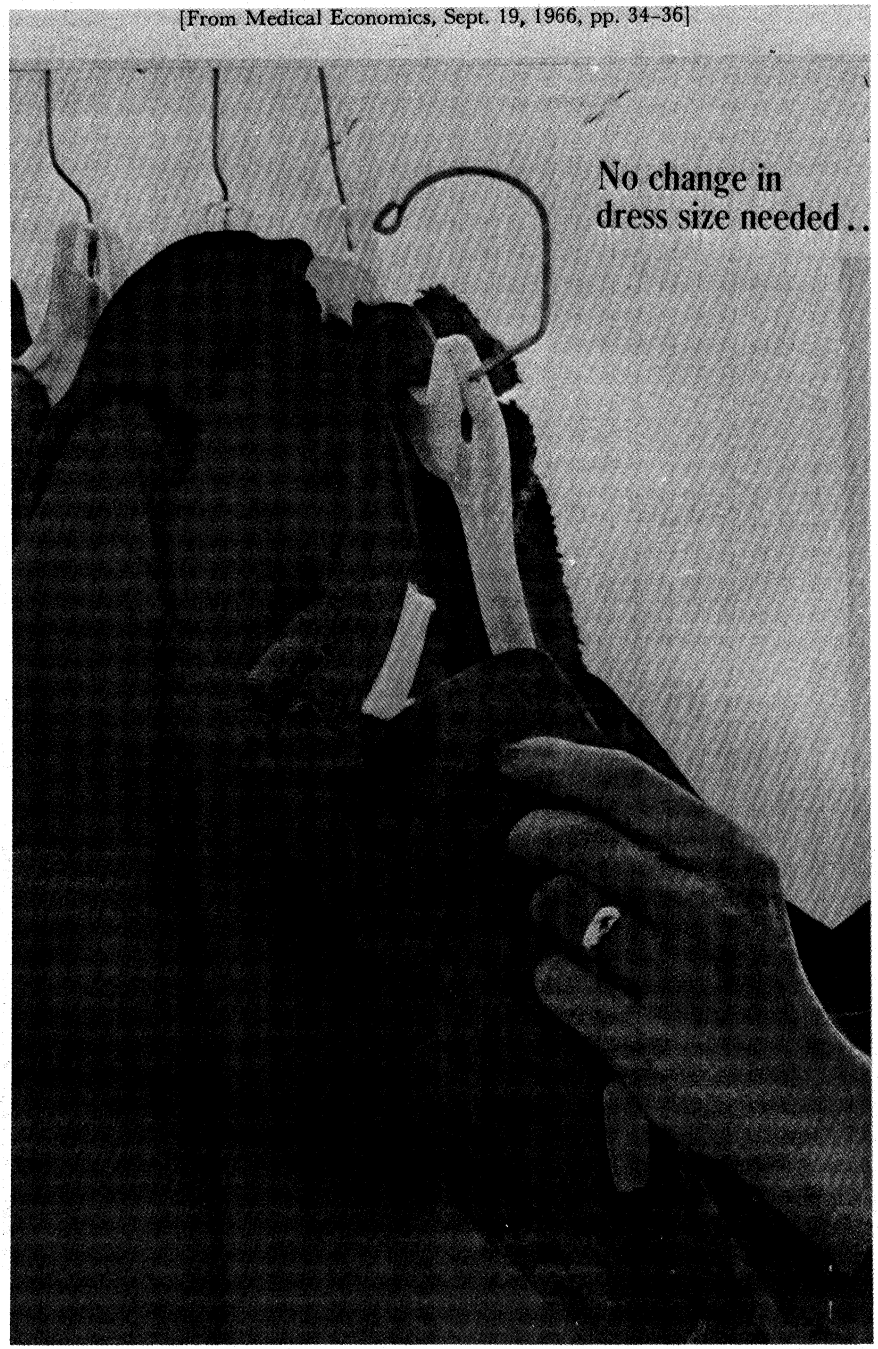
Precautions: Because of its mild anticholinergic activity, Aventyl HCl should be used primarily in patients with glaucoma or in those having a propensity for urinary retention. Care should be employed when Aventyl HCl is given in combination with sympathomimetic drugs. Its use in hypotensive drugs, along with intravenous levarterenol, methoxamine or phenylephrine for severe angina has resulted in a higher than usual degree of [illegible] from. As with similar drugs, it is advisable to observe [illegible] therapy in considering the initial choice of treatment.

Side Effects: No single side effect can be considered as occurring frequently, and most are mild and reversible. Dry mouth was noted in 24 percent of patients; sinus tachycardia in 11 percent. The following were seen occasionally (in 6 to 19 percent): constipation, dizziness, tremulousness, gastrointestinal upset, restlessness, weakness, and blurred vision. Side effects rarely noted (in 1 to 5 percent) were epigastric distress, nausea, vomiting, peculiar taste, fatigue, weight gain, weight loss, insomnia, headache, paresthesia, sweating, vomiting, rash and itching, and delayed micturition. Miscellaneous side effects were reported in less than 0.5 percent. There have been no reports of habituation or of withdrawal symptoms. No potentiation of increased incidence of side effects was observed when Aventyl HCl was used together with tranquilizers, other antidepressants (except MAO inhibitors), central stimulants, sedatives, hypnotic preparations, and anticholinergic drugs given for primary medical disorders.

Dosage: Mean adults respond well to 75 mg. three times daily, but the dose should be adjusted to the needs of the patient. Usual dosage range is divided doses:

Adults—75 to 150 mg. daily.
Children—10 to 75 mg. daily (1 to 2 mg. per Kg. of body weight).
(See package literature for complete dosage information.)

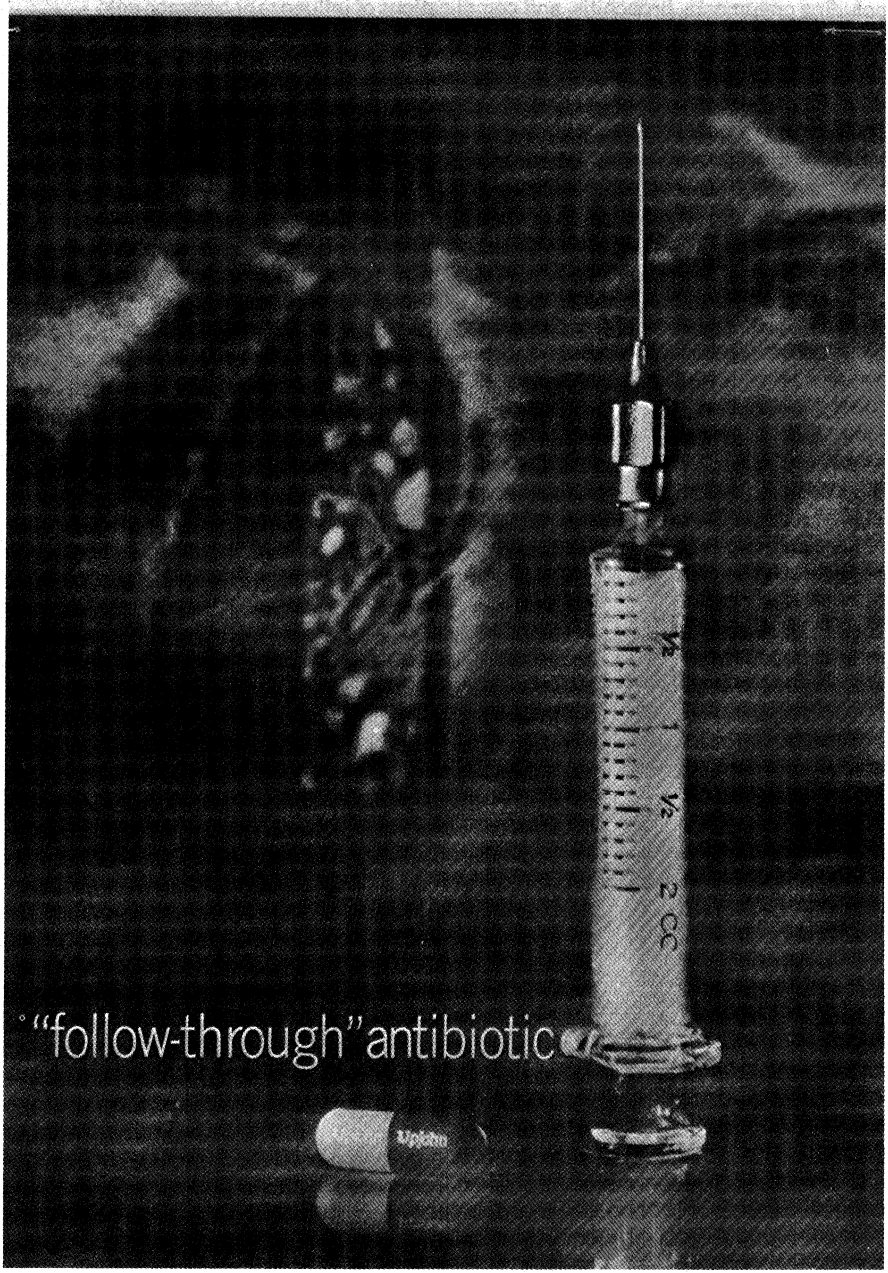
[From Medical Economics, Sept. 19, 1966, pp. 34-36]




with her sequential
oral contraceptive
Weight gain, a troublesome side effect with combination agents, is not a major problem with C-Quens for possibly two reasons:
• C-Quens does not produce the state of pseudopregnancy observed with combination products.
• The progestational component of C-Quens does not exhibit the anabolic effects noted with some testosterone derivatives.
C-Quens
Lilly


Other advantages
of therapy
with C-Quens
minimal spotting and breakthrough bleeding
low incidence of nausea
a menstrual cycle approaching the normal
the smallest amount of hormonal substance
Description:
Action:
Indication:
Effectiveness:
Contraindications:
Warning:
Precautions:
Side-Effects:
Administration and Dosage:
How Supplied:
C-Quens
Lilly
Additional information available to physicians upon request. Eli Lilly and Company, Indianapolis, Indiana 46206

[From Journal of American Medical Association, Sept. 5, 1966, pp. 60–61]



in lower respiratory infections[1-7]

including pneumonia, bronchitis, and complications of influenza or common cold

caused by Staph-,Strep-and Pneumococci

practically painless on injection—therapy may be initiated parenterally and then followed through orally without switching antibiotic.

reactions rare, even for patients sensitive to penicillin—does not share antigenicity with the penicillin group of compounds.

no reports of serious renal or neurologic abnormalities; no ototoxicity.

no tooth discoloration to date: tests by 40 investigators involving 2,500 patients show no tooth discoloration with Lincocin.

References:

1. Holloway, W. J., and Scott, E. G.: Am. J. M. Sc. 249:691 (June) 1965.
2. Duncan, I. B. R., and Jeans, B.: Canad. M.A.J. 93:685 (Sept. 25) 1965.
3. Kaplan, K.; Chew, W. H., and Weinstein, L.: Am. J. M. Sc. 250:137 (Aug.) 1965.
4. Nunnery, A. W., and Riley, H. D.: Antimicrobial Agents and Chemotherapy-1964, Ann Arbor, Michigan, Am. Soc. Microbiol., p. 142.
5. Holloway, W. J.; Kahlbaugh, R. A., and Scott, E. G.: Antimicrobial Agents and Chemotherapy-1963, Ann Arbor, Michigan, Am. Soc. Microbiol., p. 200.
6. Walters, E. W.; Romansky, M. J., and Johnson, A. C.: *Ibid.*, p. 210.
7. Harnecker, J.; Contreras, J.; Gilabert, B., and Ubilla, V.: *Ibid.*, p. 204.

Lincocin®

(lincomycin hydrochloride monohydrate)

Contraindications: Patients previously found hypersensitive to drug; patients with known pre-existing monilial infections; and, until further clinical study is made, the newborn. **Precautions:** Use of antibiotics occasionally causes overgrowth of nonsusceptible organisms. If superinfections occur, take appropriate measures. An occasional patient has developed jaundice while receiving lincomycin, although this has not been definitely shown to be drug-related. Patients receiving treatment for longer than one or two weeks should have liver function tests. One case of irreversible toxicity to the hematopoietic system and only a few cases of neutropenia and/or leukopenia have been reported; however, it is recommended that blood counts be obtained early in course of therapy. Safety for use in pregnancy not yet established. Limited experience with 345 women receiving the drug during various stages of pregnancy revealed no ill effects on mother or fetus. Due to lack of adequate clinical data, use in patients with pre-existing kidney, liver, endocrine or metabolic diseases not recommended unless special clinical circumstances so indicate. Efficacy in rheumatic fever not established. **Side Effects:** Most frequent—loose stools or diarrhea. Cases of severe diarrhea causing drug discontinuance have been reported. Side effects of small proportion: nausea, vomiting, abdominal cramps or pain, skin rash, rectal irritation, vaginitis, urticaria and itching. A few cases of hypersensitivity reactions reported. If an allergic reaction occurs, discontinue drug. The usual agents for emergency treatment should be available. **Supplied:** 500 mg. capsules and pediatric capsules, 250 mg., in bottles of 24 and 100; 2 cc. disposable syringes; 2 cc. and 10 cc. vials—each cc. of sterile solution contains lincomycin hydrochloride monohydrate equiv. to lincomycin base, 300 mg.; also 9 mg. benzyl alcohol and water for injection, q.s.; Lincocin syrup equiv. to 250 mg. per 5 cc. lincomycin base in 60 cc. and pint bottles. Lincocin pediatric drops equiv. to 250 mg. per 5 cc. lincomycin base in 30 cc. bottles with dropper. **For more detailed prescribing information on this product, see the package circular or consult your Upjohn representative.** ©1966 by The Upjohn Company J66-0376-1

Upjohn

The Upjohn Company, Kalamazoo, Michigan

[From Journal of American Medical Association, Sept. 5, 1966, pp. 205-228]

Certainly
all oral contraceptives
are highly effective
and well tolerated
...yet ORACON®
16 White–Ethinyl Estradiol, 0.1 mg. Tablets; 5 Pink–Dimethisterone, 25 mg., and Ethinyl Estradiol, 0.1 mg. Tablets.
is unsurpassed...

...physiologically ORACON® is so close to nature*

simulates a natural menstrual pattern

- produces a physiologically acceptable cycle
- simulates a normal endometrial response
- induces regular and predictable withdrawal bleeding

...in patient benefits

ORACON®

affords few side effects*

month after month, women usually experience few side effects

- virtually eliminates amenorrhea
- dramatically low early-cycle breakthrough bleeding
- low incidence of weight gain
- significantly low incidence of monilial vaginitis

*For full documentation, please write to The Medical Department Mead Johnson Laboratories, Evansville, Indiana 47721, for the Physician's Brochure.

...so close to nature

ORACON®

16 White—Ethinyl Estradiol, 0.1 mg. Tablets; 5 Pink—Dimethisterone, 25 mg., and Ethinyl Estradiol, 0.1 mg. Tablets.

the first sequential oral contraceptive

Indication: To inhibit ovulation and provide an effective oral method of contraception.

Effectiveness: Oral contraceptives, including ORACON, are highly effective.

Contraindications: Because of estrogen content, ORACON is contraindicated in known or suspected malignancy of the breasts or reproductive tract, and in young women in whom epiphyseal closure is not complete. Do not use immediately postpartum in the nursing mother because of possible inhibition of lactation or estrogenic responses in the infant. Use is also contraindicated in presence of liver dysfunction or disease, and in patients with a history of thrombophlebitis, pulmonary embolism, or cerebral vascular accident.

Warnings: Use with caution in patients with cardiac or renal dysfunction. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a marked degree. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

Precautions: Because of insufficient evidence concerning the possible effects of ORACON in patients with a history of metabolic disease or conditions which might be aggravated by possible estrogen-induced fluid retention (such as epilepsy, migraine, asthma, and cardiac or renal disease), ORACON should be used with care in such patients. Pre-existing uterine fibroids may increase in size while using this product. Any effect of prolonged use on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further studies. Discontinue before liver or endocrine function tests. Because of osteoblastic action of estrogens, carefully observe patients with metabolic bone disease or renal disease while on ORACON. Since safety in pregnancy is not proven, any patient missing 2 consecutive periods should have pregnancy ruled out before continuing the regimen. An estrogen-induced increase in cervical mucus is frequent; patients should be so advised. Continuous use for more than 18 months is not recommended at this time. Recurring breakthrough bleeding, particularly after the first few cycles, should be reported to the physician for further investigation. As a special precaution, another method of contraception should be used during the first 7 tablet days of the first cycle, or following discontinuance of ORACON for one or more months.

Side Effects: Few undesirable side effects occur with ORACON: Only 4.4% of patients discontinued medication because of side effects during clinical trials. As expected with estrogen therapy, nausea was the side effect reported most frequently. Nausea, when it occurs, is usually during the first cycle and is not severe. It may be alleviated with continued therapy or by administration at bedtime, with meals, or in divided doses. Other side effects reported during clinical studies included vomiting, abdominal cramps, bloating, anorexia, malaise, breakthrough bleeding, changes in amount and/or duration of menstrual flow, mucorrhea, and amenorrhea; headache, increased and decreased libido, weight gain or loss, nervousness, breast tenderness, dizziness, edema, diarrhea, drowsiness and premenstrual tension. Two cases of thrombophlebitis were reported during clinical trials; however, a cause-and-effect relationship has not been established.

Administration: Counting onset of menses as Day 1, the patient starts medication on Day 5 of the menstrual cycle and takes one white tablet daily from Day 5 through Day 20, then one pink tablet daily from Day 21 through Day 25. The patient should follow the dosage schedule strictly. If the regimen is interrupted, for the fullest possible protection the patient should consult her physician about the use of an additional contraceptive method for the rest of the cycle (also see Precautions). Menses usually begin 2 to 4 days after the last pink tablet has been taken. The patient starts her new cycle of medication on Day 5. If flow does not occur by the 7th day after taking the last pink tablet start the next full course of therapy on that day, thus allowing 6 days without drug. In case of breakthrough bleeding: if spotting, continue medication; if menstrual flow, discontinue medication and begin a new full course on Day 5; for recurring breakthrough bleeding or amenorrhea, see Precautions.

Availability: Available as 16 white and 5 pink tablets. Each white tablet contains 0.1 mg. ethinyl estradiol; each pink tablet contains 25 mg. dimethisterone plus 0.1 mg. ethinyl estradiol. Complete details on ORACON are available on request from Mead Johnson Laboratories, Evansville, Indiana 47721. 51666

Mead Johnson
LABORATORIES

Research for Life

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[From Medical World News, Feb. 12, 1965, pp. 42–43]

Because the immaturity of infants and children influences their response to disease and drugs[1]...

Ross Laboratories offers

Pediamycin®

erythromycin ethyl succinate, Ross



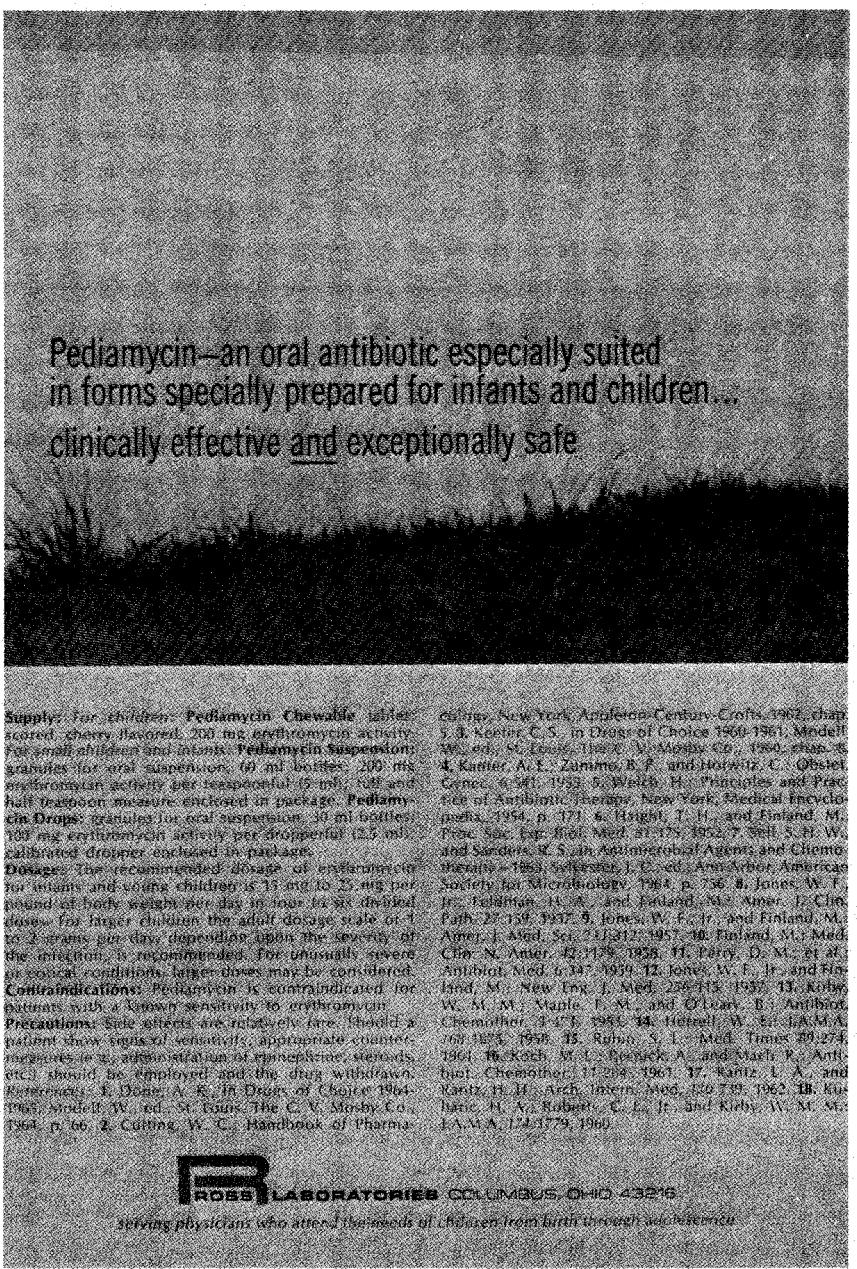
Pediamycin is effective in 86% of the common bacterial infections seen in infants and children. It is active against gram-positive cocci[2-5]: streptococci, including enterococci, pneumococci and most strains of staphylococci. It is also active against Hemophilus influenzae.[6,7] It has 4 to 16 times more activity against susceptible organisms than the tetracyclines and chloramphenicol.[8-13]

Pediamycin is especially useful in common infections of the ear, nose and throat, and in respiratory infections, including bronchitis, croup and pneumonia as well as in infections in other sites, caused by susceptible organisms.

Pediamycin has an exceptional record of safety. Erythromycin has been called "by far the least toxic of commonly used antibiotics,"[14] with "a minimum of side effects."[15] It has never been known to have an adverse effect on bone growth, to cause tooth staining or to damage the kidneys or impair the liver. Allergic reactions are extremely infrequent. Side effects such as diarrhea, nausea and vomiting, bacterial superinfections of the G.I. tract, moniliasis are rare and mild.

With Pediamycin the production of resistant organisms is low. Of 1017 strains of Staphylococcus aureus tested in vitro, 87 percent were sensitive.[16] In in vitro tests of hemolytic streptococci, all of 116 strains tested were sensitive.[17] In a clinical study, 20 percent of 218 strains of group A beta-hemolytic streptococci were resistant to tetracycline, none was resistant to erythromycin.[18]

Pediamycin is easy to administer. Its cherry flavor is liked by children. Pediamycin is provided as scored chewable tablets, suspension and drops, all forms which encourage cooperation in pediatric patients.


Pediamycin—an oral antibiotic especially suited
in forms specially prepared for infants and children...
clinically effective and exceptionally safe
Supply: For children: Pediamycin Chewable tablet-scored, cherry flavored, 200 mg erythromycin activity. For small children and infants: Pediamycin Suspension granules for oral suspension, 60 ml bottles, 200 mg erythromycin activity per teaspoonful (5 ml); tuft and half teaspoon measure enclosed in package. Pediamycin Drops: granules for oral suspension, 30 ml bottles, 100 mg erythromycin activity per dropperful (2.5 ml); calibrated dropper enclosed in package.
Dosage: The recommended dosage of erythromycin for infants and young children is 15 mg to 25 mg per pound of body weight per day in four to six divided doses. For larger children the adult dosage scale of 1 to 2 grams per day, depending upon the severity of the infection, is recommended. For unusually severe or special conditions, larger doses may be considered.
Contraindications: Pediamycin is contraindicated for patients with a known sensitivity to erythromycin.
Precautions: Side effects are relatively rare. Should a patient show signs of sensitivity, appropriate countermeasures (e.g., administration of epinephrine, steroids, etc.) should be employed and the drug withdrawn.
References: 1. Doan, A. E., in Drugs of Choice 1964-1965, Modell, W., ed., St. Louis, The C. V. Mosby Co., 1964, p. 66. 2. Cutting, W. C., Handbook of Pharmacology, New York, Appleton-Century-Crofts, 1962, chap. 3. 3. Koster, C. S., in Drugs of Choice 1960-1961, Modell, W., ed., St. Louis, The C. V. Mosby Co., 1960, chap. 8. 4. Kantor, A. E., Zumino, B. P. and Horwitz, C., Obstet. Gynec. 6:581, 1955. 5. Welch, H., Principles and Practice of Antibiotic Therapy, New York, Medical Encyclopedia, 1954, p. 171. 6. Haight, T. H. and Finland, M., Proc. Soc. Exp. Biol. Med. 81:175, 1952. 7. Bell, S. H. W. and Sanders, W. S., in Antimicrobial Agents and Chemotherapy—1963, Sylvester, J. C., ed., Ann Arbor, American Society for Microbiology, 1964, p. 736. 8. Jones, W. F., Jr., Feldman, H. A. and Finland, M., Amer. J. Clin. Path. 27:159, 1957. 9. Jones, W. F., Jr. and Finland, M., Amer. J. Med. Sci. 231:312, 1957. 10. Finland, M., Med. Clin. N. Amer. 42:1179, 1958. 11. Perry, D. M., et al., Antibiot. Med. 6:147, 1959. 12. Jones, W. F., Jr. and Finland, M., New Eng. J. Med. 256:115, 1957. 13. Kirby, W. M. M., Maple, P. M., and O'Leary, B., Antibiot. Chemother. 3:473, 1953. 14. Hetrell, W., Jr., J.A.M.A. 168:1873, 1958. 15. Rubin, S. L., Med. Times 89:274, 1961. 16. Koch, W. C., Bostick, A. and Mark, P., Antibiot. Chemother. 11:264, 1961. 17. Kantz, L. A., and Kantz, H. H., Arch. Intern. Med. 110:739, 1962. 18. Kusiak, H. A., Roberts, C. L., Jr. and Kirby, W. M. M., J.A.M.A. 174:1779, 1960.
ROSS LABORATORIES COLUMBUS, OHIO 43216
serving physicians who attend the needs of children from birth through adolescence

[From Journal of American Medical Association, Sept. 5, 1966]

JAMA VOL 197, NO 10 SEPTEMBER 5, 1966

THE JOURNAL of the American Medical Association



Harriet Tetelbaum International College of Surgeons, Chicago

A Japanese pioneer in the use of anesthesia in surgery was Seishu Hanaoka, who 40 years before Long used ether, had removed breast cancers and kidney stones from sleeping patients. He doped them with a narcotic compound of six plant extracts, including henbane and unsmirched, members of the nightshade family. The method is reminiscent of much earlier attempts. This painting on silk, specially commissioned and presented to the International College of Surgeons, depicts a legend that grew around the surgeon's experiment. His elderly mother suggested that, as she expected to die shortly anyway, the proposed anesthetic be tried on her. But Hanaoka administered it to his wife for, as all three agreed, he could find another wife but he could never get another mother. The painting is reproduced here to help introduce a new regular JOURNAL feature, Anesthesia Problem of the Month (p. 789).

This is a new, everyday penicillin for common bacterial respiratory infections with extra therapeutic coverage at no extra cost.*

Clinical success. Tegopen (sodium cloxacillin monohydrate) assures you a high degree of clinical success against respiratory infections. A recent comprehensive analysis of office patients administered the drug proves the point: *96% of 259 bacterial respiratory infections treated were cured or improved.*[1]

***Kills common respiratory Gram-positive cocci.** In contrast to the penicillinase-limited Gram-positive spectrum of penicillins G and V, Tegopen (sodium cloxacillin monohydrate) destroys strep, pneumo and virtually all staphylococci.

Bactericidal in action. Tegopen (sodium cloxacillin monohydrate) is bactericidal, killing the offending organism. In contrast, erythromycin[2] and triacetyloleandomycin[3] are essentially bacteriostatic agents.

Minimal side effects. There is little likelihood of dose-related toxicity with Tegopen (sodium cloxacillin monohydrate).

Low in cost. Even with all of its extra advantages, Tegopen (sodium cloxacillin monohydrate) is priced comparably to penicillins G and V, and 33% less than either erythromycin or triacetyloleandomycin.

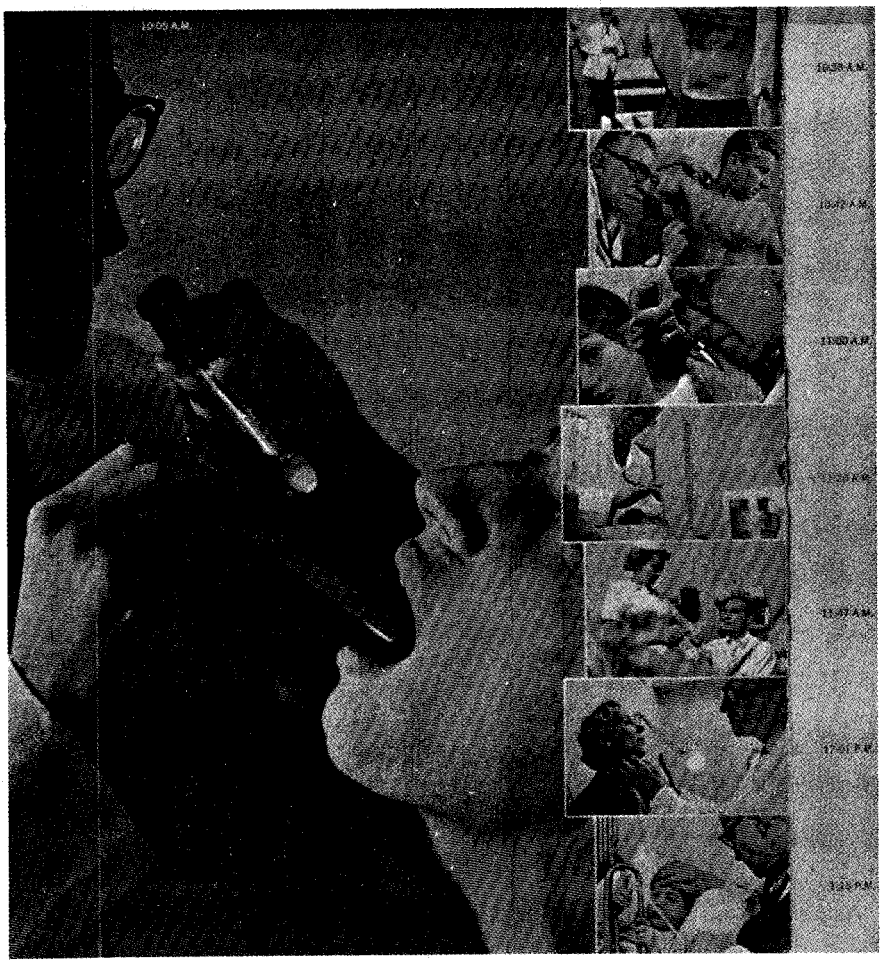
BRISTOL THERAPEUTIC SUMMARY: For complete information, consult Official Package Circular. *Indications:* Infections due to streptococci, pneumococci and staphylococci, particularly penicillin G-resistant strains of the latter. *Contraindications:* A history of severe allergic reactions to penicillins. *Precautions:* Typical penicillin-allergic reactions may occur, particularly in hypersensitive persons. Mycotic or bacterial infections may occur. Safety for use in pregnancy is not established. Assess renal, hematopoietic and hepatic function periodically during long-term therapy. *Adverse Reactions:* Nausea, epigastric discomfort, flatulence, diarrhea, eosinophilia, and allergic manifestations. Moderate SGOT elevations have been noted. *Usual Dosage:* Adults: 250 mg. *q. 6 h.* Children: 50 mg./Kg./day. Children weighing more than 20 Kg. should be given the adult dose. Treat beta-hemolytic streptococcal infections for at least 10 days. Administer 1 to 2 hours before meals.

References: 1. Data on file at Bristol Laboratories. 2. Geraci, J.E. (Panel Discussion, M. Finland, Moderator): Antibiot. Ann. 1958–59: 1051, 1959. 3. Thompson, W.T., Jr.: South. M. J. *56*:844 (Aug.) 1963.

BRISTOL LABORATORIES
Division of Bristol-Myers Co.
Syracuse, New York

• IN TONSILLITIS • PHARYNGITIS • OTITIS MEDIA • SINUSITIS
• BRONCHITIS • PNEUMONITIS

new TegoPen®
SODIUM CLOXACILLIN MONOHYDRATE



10:38 A.M.

10:42 A.M.

11:00 A.M.

There is a new, everyday penicillin for common bacterial

11:20 A.M.

respiratory infections.

An improvement over penicillin G and V, and the medium-

11:47 A.M.

spectrum antibiotics.

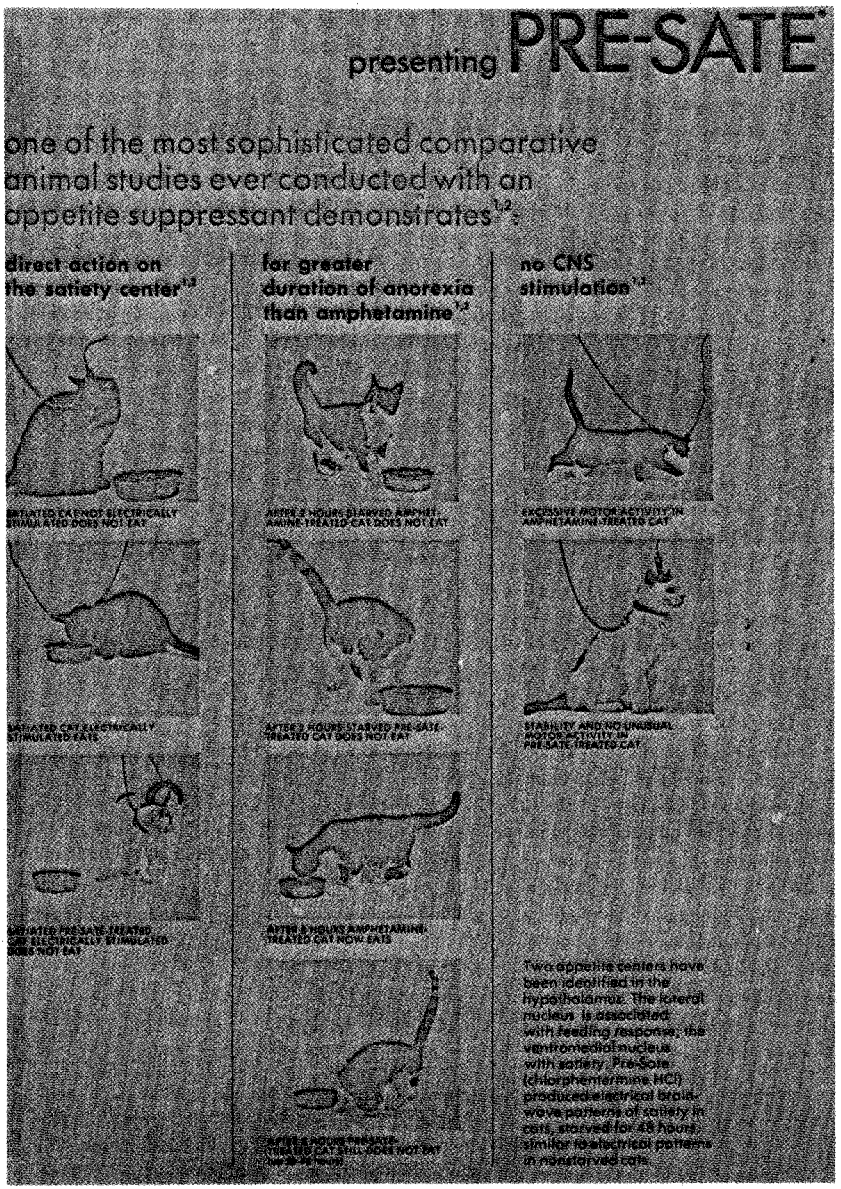
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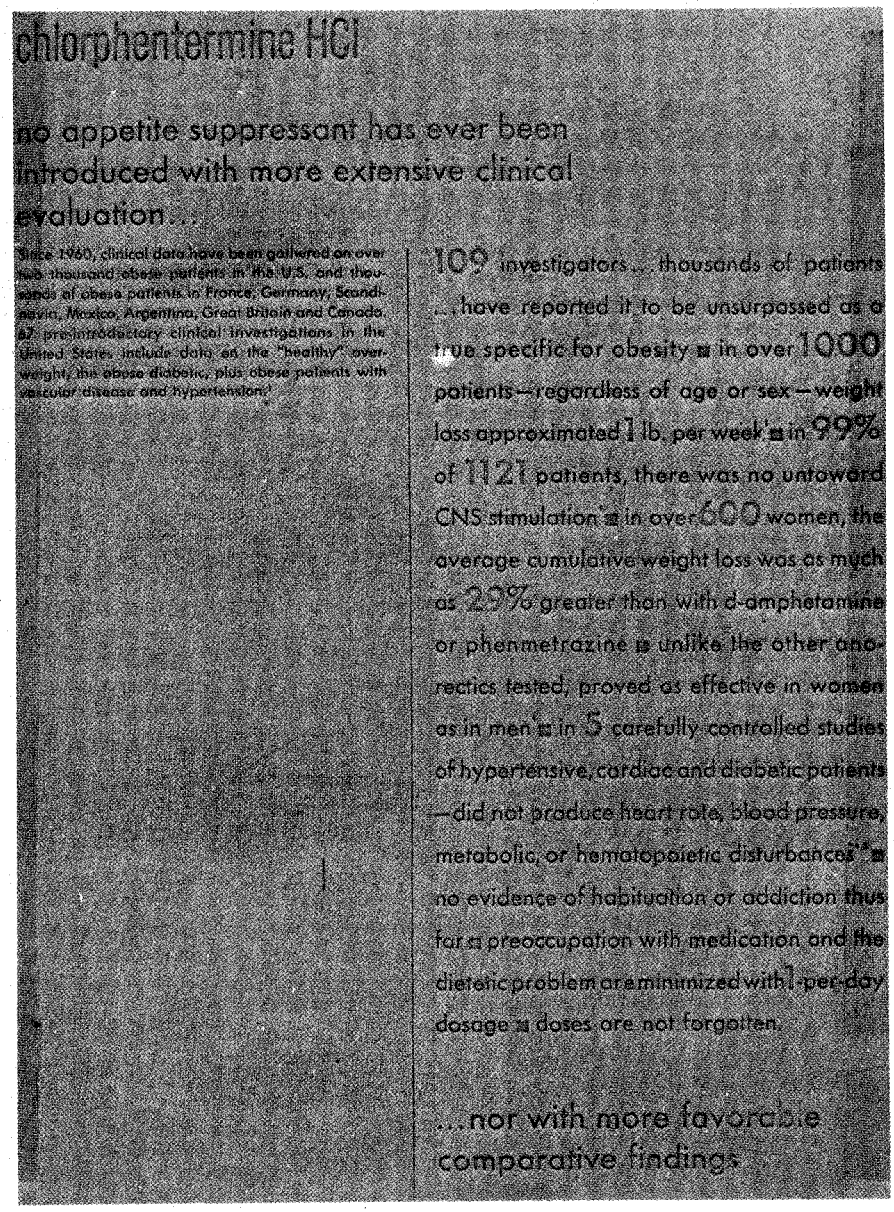
12:01 P.M.

1:15 P.M.

[From Journal of American Medical Association, Oct. 18, 1965, pp. 11–16]




presenting PRE-SATE
one of the most sophisticated comparative animal studies ever conducted with an appetite suppressant demonstrates[1,2]:
direct action on the satiety center[1,2]
far greater duration of anorexia than amphetamine[1,2]
no CNS stimulation[1,2]
AMPHETAMINE-TREATED CAT DOES NOT EAT
AFTER 8 HOURS STARVED AMPHETAMINE-TREATED CAT DOES NOT EAT
EXCESSIVE MOTOR ACTIVITY IN AMPHETAMINE-TREATED CAT
AMPHETAMINE-TREATED CAT ELECTRICALLY STIMULATED EATS
AFTER 8 HOURS STARVED PRE-SATE-TREATED CAT DOES NOT EAT
STABILITY AND NO UNUSUAL MOTOR ACTIVITY IN PRE-SATE-TREATED CAT
AMPHETAMINE-TREATED CAT ELECTRICALLY STIMULATED DOES NOT EAT
AFTER 8 HOURS AMPHETAMINE-TREATED CAT NOW EATS
AFTER 8 HOURS PRE-SATE-TREATED CAT STILL DOES NOT EAT
Two appetite centers have been identified in the hypothalamus. The lateral nucleus is associated with feeding response; the ventromedial nucleus with satiety. Pre-Sate (chlorphentermine HCl) produced electrical brain-wave patterns of satiety in rats, starved for 48 hours, similar to electrical patterns in nonstarved rats.


chlorphentermine HCl
no appetite suppressant has ever been introduced with more extensive clinical evaluation...
Since 1960, clinical data have been gathered on over two thousand obese patients in the U.S. and thousands of obese patients in France, Germany, Scandinavia, Mexico, Argentina, Great Britain and Canada. All preintroductory clinical investigations in the United States include data on the "healthy" overweight, the obese diabetic, plus obese patients with vascular disease and hypertension.
109 investigators... thousands of patients ...have reported it to be unsurpassed as a true specific for obesity ■ in over 1000 patients—regardless of age or sex—weight loss approximated 1 lb. per week ■ in 99% of 1121 patients, there was no untoward CNS stimulation ■ in over 600 women, the average cumulative weight loss was as much as 29% greater than with d-amphetamine or phenmetrazine ■ unlike the other anorectics tested, proved as effective in women as in men ■ in 5 carefully controlled studies of hypertensive, cardiac and diabetic patients —did not produce heart rate, blood pressure, metabolic, or hematopoietic disturbances ■ no evidence of habituation or addiction thus far ■ preoccupation with medication and the dietetic problem are minimized with 1-per-day dosage ■ doses are not forgotten.
...nor with more favorable comparative findings.

1

steady weight loss,
fewer patient "dropouts" than with phenmetrazine and d-amphetamine

In hundreds of patients, there was less discontinuance of program with Pre-Sate (chlorphentermine HCl) than with phenmetrazine or d-amphetamine.

Rate of discontinuation of program[1]

	Pre-Sate	phenmetrazine	d-amphetamine
Total patients	1121	203	174
Number dropouts	57	24	13

In 6 double-blind, comparative clinical studies,[1,3,4] employing a single daily dose of Pre-Sate (chlorphentermine HCl), patients lost weight steadily. In over 1000 patients—regardless of age or sex—weight loss approximated 1 lb. per week, even during the difficult fifth to tenth weeks of dieting.

More effective in women

Pre-Sate (chlorphentermine HCl) is equally potent within all age groups, and more effective in women than d-amphetamine or phenmetrazine.[1]

In over 600 women, the average cumulative weight loss in pounds per week was greater than with d-amphetamine or phenmetrazine[1]

age	under 21	21-30	31-45	46-60	over 60
medication					
Pre-Sate chlorphentermine HCl	1.04	1.07	0.98	0.98	0.96
placebo	.45	.41	.52	.45	.86
d-Amphetamine	.58	.52	.75	.79	1.02
phenmetrazine	.43	.89	.88	1.18	.80

new
PRE-SATE®
chlorphentermine HCl

2

significantly fewer CNS side effects
than with d-amphetamine[1,3,5,6] and phenmetrazine[1,4]

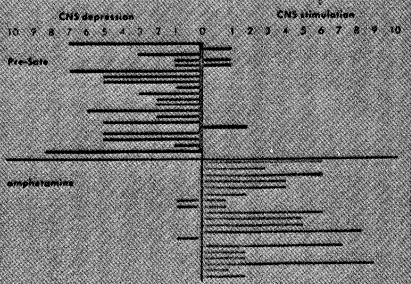
In contrast to phenmetrazine which produced a significant number of CNS side effects, Pre-Sate (chlorphentermine HCl) produced no CNS disturbances in a double-blind clinical test of 60 patients.[4]

Of 1,121 patients tested[1] with Pre-Sate (chlorphentermine HCl), 1,110 evidenced no untoward CNS stimulation.

In a double-blind, crossover study it was reported that "No evidence of central nervous system stimulation and no serious side effects developed during a four-week period on chlorphentermine (Pre-Sate)."[7]

In double-blind studies by 3 independent investigators Pre-Sate (chlorphentermine HCl) was found to have no untoward effect on fine coordinated movement, mental processes, or processes involving integration of special senses of sight or hearing with other centers of the central nervous system.[1,5] These clinical findings were corroborated in special laboratory studies employing critical "Flicker-Fusion Threshold Tests," one of the most reliable methods of measuring CNS effect of a drug.[1]

Critical flicker-fusion threshold tests[1]: Two anorectics



This test is chiefly an index of the subject's ability to discriminate between a steady beam of light and a rapidly flickering beam of light.

In contrast to the usual stimulatory effects of the amphetamines, numerous investigators have reported the lack of such untoward effects with chlorphentermine (Pre-Sate).[1,3,5,6]

3

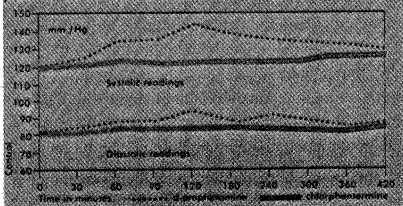
no adverse effect on the cardiovascular parameters[1,2]

In normotensive patients

In two independent studies in overweight subjects without cardiovascular disorders, Pre-Sate (chlorphentermine hydrochloride) had no biologically significant effect on blood pressure and pulse rate.[1]

A third study tested the safety of a greater-than-recommended dose (100 mg.). Daily administration of the drug in this dosage for *six months* caused no alteration in blood pressure, pulse or ECG.[1]

Blood pressure readings of normotensive obese patients after medication



In patients with hypertension

Hundreds of patients with cardiovascular disorders have received Pre-Sate (chlorphentermine hydrochloride), and no adverse effects on blood pressure, ECG or pulse rate have been evidenced. Most of the patients in this category had hypertension.[1] These findings indicate that the drug may prove useful in treating obesity complicated by mild to moderate cardiovascular disorders; however, until continuing studies are completed, caution should be employed in its use in patients with hypertension and acute coronary disease.

Compared to d-amphetamine in patients with cardiovascular disorders

Russek[3] contrasted the frequent (85.7%) cardiovascular side effects with d-amphetamine in one group of patients to the absence of such effects in 42 obese cardiac patients who were given Pre-Sate (chlorphentermine hydrochloride), daily for periods up to 27 weeks. All patients receiving the new drug had discontinued d-amphetamine either because of side effects or contraindications.

Side effects in patients with cardiovascular disorders*

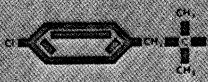
	Pre-Sate	d-amphetamine
Cardiovascular disturbances	0	85.7%
CNS stimulation	2.9%	71.4%

*Adapted from Russek, H. I.: *Am. J. M. Sc.* 249:305, 1965.

4

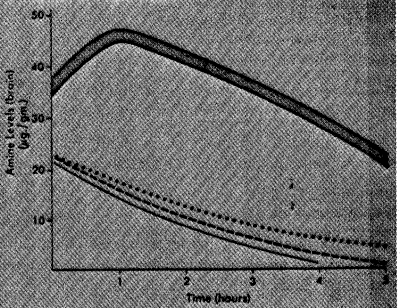
more prolonged anorexia than with phentermine, mephentermine, d-amphetamine[1,9,10]

Because of the introduction of a chlorine atom in the *para* position, Pre-Sate (chlorphentermine HCl) is qualitatively different in pharmacologic action from all



other anorectic agents . . . achieves higher brain concentrations and more prolonged effect than currently available anorectics.[1,9,10]

Persistence of chlorphentermine [Pre-Sate] in brain tissue*

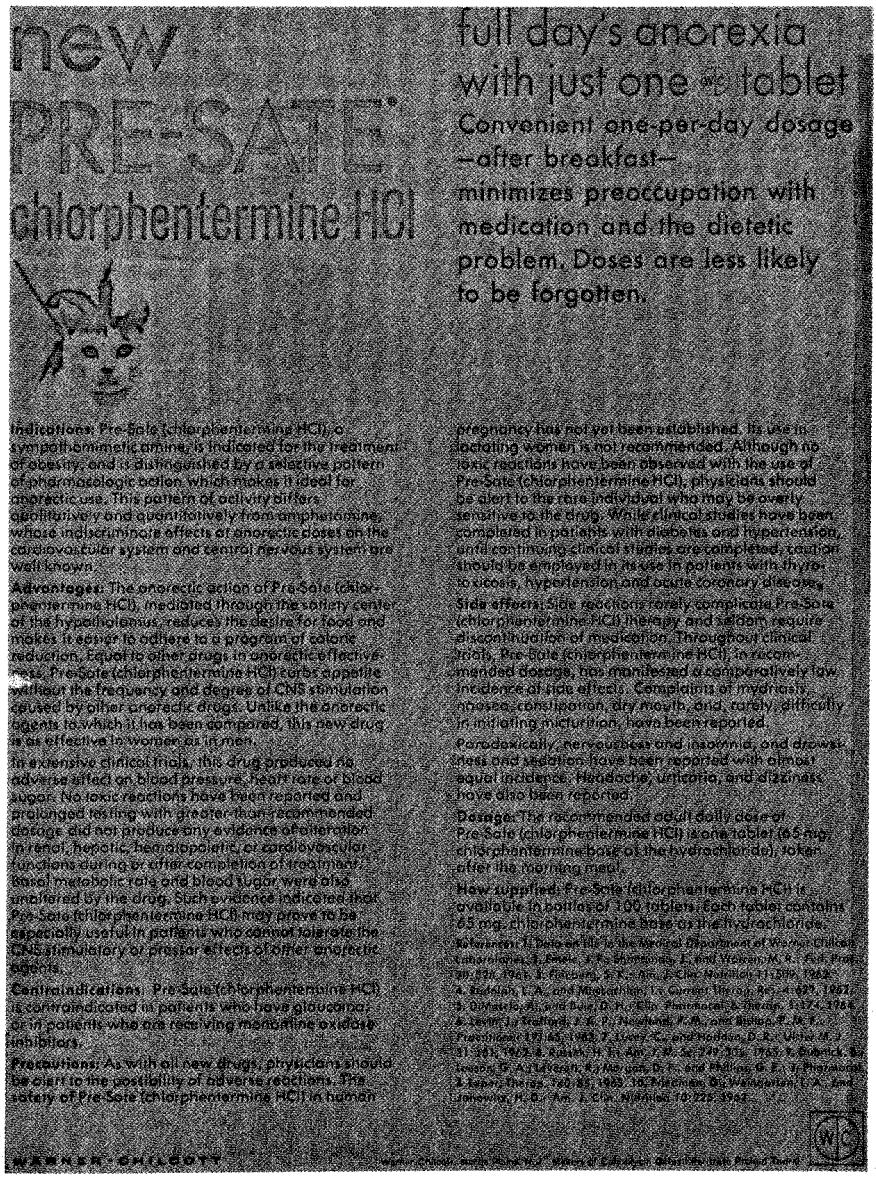


Disappearance of amines from brains of mice after a single injection (15 mg./kg., I.V.).

Each point represents the average of values obtained in 3 experiments.

chlorphentermine — maphentermine
phentermine — d-amphetamine

Because Pre-Sate (chlorphentermine HCl) is an inherently long-acting molecule, appetite suppression is achieved with convenient one-per-day dosage.[1] Neither addiction nor habituation has occurred with Pre-Sate (chlorphentermine HCl) therapy.[1]



(Whereupon, at 11:45 a.m., the subcommittee was adjourned.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, JULY 30, 1969

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 9:40 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Dole.

Also present: Benjamin Gordon, staff economist; Elaine C. Dye, clerical assistant; and James P. Duffy III, minority counsel.

Senator NELSON. Our witnesses this morning are Dr. Richard Pillard and Dr. Daniel Freedman.

We will hear first from Dr. Pillard, who is assistant professor of psychiatry at Boston University School of Medicine. And then we will hear from Dr. Freedman.

Your statement will be printed in full in the record,[1] and you may present it however you wish. If you desire to extemporize on any particular point, we would be happy to have you do so. I assume you have no objection if we ask questions as you proceed?

Dr. PILLARD. No, sir.

Senator NELSON. We are pleased to have both of you here today. We have been extensively exploring various aspects of prescription drugs, their use, pricing, and manufacture, and so forth. And you join a long list of very distinguished witnesses who have appeared before the committee in the past 2 years, or more than 2 years. And we are pleased that you are willing to take the time to make your contribution to the record that we are accumulating here on this important subject.

STATEMENT OF DR. RICHARD C. PILLARD, ASSISTANT PROFESSOR OF PSYCHIATRY, BOSTON UNIVERSITY SCHOOL OF MEDICINE, BOSTON, MASS.

Dr. PILLARD. Thank you, Mr. Chairman.

My name is Richard C. Pillard. I am a physician, assistant professor of psychiatry at Boston University School of Medicine and head of the basic studies unit of the psychopharmacology laboratory there. I am also the recipient of an NIMH Research Scientist Development Award.

[1] See p. 5414.

81-280 O—69—pt. 13——10

(The curriculum vitae of Dr. Pillard follows:)

CURRICULUM VITAE

Pillard, Richard Colestock—

Title: Assistant Professor of Psychiatry, Boston University School of Medicine and Head, Basic Studies Unit, Psychopharmacology Laboratory; Assistant Professor of Psychiatry, Boston University School of Graduate Dentistry; Assistant Visiting Physician in Psychiatry, University Hospital.

Address: Boston University School of Medicine, 80 East Concord Street, Boston, Mass.

Born: October 11, 1933, Springfield, Ohio; U.S. Citizen; Social Security Number 281-28-3873.

Education: Swarthmore College, Swarthmore, Pennsylvania, 1951–1952; B.A. Antioch College, Yellow Springs, Ohio, 1952–1955; M.D. University of Rochester School of Medicine, Rochester, New York, 1955–1959; Intern in Medicine, 1st (Tufts) Medical Service, Boston City Hospital, 1959–1960; Resident in psychiatry and (after 1961) Junior staff member, Boston State Hospital, 1960–1962; Resident in psychiatry, University Hospital outpatient service (including child psychiatry ¼ time); Head Resident in psychiatry, University Hospital inpatient service, 1963–1964; Research Fellow in Psychiatry, Boston University School of Medicine, 1964–1966.

Experience: 1968—Head, Basic Studies Unit, Psychopharmacology Laboratory; 1967—Research Scientist Development Award, United States Public Health Service, and Assistant Professor of Psychiatry, Boston University School of Medicine; 1966–67 Special Research Fellow, United States Public Health Service, and Instructor in Psychiatry, Boston University School of Medicine; 1963–67—Assistant Psychiatrist, Boston State Hospital; 1963–64—Psychiatrist, Boston University Health Service; 1963—Private Practice of Psychiatry.

Memberships: Massachusetts Medical Society; American Psychiatric Association; Northern New England District Branch of A.P.A.; American Association of University Professors; Society for Psychophysiological Research.

Honors: John Murray Prize.

Listings: American Men of Science; Dictionary of International Biography; American Psychiatric Association Directory.

Publications: Jacobs, M. A. & Pillard, R. C. Approach to studying drug effects in ambulatory patients. *Arch Gen Psychiat.* 1965, *13*, 163–171.

Globus, G. G. & Pillard, R. C. Tausk's Influencing Machine and Kafka's *In the Penal Colony. Amer Imago*, 1966, *23*, 191–207. Presented at the Spring meetings of the American Psychoanalytic Association, May, 1965, as The Origin of the Influencing Machine in Schizophrenia and Kafka's *In the Penal Colony:* A Parallel.

Pillard, R. C., Carpenter, J., Atkinson, K. W. & Fisher, S. Palmar sweat prints and self-ratings as measures of film-producing anxiety. *Percept Mot Skills*, 1966, *23*, 771–777.

Pillard, R. C., Atkinson, K. W. & Fisher, S. The effect of different preparations on film-induced anxiety, *Psych Rec.* 1967, *17*, 35–41.

McNair, D. M., Droppleman, L. F., & Pillard, R. C. Differential sensitivity of two palmar sweat measures. *Psychophysiol*, 1967, *3*, 280–184.

Pillard, R. C. & Fisher, C. Effects of chlordiazepoxide and secobarbital on film-induced anxiety. *Psychopharmacologia*, 1967, *12*, 18–23.

Fisher, S., Pillard, R. C. and Yamada, L. Hard-core anxiety in dental patients: implications for drug screening. *Neuropsychopharmacology*, (in press).

Greenberg, R. & Pillard, R. C. Effects of dream deprivation on response to film-induced stress. Read at the Eighth Annual Meeting of the Association for the Psychophysiological Study of Sleep, Spring 1968.

Dr. PILLARD. As a researcher, teacher, and practitioner of psychiatry I am concerned about advertising claims which are being made for psychotropic drugs. These advertisements appear in medical journals and in the free "throwaway" magazines which are sent to physicians. Most of them exaggerate the efficacy of the drug, extend its indications, or distort the evidence upon which its use is based. Almost none are

properly balanced in the sense that the advantages of the drug are proclaimed, while its limitations and side effects are minimized, or not mentioned at all, except in the package circular information required by law.

And a few pages later I will give some specific examples of this. More than this, I am concerned about the general effect which psychotropic drug advertising has on the prescribing habits of the psychiatrist and on the way he thinks about his patients.

Before elaborating these concerns I want to pay a tribute to the pharmaceutical industry. The field of psychopharmacology is only 15 years old but has already made an impressive contribution to the recovery of mentally ill people. This would, of course, never have been possible without the variety of high quality psychotropic drugs which are available, thanks to the drug industry. I hope—and I mean this very sincerely—that my testimony will help to promote further achievement and not be considered an attack or a derogation of their accomplishments.

I have divided this into three short sections dealing with the main classes of psychotropic drugs. First, the antipsychotics.

The most important psychotropic drugs are the phenothiazine chemical family, used in the treatment of schizophrenia. These are unquestionably effective and are, along with reserpine and the butyrophenones—which are two other classes of psychotropic drugs—the only treatments of proved value in this illness. There are approximately 17 phenothiazines currently manufactured, most of which are heavily promoted because the market for them is very large. Although their molecular structures differ slightly and they produce different side effects, all appear to be the same with respect to their main therapeutic action, which is to reduce schizophrenic symptoms. This has been shown in a number of studies. John Davis, in a review, summarizes this research saying: "Numerous studies showed the other phenothiazines to be approximately equal to chlorpromazine in their therapeutic effect * * *. For example, a multiple-variance analysis in the VA cooperative study showed no difference between perphenezine (Trilafon), trifluprom azine (Vesprin), prochlorperazine (Compazine), and chlorpromazine (Thorazine)."

You will notice that in order to pronounce these generic names you have to practice with pebbles in your mouth. You have had other testimony on that, so I will not comment on it further.

"The same results were found with a State hospital population, in the carefully done studies of Kurland et al."

Senator NELSON. Do these generic names sufficiently describe the drugs so that, if you didn't know the drug, you could identify what is in it?

Dr. PILLARD. The fact that they all say "zine" on the end sort of hints that they are phenothiazines. Otherwise, I think you wouldn't know. There are some—for example, the chlorpromazine indicates that there is a chlorine radical in it. The trifluprom azine is an abbreviation of the full chemical name, which is very lengthy, and it would tell a chemist a little bit about the molecular structure, but you couldn't really write out the molecule on hearing that.

Senator NELSON. When were these drugs developed.

Dr. PILLARD. Well, the grandfather of the lot is chlorpromazine, which was developed in France, I believe, in 1954, by two French scientists—1948, Dr. Freedman tells me. It was first used extensively in this country in 1954 and 1955, but it was developed in 1948.

Senator NELSON. By two French scientists?

Dr. PILLARD. Deniker and Delay.

Mr. GORDON. May I ask a question at this point?

You just mentioned a VA study.

Dr. PILLARD. Yes.

Mr. GORDON. Was that made known to the medical profession; the fact that these drugs are essentially the same?

Dr. PILLARD. The studies were published, and been cited in subsequent reviews. So they have been made known in the sense that they have appeared in the medical literature.

Mr. GORDON. Does the average practicing physician know about this?

Dr. PILLARD. I am not sure he knows that study by name, but I think that most of them realize that the different phenothiazines are approximately equal. There are some exceptions to that which I will go into, but I think most people recognize this.

Senator NELSON. But the basic drug was developed by two French scientists?

Dr. PILLARD. Yes.

Senator NELSON. And then the other drugs that you have named here are of the same compound, are they?

Dr. PILLARD. Well, they are the same chemical family, phenothiazine, but they are slightly different, there are molecular alterations.

Let Dr. Freedman comment on this, he is an expert on it.

Dr. FREEDMAN. These were developed originally from antihistamines. I think the first synthesized antihistamine is the one that we would know as diphenylhydramine or Benadryl. And they were used in anesthesia to help stabilize the patient's temperature and bodily functions. And they first accidentally discovered or tried by Delay and Deniker to see if they would also calm patients who were agitated. The chemical developments we are speaking of, these phenothiazine compounds with slight molecular alterations can become an antipruritic agent. Each one of them is concentrated in different parts of the brain. So they do differ.

They differ mostly, I am sure you would agree, in terms of side effects, and somewhat drastically in terms of side effects. All you have to do is start playing games with a molecule and you get drugs that may have different biological effects and uses. The ones that are available for psychoses, in terms of efficacy, as proven by those studies, are similarly efficacious, but they may not be similarly advantageous.

Mr. GORDON. Concerning these molecular modifications—would an organic chemist or a person skilled in the art know exactly how to do these things?

Dr. FREEDMAN. Yes. Synthetic chemists are the people who rearrange these molecules.

We can already group them into several different kinds. Some have what we call a P. periliro tail on the nucleus. They have a different range of subjective effects, and tend to be more alerting or less drowsiness-producing.

Mr. GORDON. The reason I asked this question is, I am just wondering if these are patented drugs, that is, not the original ones, but the modifications. As I understand it, a patent cannot be issued on an invention or discovery which would be obvious to a person skilled in the art.

Dr. FREEDMAN. Well, the phenothiazine nucleus, if I recall, was an antihelmentic, it was used against parasites. So that it is sort of common in itself. The butyrophenones which he mentioned are an entirely different molecular structure. Before a rearrangement can become a drug many biological tests must be made to arrive at a safe phenothiazine. I am not an expert on this. So you will get no more information. I don't know about patents.

Senator NELSON. Please proceed.

Dr. PILLARD. I am continuing the quote here at the bottom of page 2. This is from the Davis review:

> We selected the studies which were methodologically best. They indicated that chlorpromazine, perphenazine, triflupromazine, fluphenazine (Prolixin), trifluoperazine (Stelazine), prochlorperazine and thioridazine (Mellaril) were about equally effective * * *

The overall therapeutic equivalence of these phenothiazines is a generally accepted fact.

It is also true, however, that patients will vary somewhat in their response to these drugs; at times a patient who is doing poorly on one will seem to improve on another. If this sort of differential response could be predicted it would be good to know because each patient could be assigned the drug most effective against his particular symptoms. Can we identify constellations of symptoms or subtypes of schizophrenia each of which is most appropriately treated by a different phenothiazine? Galbrecht and Klett addressed themselves to this question by studying 310 schizophrenics randomly given one of three different phenothiazines. They used a method of computerized data analysis which would discover whether different types of patients were responding systematically to one drug or another. They conclude: "results from the present study failed to support the hypothesis that those patients who received their drug of choice (a computer's choice—not the patient's) would respond more favorably than those randomly assigned to the other drug—*in no case was evidence of differential drug action obtained*" (my italics).

Senator NELSON. They found that each of them was equally efficacious?

Dr. PILLARD. Right.

Senator NELSON. Did they find any differences in side effects?

Dr. PILLARD. They didn't report on that. In the sense that side effects might have influenced the main therapeutic effect, I presume they didn't, because they reported that they were equally efficacious.

This is an impressive statement, since Galbrecht and Klett are experienced researchers using the newest methods of data collection and analysis. Hollister, in a recent review of psychotropic drug treatment cites no research which contradicts Galbrecht and Klett's conclusion.

Evidence such as this, which never finds its way into pharmaceutical advertising, suggests that there is no way at present to predict the

best drug for a given patient. It suggests that the most rational way to begin therapy is with the least expensive drug, switching to something else only if the least expensive drug doesn't work or if idiosyncratic side effects should be encountered.

Of course, this will be a very important issue in a year or two when chlorpromazine comes off patent, because it will be less expensive than others. I feel diffident to suggest such a simple approach to antipsychotic therapy in view of the enormous promotion which different companies have given to the nuances of their competing products and of the clinical lore which has grown up in the wake of this promotion, but, at the present time, evidence for predictable differences in therapeutic effect does not exist.

I haven't really addressed myself much to side effects, because there have been no extensive studies of apparent differences. But apparently while they do differ somewhat in their side effects this doesn't interfere with or potentiate the therapeutic effect.

Exhibit 1,[1] which is attached in a Xerox copy to our statement is a good example of the current promotional effort. This advertisement (American Journal of Psychiatry, June 1969) recommends the combination of two phenothiazines, chlorpromazine and trifluoperazine. It says:

Often extends control when single agents prove less than satisfactory. When the schizophrenic patient's progress is hampered by persistence of certain symptoms, consider switching to Combined Stelazine-Thorazine Therapy.

Senator NELSON. Where is that quote from? Is that in the ad?

Dr. PILLARD. It is in the advertisement, and it is hooked on to the copy at the end of your exhibits, which are Xeroxed.

Senator NELSON. Exhibit 1, page 2. I see.

All right. It is all part of the same ad?

Dr. PILLARD. Yes, those two sentences that I quoted at the bottom of page 4 and page 5 are direct quotes from that advertisement.

Senator NELSON. Is there any evidence to support that claim?

Dr. PILLARD. I don't think there is. And I am going to address myself to that in the next two paragraphs.

Casey and others tested precisely this claim. They studied 520 schizophrenic patients who had not responded satisfactorily to chlorpromazine alone. These patients were given different combinations of drugs including the Stelazine-Thorazine combination recommended in the ad. The authors conclude: "None of the drug combinations was superior to chlorpromazine and placebo." Again, this was highly competent research, a phrase of the VA cooperative studies of chemotherapy in psychiatry. It was published 8 years ago. long before the Stelazine-Thorazine campaign was started and nothing has been discovered since then to cause Casey's conclusion to be revised.

You may wonder how this advertisement—how such a campaign could have ever have been conceived. It does happen that a patient may be started in treatment with a dose of drug A, which is too low, so that when a similar drug B, is added, the patient improves. This improvement is most likely to result in an optimum total dose of phenothiazine, not to result in any special virtues in the drug com-

[1] See p. 5419.

bination. And I quote in the footnote an article which did conclude in favor of a combination of phenothiazine but which failed to take this point into account. The advertisement, to be fair and informative, should point this out, that is, that optimum and total dose is probably the cause for any improvement that the patient shows.

Senator NELSON. Of course, if they put that in the ad there would be no reason for buying the drug.

Dr. FREEDMAN. That need not—scientifically—be so. But at least any physician trying it would know that he was not providing a new therapy—a new therepeutic regimen (which is different than a new drug).

Dr. PILLARD. The advertisement should also point out that the combination is much more expensive; 100 Thorazine tablets in a hundred milligram dose sell for $12.25—and all the prices I am giving are the average retail prices at three pharmacies in Boston; 100 Stelazine tablets in the equivalent 5 milligram dose are $14.35. You have to understand that the drugs have a different potency so that 100 milligrams of one is roughly equivalent to 5 milligrams of another. So that the two together are a total of $26.60. However, 100 tablets of Thorazine in the 200 milligram dose, you see, the stronger dose, are only $16.65. Therefore the patient would save $9.95 if he could be treated just as effectively with a larger dose of the single drug. It has been shown in other studies that many schizophrenic patients are undertreated, so if you give them, in addition, a different phenothiazine they would get better. But the first thing that should be done is, they should be given more, a larger dose of the same drug they have been getting.

To avoid misunderstanding I should say that there may be rare patients who will benefit from one of the less frequently used phenothiazines or from a combination. If the patient is not responding, then certainly the physician should adjust dosage, medication type and so on. I am not against the doctor's using his brains. What I do question is the judgment that an expensive and unproved treatment is worth promotion. Every psychiatrist who opens a journal will think of Stelazine-Thorazine. How many will think of the VA Cooperative Study from 1961?

Now I move on to antidepressants.

Exhibit 2,[1] which, again, is attached, shows a woman in tears at her son's marriage. I have only included the right-hand page of the two-page advertisement, but I will submit the whole advertisement to you so that it can be published in the record. It says in part, and I quote again from the advertisement:

> Often in the mind of the lonely, widowed, depression-prone individual, she's not gaining a daughter, she's losing a son. The occasion may be marred by depression with such symptoms as feelings of sadness, incapacity, helplessness and hopelessness. Tofranil often relieves symptoms of depression.

I also want to insert here that I don't mean to be picking on the drugs of particular manufacturers. If anything, I am selecting drugs which are unquestionably effective, there should be no doubt about this, these are good drugs. What I am discussing is the promotional material which is used for them.

[1] See p. 5421.

The quoted statements are individually correct. Such occasions may be marred by depression and imipramine—which is the generic name of Tofranil—is an effective antidepressant. The implication, that antidepressant therapy is indicated in the griefs of everyday life, is another matter. For one thing all antidepressants are slow to act. Two to 4 weeks of treatment are required to achieve clinical effect by which time the great majority of grief reactions have spontaneously cleared. This advertisement is part of a trend to suggest the use, both of antidepressants and tranquilizers, not only for specific mental illness, but to soothe life's ordinary woes.

Senator NELSON. In what publication did exhibit No. 2 ad appear?

Dr. PILLARD. I took this particular one from the Archives of Psychiatry in June of 1968. But as I note in a footnote, most of these advertisements are part of a campaign. They will appear in a number of psychiatric journals in a given month, and in many cases will run for several months.

Senator NELSON. Is it the general practice of the advertiser of these drugs simply to put them in the journals which are read by psychiatrists rather than the general medical journals, New England Journal, JAMA, or something like that?

Dr. PILLARD. Usually they are in the general psychiatric journals, although the tranquilizers which are used by general practitioners will also crop up in other publications.

Senator NELSON. Are these advertised in general medical publications?

Dr. PILLARD. Do you know, Dr. Freedman?

Dr. FREEDMAN. I have seen them, you see less phenothiazine ads in the general medical publications—this is just an impression—and more of the antidepressant and anti-anxiety drugs in JAMA and other journals.

Mr. GORDON. Isn't the Archives of Psychiatry a publication of the American Medical Association?

Dr. PILLARD. Yes.

Mr. GORDON. Now, the AMA has a set of principles which govern not only advertising in the Journal of the AMA, but also in all of its scientific publications.

Dr. PILLARD. Yes. I presume it should apply to this.

Mr. GORDON. It should apply to that, too?

Dr. PILLARD. Yes.

Another example is seen in exhibit 3 [1]—well, this is an answer to your question, because exhibit 3 I took from Medical World News, which is a throwaway sent to all physicians—which is for the tranquilizer hydrozine under the brand name Vistaril. In large type appear the words "School, the dark, separation, dental visits, 'monsters;' . . . The everyday anxieties of childhood sometimes get out of hand."

And those words are written over the picture of a pretty little girl in tears—she didn't reproduce very well, but she is there. This appears in a general medical magazine although even specialists in child psychiatry seldom use tranquilizers and then only for limited and specific

[1] See p. 5423.

indications. Another for Stelazine (Archives of Psychiatry, February 1969) says— this is not an exhibit, I am just quoting from the text, I didn't include this.

The quote says: "* * * can help you control your patient's excessive anxiety resulting from unavoidable, day-to-day pressures. * * *" I'm sure the drug companies would say, if pressed, that they mean these drugs to be used only in specific cases of neurotic or psychotic illness, not in all lonely widows and frightened children. Sometimes the proper qualifications are made in the small type. But the general cast of the advertisement, the words "everyday anxieties" * * * "day-to-day pressures" certainly create the impression that we are all candidates for drug therapy.

Senator NELSON. This exhibit 3, where did that ad appear?

Dr. PILLARD. That came from Medical World News, July 1969.

Senator NELSON. And is that the complete ad?

Dr. PILLARD. No. There is a third page which contains the package circular information. And I will submit that so that you will have the complete ad for the record.

Senator NELSON. In which it lists the indications, the contraindications, and side effects.

Dr. PILLARD. Yes.

Senator NELSON. Is it your impression from reading the first two pages that the drug is being promoted for the use of a child who is not a psychotic case?

Dr. PILLARD. Yes; that is my impression.

I would like to insert here, since I wrote this, I discovered that a Dr. John Visher, who is the speaker-elect of the Assembly of District Branches of the American Psychiatric Association, in a report to the trustees of the APA said:

> Many of the advertisements for psychotropic drugs in the medical and psychiatric literature expand the indications for these drugs beyond their use in mental illness to include their use as palliatives to ordinary problems of living.

So I think this is a general concern of the profession.

Apart from the question of whether tranquilizers and antidepressants are effective in these situational reactions—and there is not really much evidence that they are—there is a judgment to be made whether it is most healthy for people to be reacting to or chemically protected from those emotions which are an inevitable part of a full and normal life. I know of no studies on this issue. The effects of chronic psychotropic drug treatment on a "normal" person's functioning are not fully known.

To return to Tofranil for a moment, another objection I have to that presentation—that is, the presentation in exhibit 2—is that it does not emphasize the side effects which may occur. The sentence "use of Tofranil in patients receiving M.A.O.I.'s is contraindicated" appears in the text. The initials refer to monoamine oxidase inhibitors which are also antidepressants but of a different chemical class from Tofranil. The physician is warned not to use these two drugs together. That the patient may die if this warning is overlooked is buried in the package circular information. How well buried it is is shown in exhibit No. 4 [1]

[1] Dr. Pillard's Exhibit No. 4 has been reproduced in two pages and will be found beginning at p. 5426.

(Behavioral Neuropsychiatry, April 1969). This is a three-page ad; the left-hand page is blank, the right-hand page contains the text and over on the following page is the package circular information. It is now very common to see package circular information divorced in this way from the body of the advertisement and I regard this as evading the responsibility to publicize drug hazards fully and honestly.

You don't have it in your exhibit because I didn't want to Xerox 100 blank pages. I show it to you here. It is a complete blank page on the left. The right-hand page contains the advertising text. And then you have to turn over—the right-hand page is labeled page 1 in your exhibit, that is the right-hand page of the advertisement. And then you have to turn this over, which is page 2 of your exhibit, to get to the package circular information. It is now very common to see package circular information divorced in this way providing the advertisement——

Senator NELSON. Is that a relatively new technique?

Dr. PILLARD. I have just been noticing it in the past year or so. I believe it is new.

I regard this as an evasion of the responsibility to publicize drug hazards fully and fairly.

It has become very common, exhibit 3, I believe, is the same principle. You don't have the package circular information you asked about. Well, it is on the next page, you see, so that the doctor as he looks at a two-page ad doesn't see the package circular information.

Now I turn to tranquilizers. I have already referred to the practice of promoting tranquilizers for the relief of all sorts of normal appropriate anxiety states. Exhibit No. 5 [1] refers to an advertisement for the tranquilizer Valium. And this is from the International Journal of Psychiatry, November 1967. This advertisement was based on an experiment by Clemens and Selesnick which showed that anxious neurotics, if pretreated with Valium, had diminished physiological reactivity to an anxiety producing motion picture. The advertisement did not mention some important qualifications: that physiological reactivity is diminished by other drugs which have no tranquilizing activity and that the method by which reactivity was measured was never reported.

It was promised in a footnote in the Journal article, but I have never seen it published. This is an important point. I have seen an example in which any one of six patients could have been considered "most reactive" to a drug depending upon which of six reactivity measures was used. This is not intended as a criticism of Clemens and Selesnick; their experiment was imaginative and they reported their results fairly. The point is that background information and qualifications which might appear in a scientific article can be omitted and the results exaggerated beyond what the authors intended.

I see yesterday that A. C. Bachrach, who is associate professor of clinical medicine at the University of California, is suing a drug firm, Farbenfabriken Bayer, because he said they used his results unfairly,

[1] See p. 5428.

they damaged his reputation, he is suing them for $1,100,000. He says, "a responsible physician should not allow a pharmaceutical house to exploit his reputation to promote the sale of a drug without his knowledge, much less his permission." He didn't even know that they had used his findings in an advertisement, it appeared in a foreign journal, so he didn't see it. And the drug company in this case has admitted that they misrepresented his findings, at least according to this article that I have.

Now, some general comments.

Beyond these specific objections there is a broader issue on which I want to comment. No one knows exactly what calculations enter into a doctor's therapeutic decisions. Ideally he relies on research findings and on the clinical experience of experts accumulated over the years and published in the medical literature, tempered by his own judgment and his knowledge of the patient's particular circumstances. All of us have the duty to be aware of new information and to reevaluate our therapeutics in its light. This is a humbling experience. We constantly see our highest hopes and strongest clinical impressions dissolve when hard evidence is collected.

This is perhaps more true in the field of psychiatry where symptoms may be more heavily influenced by nonpharmacologic factors and for this reason we—and I mean we in the field of psychiatric research—have invested particular effort to develop strategies of drug testing which control the element of personal bias. Even so, an attitude of skepticism, and respect for evidence is difficult to maintain. It is hard to teach students and hard to preserve in oneself. The history of our science shows—and this is the recent history of our science, not just leeches and herbs, but right today—any number of worthless and even harmful treatments which were at first highly regarded. My concern is that drug companies, with all the resources they have to prompt doctors to prescribe drugs, will just overwhelm the more conservative point of view. This is happening. The public surfeit with medications and drugs is one of our major health problems. Adverse drug reactions affect more than a third of hospitalized patients.

One might wonder whether increased vigilance by the FDA and by the journal advertising committees could influence this situation. I believe that these groups have lessened some of the more obvious abuses but they will never be able to complete the job of separating the wheat from the chaff in drug advertising because—to make my position perfectly clear—there is no wheat.

Mr. GORDON. What do you mean by that?

Dr. PILLARD. I think the recommendations will make that clear. I think a lot of time is spent in separating the worst advertisements from the less bad. And my position is that if medical journals would discontinue advertising altogether this effort would be saved. I am going to come to that in the recommendations.

Senator NELSON. This point on advertising and promotion and claims made for drugs and ads in medical journals has been made on other occasions. If there were no advertising, where would the physician get his information?

Dr. PILLARD. That is an easy one to answer. The same way that surgeons would find out about a new operation. If somebody discovers a new way to do a hysterectomy there is no advertisement which tells the surgeon about this, but they find it out.

I can give you even a better example in the psychotropic drug field, which concerns the drug lithium carbonate. This drug is not advertised, in fact it is not even manufactured for commercial use. Nobody wants to make it. But my impression is that psychiatrists around the country are quite aware of lithium carbonate, and they prescribe it in judicious amounts. To be sure, it is used for a rare illness, manic psychosis, which is a rare illness. But I am very impressed by how knowledgeable psychiatrists are about this drug which has never been advertised, it has only appeared in meetings, medical journals and so forth. I think if these advertisements were done away it would clear the air and rid us—and we would have more information and less pseudo-information.

Now, I go into recommendations.

1. I support the recommendations of the Task Force on Prescription Drugs. They are an ambitious set of proposals and if even one of them, the establishment of a compendium with price information, could be effected, it would be a contribution to medical practice.

I have just been reading some of the testimony you have had from others who oppose the compendium. And I must say the fact that it would be a large book doesn't impress me at all. Dictionaries are big and the Encyclopedia Britannica stretches across the room, but that doesn't discourage people from using them if they want the information.

2. Medical journals ought to stop all drug advertising. They should do this for the benefit of their readers, for the reasons I have discussed above, and also for the sake of their own editorial objectivity. It is impossible to estimate the extent to which editorial judgment is influenced by the advertisers—hopefully not at all—but we should eliminate even the possibility of such influence.

And I want to insert a point which I think is very important. The journal should undertake as an editorial responsibility to teach the members of the profession about different treatments which they think are being either overused or underused. The editorial boards are distinguished persons, and they should show this as an educational responsibility to the rest of us in the profession. If they believe that a particular drug is being misprescribed or overprescribed or which has dangerous side effects which are being overlooked, this should be stated clearly in an editorial. This is rarely done in psychiatric journals, it is rarely done in any medical journal.

And indeed I don't think it can be done. Because if the editors plug one drug and pan another they are always open to criticism that they are responding to the pressure of the advertisers. If there were no question about it I think they would feel more free to say what they think with respect to this drug treatment.

It has been argued that journal advertising is useful in that it keeps down subscription fees and those who don't like to read ads can simply skip over them. This argument is without merit. Remember that what the drug companies do is paid for by a group of *involuntary consum-*

ers—the Nation's sick people. If these involuntary consumers understood that not only were their fees supporting the world's most highly paid profession but also that they were subsidizing their doctor's medical journal subscriptions, books, samples, medical bags and so forth—if this were generally understood I think that the public outcry would be something to contend with.

Doctors ought to pay for their reading matter just like psychologists, lawyers, chemists, and schoolteachers. The total increase in subscription costs for a year would be less than what the doctor earns in an hour.

Support for this position is building up as can be seen from letters recently published in the New England Journal of Medicine.

Dr. James Faulkner, chairman of the publications committee of the Massachusetts Medical Society which owns the Journal, has shown his awareness of the problems of drug advertising. Whether the council of the medical society will make a serious study of the matter I don't know; at least they will have to realize the extent to which they are dependent upon the pharmaceutical industry.

I have some figures from the annual report of the medical society. I won't go into them, but I can give them to you if you would like to see them. It says that over $2 million is received by the New England Journal in advertising revenue, whereas the amount from subscription fees is around $650,000, I believe. The accurate figures are here.[1]

3. Distribution of free drug samples should be stopped. Prescription drugs should be obtainable only on prescription and only from the pharmacist. Doctors receive in their mail every day samples of drugs for most of which they have no use. They are impossible to dispose of safely. We get into the habit of giving out sleeping pills and tranquilizers that come in the mail without the sort of serious thought that would go into writing a prescription. In most cases new products are promoted this way. Dangerous medications like some of the early anti-depressants, MER–29, and others were distributed. More people took them than otherwise would have and the task of recall when it had to be undertaken was impossible. If all medication were dispensed via prescription the patient would have the protection of knowing that a record exists of just what he received.

I brought along a few samples. They are scored so that you can take off the identifying information, the doctor does, and he gives the patient an anonymous sample like this, so if there is a side effect or reaction of the patient somewhere else, if he can't reach his doctor, he may not know what pill he has received.

This suggestion goes beyond the Task Force recommendation. Their recommendation was that the free samples be given on request of the doctor. But I am proposing that no free samples of any kind be distributed.

The process of requesting pills by checking a postcard can be made so easy as to be no protection at all. Obviously there is no reason to defend the free sample practice by saying that samples are needed for indigent patients. Samples could be sent to the pharmacist who could give them to patients for whom that medicine is prescribed. But the most important thing is to make sure that our mechanism of providing

[1] For 1968, from advertising: $2,241,554.42; from subscriptions: $662,328.83.

medical care, including medication, insures that every person will get what he needs at a reasonable price. If free samples are needed at all it is a sign that something is wrong.

4. Pharmaceutical companies should undertake a serious reconsideration of their promotional strategy. They should cease or drastically reduce published advertising and reflect the savings in lower drug prices. A year of drug advertising costs more than it would to send every doctor in the country to a year of medical school. Both the medical and legal professions prohibit advertising because they realize that it would interfere with their function of serving the public interest but also I believe because they realize that in the longrun the profession as a whole had nothing to gain. The drug industry is not the only one which ought to consider this example.

These suggestions could be put into effect by the medical profession and the industry without any legislation.

I am really convinced that the AMA could effect these modest recommendations with no difficulty at all.

One hopes that they will be receptive to changes. This committee has done a service by providing all points of view with the chance to be expressed.

Thank you.

Senator NELSON. Thank you very much for your excellent presentation, Doctor.

(The complete prepared statement and exhibits submitted by Dr. Pillard follow:)

STATEMENT OF DR. RICHARD C. PILLARD, ASSISTANT PROFESSOR OF PSYCHIATRY, BOSTON UNIVERSITY SCHOOL OF MEDICINE

My name is Richard C. Pillard. I am a physician, assistant professor of psychiatry at Boston University School of Medicine and head of the Basic Studies Unit of the Psychopharmacology Laboratory there. I am also the recipient of an NIMH Research Scientist Development Award.

As a researcher, teacher and practitioner of psychiatry I am concerned about advertising claims which are being made for psychotropic drugs. These advertisements appear in medical journals and in the free "throwaway" magazines which are sent to physicians. Most of them exaggerate the efficacy of the drug, extend its indications, or distort the evidence upon which its use is based. Almost none are properly balanced in the sense that the advantages of the drug are proclaimed while its limitations and side effects are minimized or not mentioned at all except in the package circular information required by law. More than this, I am concerned about the general effect which psychotropic drug advertising has on the prescribing habits of the psychiatrist and on the way he thinks about his patients.

Before elaborating these concerns I want to pay a tribute to the pharmaceutical industry. The field of psychopharmacology is only 15 years old but has already made an impressive contribution to the recovery of mentally ill people. This would, of course, never have been possible without the variety of high quality psychotropic drugs which are available thanks to the drug industry. I hope that my testimony will help to promote further achievement and not be considered an attack or a derogation of their accomplishments.

ANTIPSYCHOTICS

The most important psychotropic drugs are the phenothiazine chemical family, used in the treatment of schizophrenia. These are unquestionably effective and are, along with reserpine and the butyrophenones, the only treatments of proved value in this illness. There are approximately 17 phenothiazines currently manufactured most of which are heavily promoted because the market for them is very

large. Although their molecular structures differ slightly and they produce different side effects, all appear to be the same with respect to their main therapeutic action, which is reduction of schizophrenic symptoms. This has been shown in a number of studies. John Davis, in a review,[1] summarizes this research saying: "Numerous studies showed the other phenothiazines to be approximately equal to chlorpromazine in their therapeutic effect . . . For example, a multiple variance analysis in the VA Cooperative Study showed no difference between perphenazine (Trilafon), triflupromazine (Vesprin), prochlorperazine (Compazine), and chlorpromazine (Thorazine). The same results were found with a state hospital population, in the carefully done studies of Kurland *et al.* . . . Again we selected the studies which were methodologically best. They indicated that chlorpromazine, perphenazine, triflupromazine, fluphenazine (Prolixin), trifluoperazine (Stelazine), prochlorperazine and thioridazine (Mellaril) were about equally effective . . ." The overall therapeutic equivalence of these phenothiazines is a generally accepted fact.[2]

It is also true however that patients will vary somewhat in their response to these drugs; at times a patient who is doing poorly on one will seem to improve on another. If this sort of differential response could be predicted it would be good to know because each patient could be assigned the drug most effective against his particular symptoms. Can we identify different constellations of symptoms or subtypes of schizophrenia each of which is most appropriately treated by a different phenothiazine? Galbrecht and Klett[3] addressed themselves to this question by studying 310 schizophrenics randomly given one of three different phenothiazines. They used a method of computerized data analysis which would discover whether different types of patients were responding systematically to one drug or another. They conclude: "results from the present study failed to support the hypothesis that those patients who received their drug of choice [a computer's choice—not the patient's] would respond more favorably than those randomly assigned to the other drug . . . *in no case was evidence of differential drug action obtained.*" (my italics) This is an impressive statement since Galbrecht and Klett are experienced researchers using the newest methods of data collection and analysis. Hollister, in a recent review of psychotropic drug treatment[4] cites no research which contradicts Galbrecht and Klett's conclusion.

Evidence such as this, which never finds its way into pharmaceutical advertising, suggests that there is no way at present to predict the best drug for a given patient. It suggests that the most rational way to begin therapy is with the least expensive drug, switching to something else only if the least expensive drug doesn't work or if idiosyncratic side effects should be encountered. I feel diffident to suggest such a simple approach to anti-psychotic therapy in view of the enormous promotion which different companies have given to the nuances of their competing products and of the clinical lore which has grown up in the wake of this promotion, but, at the present time, evidence for predictable differences in therapeutic effect does not exist.

Exhibit #1 is a good example of the current promotional effort. This advertisement (American Journal of Psychiatry, June 1969)[5] recommends the combination of two phenothiazines, chlorpromazine and trifluoperazine. It says: "Often extends control when single agents prove less than satisfactory. When the schizophrenic patient's progress is hampered by persistence of certain symptoms, consider switching to Combined Stelazine-Thorazine Therapy."

Casey *et al.*[6] tested precisely this claim. They studied 520 schizophrenic patients who had not responded satisfactorily to chlorpromazine alone. These patients were given different combinations of drugs including the Stelazine-Thorazine combination recommended in the ad. The authors conclude: "None of the drug combinations was superior to chlorpromazine and placebo." Again, this was highly competent research, a phase of the VA Cooperative Studies of Chemotherapy in Psychiatry. It was published eight years ago, long before the Stelazine-Thorazine campaign was started and nothing has been discovered since then to cause Casey's conclusion to be revised.

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[1] "Archives of General Psychiatry," vol. 13, pp. 552–572, 1965.
[2] Mepazine and promazine may be exceptions but are hardly ever used in schizophrenia.
[3] *Journal of Nervous and Mental Disease*, vol. 147, pp. 173–183, 1968.
[4] *Clinical Pharmacology and Therapeutics*, vol. 10, pp. 170–198, 1969.
[5] Specific citations are given for each advertisement. However they all appeared in a number of journals, often over a period of months.
[6] "American Journal of Psychiatry," vol. 117, pp. 997–1003, 1961.

It does happen that a patient may be started in treatment with a dose of Drug A which is too low so that when a similar Drug, B, is added, the patient improves. This improvement is most likely the result of an optimum total dose of phenothiazine, not the result of any special virtues in the drug combination.[7] The advertisement, to be fair and informative should point this out. It should also point out that the combination is much more expensive. One hundred Thorazine tablets in the 100 mg. dose sell for $12.25. One hundred Stelazine tablets in the equivalent 5 mg. dose are $14.35—a total of $26.60. One hundred tablets of Thorazine in the 200 mg. dose are only $16.65. Therefore the patient would save $9.95 if he could be treated just as effectively with a larger dose of a single drug.[8]

To avoid misunderstanding I should say that there may be rare patients who will benefit from one of the less frequently used phenothiazines or from a combination. If the patient is not responding, then certainly the physician should adjust dosage, medication type and so on. I am not against the doctor's using his brains. What I do question is the judgment that an expensive and unproved treatment is worth promotion. Every psychiatrist who opens a journal will think of Stelazine-Thorazine. How many will think of the VA Cooperative Study from 1961?

ANTIDEPRESSANTS

Exhibit #2 (Archives of Psychiatry, June 1968) shows a woman in tears at her son's marriage. It says in part: "Often in the mind of the lonely, widowed, depression-prone individual, she's not gaining a daughter, she's losing a son. The occasion may be marred by depression with such symptoms as feelings of sadness, incapacity, helplessness and hopelessness. Tofranil often relieves symptoms of depression."

These statements are individually correct. Such occasions may be marred by depression and imipramine (Tofranil) is an effective antidepressant. The implication, that antidepressant therapy is indicated in the griefs of everyday life, is another matter. For one thing all antidepressants are slow to act. Two to four weeks of treatment are required to achieve clinical effect by which time the great majority of grief reactions have spontaneously cleared. This advertisement is part of a trend to suggest the use, both of antidepressants and tranquilizers, not only for specific mental illness, but to soothe life's ordinary woes.

Another example is seen in Exhibit #3 (Medical World News, July 1969) for the tranquilizer, hydroxyzine (Vistaril). In large type appear the words "School, the dark, separation, dental visits, 'monsters;' . . . The everyday anxieties of childhood sometimes get out of hand." This appears in a general medical magazine although even specialists in child psychiatry seldom use tranquilizers and then only for limited and specific indications. Another for Stelazine (Archives of Psychiatry, February 1969) says ". . . can help you control your patient's excessive anxiety resulting from unavoidable, day-to-day pressures . . ." I'm sure the drug companies would say, if pressed, that they mean these drug to be used only in specific cases of neurotic or psychotic illness, not in all lonely widows and frightened children. Sometimes the proper qualifications are made in the small type. But the general cast of the advertisement, the words "everyday anxieties" . . . "day-to-day pressures" certainly create the impression that we are all candidates for drug therapy.

Apart from the question of whether tranquilizers and antidepressants are effective in these "situational" reactions—and there is not really much evidence that they are[9]—there is a judgment to be made whether it is most healthy for people to be reacting to or chemically protected from those emotions which are an inevitable part of a full and normal life. I know of no studies on this issue. The effects of chronic psychotropic drug treatment on a "normal" person's functioning are not fully known.

To return to Tofranil for a moment, another objection I have to that presentation is that it does not emphasize the side effects which may occur. The sentence

[7] Some studies (e.g., "American Journal of Psychiatry," vol. 121, pp. 597–600, 1964), have found in favor of drug combinations but have overlooked this methodological point.

[8] Average retail prices from three Boston pharmacies.

[9] See for example Laites ("Journal of Abnormal and Social Psychology," vol. 59, pp. 156–161, 1959) and Pillard & Fisher ("Psychopharmacologia," vol. 12, pp. 18–23, 1967) for a discussion of some issues relating to drug effects on situational anxiety.

"use of Tofranil in patients receiving M.A.O.I.'s is contraindicated" appears in the text. The initials refer to monoamine oxidase inhibitors which are also antidepressants but of a different chemical class from Tofranil. The physician is warned not to use these two drugs together. That the patient may die if this warning is overlooked is buried in the package circular information. How well buried it is is shown in Exhibit #4 (Behavioral Neuropsychiatry, April 1969). This is a three-page ad; the left-hand page is blank, the right-hand page contains the text and over on the following page is the package circular information. It is now very common to see package circular information divorced in this way from the body of the advertisement and I regard this as evading the responsibility to publicize drug hazards fully and honestly.

TRANQUILIZERS

I have already referred to the practice of promoting tranquilizers for the relief of all sorts of normal and appropriate anxiety states. Exhibit #5 refers to an advertisement for the tranquilizer Valium (International Journal of Psychiatry, November 1967). This advertisement was based on an experiment by Clemens and Selesnick[10] which showed that anxious neurotics, if pretreated with Valium, had diminished physiological reactivity to an anxiety-producing motion picture. The advertisement did not mention some important qualifications: that physiological reactivity is diminished by other drugs which have no tranquilizing activity and that the method by which reactivity was measured was never reported. This is an important point. I have seen an example in which any one of six patients could have been considered "most reactive" to a drug depending upon which of six reactivity measures was used. This is not intended as a criticism of Clemens and Selesnick; their experiment was imaginative and they reported their results fairly. The point is that background information and qualifications which might appear in a scientific article can be omitted and the results exaggerated beyond what the authors intended. This particular advertisement has now been withdrawn but I mention it because it was the subject of the most extensive advertising campaign which I have ever seen for a psychotropic drug.

GENERAL COMMENTS

Beyond these specific objections there is a broader issue on which I want to comment. No one knows exactly what calculations enter into a doctor's therapeutic decisions. Ideally he relies on research findings and on the clinical experience of experts accumulated over the years and published in the medical literature, tempered by his own judgment and his knowledge of the patient's particular circumstances. All of us have the duty to be aware of new information and to reevaluate our therapeutics in its light. This is a humbling experience. We constantly see our highest hopes and strongest clinical impressions dissolve when hard evidence is collected. This is perhaps more true in the field of psychiatry where symptoms may be more heavily influenced by non-pharmacologic factors and for this reason we have invested particular effort to develop strategies of drug testing which control the element of personal bias. Even so, an attitude of skepticism, and respect for evidence is difficult to maintain. It is hard to teach students and hard to preserve in oneself. The history of our science shows any number of worthless and even harmful treatments which were at first highly regarded. My concern is that drug companies, with all the resources they have to prompt doctors to prescribe drugs, will just overwhelm the more conservative point of view. This is happening. The public surfeit with medications and drugs is one of our major health problems. Adverse drug reactions affect more than a third of hospitalized patients.[11]

One might wonder whether increased vigilance by the FDA and by the journal advertising committees could influence this situation. I believe that these groups have lessened some of the more obvious abuses but they will never be able to complete the job of separating the wheat from the chaff in drug advertising because—to make my position perfectly clear—there is no wheat.

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[10] "Diseases of the Nervous System," vol. 28, pp. 98–104, 1967.
[11] 35% according to Borda (*J. American Medical Assn.*), vol. 205, p. 645 (1968).

RECOMMENDATIONS

(1) I support the recommendations of the task force on prescription drugs. They are an ambitious set of proposals and if even one of them, the establishment of a compendium with price information, could be effected, it would be a contribution to medical practice.

(2) Medical journals ought to stop all drug advertising. They should do this for the benefit of their readers, for the reasons I have discussed above, and also for the sake of their own editorial objectivity. It is impossible to estimate the extent to which editorial judgment is influenced by the advertisers—hopefully not at all—but we should eliminate even the possibility of such influence.

It has been argued that journal advertising is useful in that it keeps down subscription fees and those who don't like to read ads can simply skip over them. This argument is without merit. Remember that what the drug companies do is paid for by a group of *involuntary consumers*—the nation's sick people. If these involuntary consumers understood that not only were their fees supporting the world's most highly paid profession but also that they were subsidizing their doctors' medical journal subscriptions, books, samples, medical bags and so forth—if this were generally understood I think that the public outcry would be something to contend with.

Doctors ought to pay for their reading matter just like psychologists, lawyers, chemists and school teachers. The total increase in subscription costs for a year would be less than what the doctor earns in an hour.

Support for this position is building up as can be seen from letters recently published in the New England Journal of Medicine. Dr. James Faulkner, chairman of the publications committee of the Massachusetts Medical Society which owns the Journal, has shown his awareness of the problems of drug advertising. Whether the Council of the Medical Society will make a serious study of the manner I don't know; at least they will have to realize the extent to which they are dependent upon the pharmaceutical industry.

(3) Distribution of free drug samples should be stopped. Prescription drugs should be obtainable only on prescription and only from a pharmacist. Doctors receive in their mail every day samples of drugs for most of which they have no use. They are impossible to dispose of safety. We get into the habit of giving out sleeping pills and tranquilizers that come in the mail without the sort of serious thought that would go into writing a prescription. In most cases new products are promoted this way. Dangerous medications like some of the early antidepressants, MER–29, and others were distributed. More people took them than otherwise would have and the task of recall when it had to be undertaken was impossible. If all medication were dispensed via prescription the patient would have the protection of knowing that a record exists of just what he received.

This suggestion goes beyond the Task Force recommendation because the process of requesting pills, by checking a postcard, can be made so easy as to be no protection at all.

Obviously there is no reason to defend the free sample practice by saying that samples are needed for indigent patients. Samples could be sent to the pharmacist who could give them to patients for whom that medicine is prescribed. But the most important thing is to make sure that our mechanism of providing medical care, including medication, ensures that every person will get what he needs at a reasonable price. If free samples are needed at all it is a sign that something is wrong.

(4) Pharmaceutical companies should undertake a serious reconsideration of their promotional strategy. The should cease or drastically reduce published advertising and reflect the savings in lower drug prices. A year of drug advertising costs more than it would to send every doctor in the country to a year of medical school. Both the medical and legal professions prohibit advertising because they realized that it would interfere with their function of serving the public interest but also I believe because they realized that in the long run the profession as a whole had nothing to gain. The drug industry is not the only one which ought to consider this example.

These suggestions could be put into effect by the medical profession and the industry without any legislation. One hopes that they will be receptive to changes. This committee has done a service by providing all points of view with the chance to be expressed. Thank you.

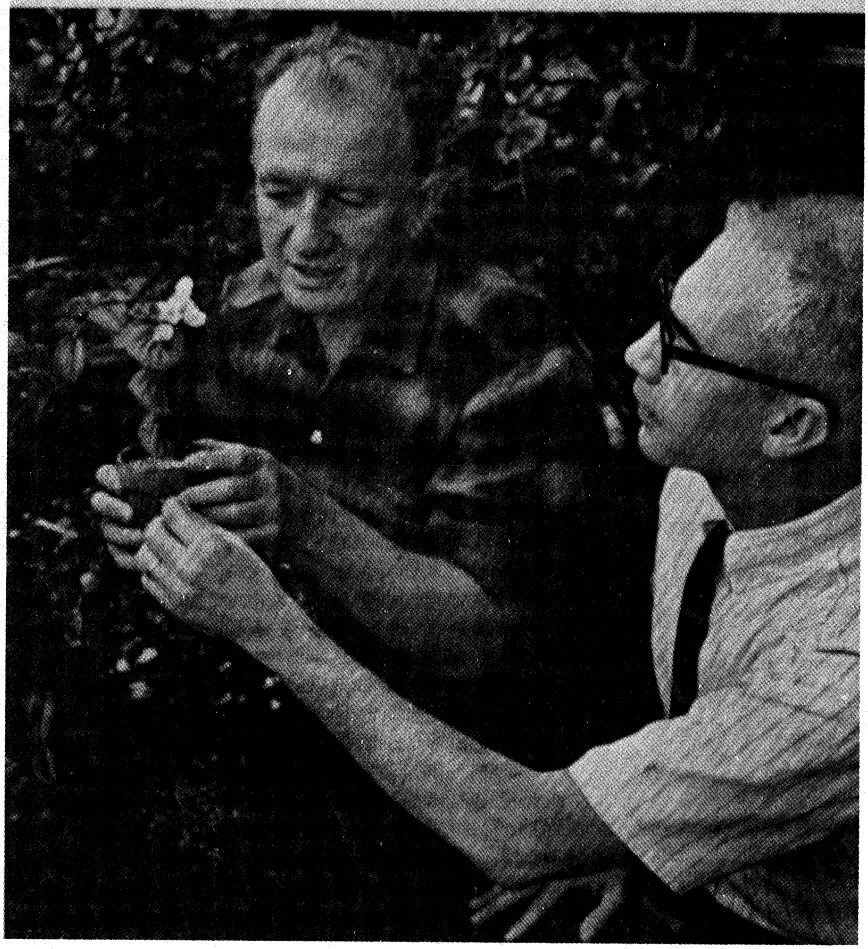
[EXHIBIT 1]

[From the American Journal of Psychiatry, June 1969]



Often extends control when single agents prove less than satisfactory

When the schizophrenic patient's progress is hampered by persistence of certain symptoms, consider switching to Combined Stelazine (trifluoperazine HCl, SK&F) - Thorazine (chlorpromazine, SK&F) Therapy. In addition to extending control of symptoms, this combination has often made possible more meaningful participation in other therapies.



[EXHIBIT 2]

[From the Archives of Psychiatry, June 1968]



Indications: Tofranil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of Tofranil and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before Tofranil may be substituted. Initial Tofranil dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, Tofranil should not be used during the first trimester of pregnancy.
Cardiovascular complications, including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment with Tofranil. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy.
Because of its anticholinergic effect, caution should be observed in prescribing Tofranil for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patients receiving thyroid medication when Tofranil was added to the regimen. Imipramine may block the pharmacologic activity of guanethidine and other related adrenergic neuron-blocking agents.
The drug is not recommended at the present time in patients under 12 years of age.
Adverse Reactions: Dryness of the mouth, tachycardia, constipation, disturbances of accommodation, sweating, dizziness, weight gain, urinary frequency or retention, nausea and vomiting, peripheral neuritis, mild parkinson-like syndrome, tremors, rare cases of fainting in elderly patients, confusional states (with such symptoms as hallucinations and disorientation), activation of psychosis in schizophrenics and agitation (includ-

When a milestone in life is marred by depression...



Often in the mind of the lonely, widowed, depression-prone individual, she's not gaining a daughter... she's losing a son. The occasion may be marred by depression with such symptoms as feelings of sadness, incapacity, helplessness and hopelessness.

Tofranil often relieves symptoms of depression.

As maintenance therapy during the active phase of depression, it may help prevent relapse.

The use of Tofranil in patients receiving M.A.O.I.'s is contraindicated.

In patients with cardiovascular disease, hyperthyroidism or increased intraocular pressure; or in those receiving anticholinergics (including antiparkinsonism agents), thyroid medication, or antihypertensive adrenergic neuron-blocking agents; and in those in their first trimester of pregnancy, the special precautions listed in the prescribing information should be carefully observed.

Toxic reactions severe enough to require discontinuation of Tofranil are uncommon. However, for complete details, please refer to the full prescribing information.

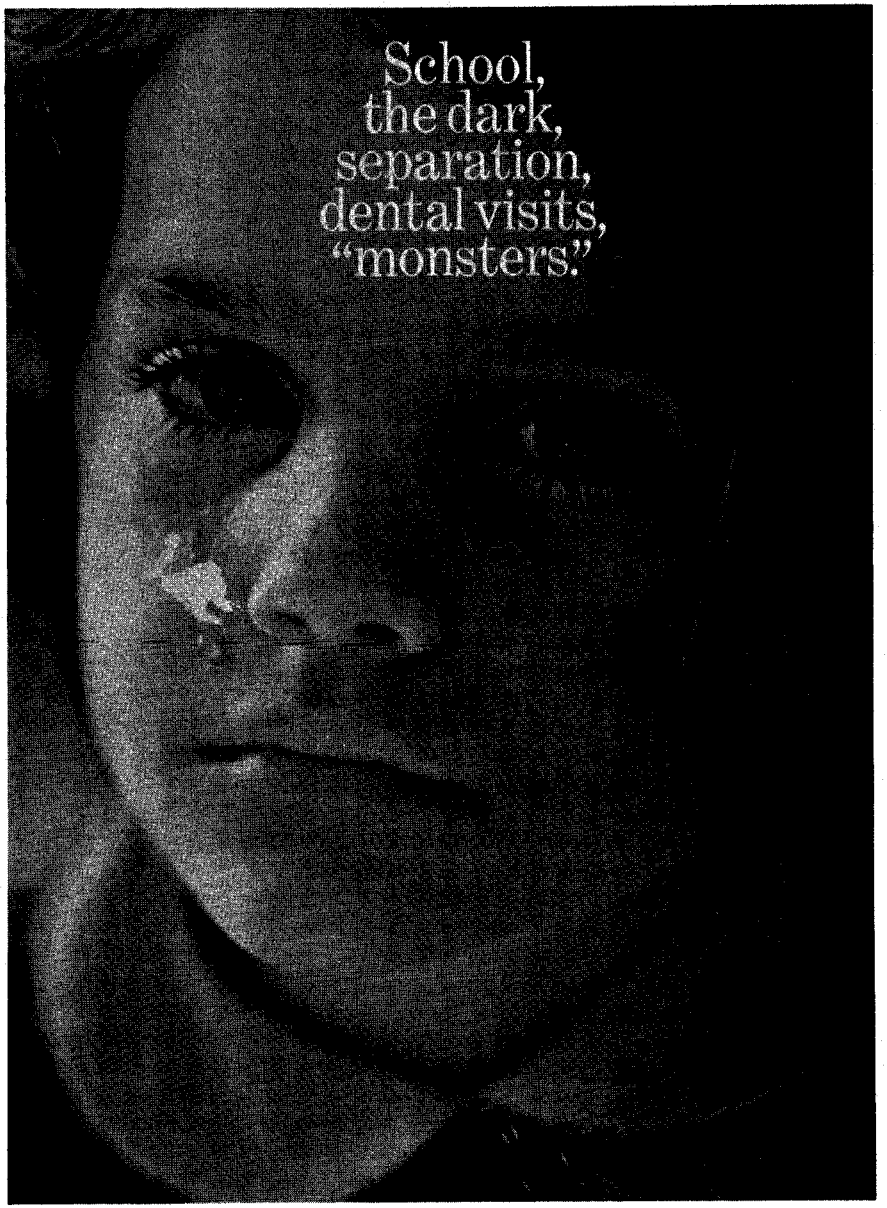
Tofranil® Geigy
imipramine
hydrochloride

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York 10502

ing hypomanic and manic episodes) which may require dosage reduction and/or addition of a tranquilizer or temporary discontinuation of the drug, epileptiform seizures, orthostatic hypotension and substantial blood pressure fall in hypertensive patients, purpura, transient jaundice, bone marrow depression including agranulocytosis, sensitization and skin rash including photosensitization, eosinophilia, and mild withdrawal symptoms on sudden discontinuation after prolonged treatment with high doses. Occasional hormonal effects (impotence, decreased libido, and estrogenic effects) may be observed. Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those using anticholinergic agents (including antiparkinsonism drugs).
Outpatient Adult Dosage: Initially, 75 mg. daily, increased, if necessary, to 150 or 200 mg. Maintenance dosage may be lower, 50 to 150 mg. daily, if possible.
Geriatric and Adolescent Dosage: Initially, 30 or 40 mg. daily, which may be increased according to response and tolerance. It is usually unnecessary to exceed 150 mg. daily.
A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
Availability: Tofranil: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg. for geriatric and adolescent use; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration. (B)40-860-C
For complete details, please refer to the full Prescribing Information.

[EXHIBIT 3]

[From Medical World News, July 1969]



The everyday anxieties of childhood sometimes get out of hand

A child can usually deal with his anxieties. But sometimes the anxieties overpower the child. Then, he needs your help.

Your help may include Vistaril® (hydroxyzine pamoate). Vistaril can calm the uncontrollably anxious child while you uncover and treat the causes of his problem. Parent concern over a difficult situation is lessened when the child is emotionally calm. Nausea and vomiting, which may accompany childhood anxiety, are also relieved with Vistaril.

Vistaril, given an hour before bedtime, can help relieve excess anxiety, and encourage restful sleep. Vistaril can be easily discontinued when the causative factors are corrected.

Vistaril provides the uncomplicated calm. It does not oversedate, although some drowsiness has been reported. Paradoxic excitation and confusion have not occurred with Vistaril.

Vistaril can even help calm the hyperactive child. During the day, Vistaril may make it easier for him to concentrate on tasks for longer periods of time. At night, Vistaril can help relieve the restlessness which is often part of the hyperactive child's sleep pattern.

For the younger patient, Vistaril Oral Suspension has a pleasant lemon flavor. For older children, Vistaril capsules are available in 25 mg. and 50 mg. strengths.

Vistaril®

HYDROXYZINE PAMOATE

Oral Suspension/Capsules

A more effective way to treat pediatric anxiety

Pfizer **LABORATORIES DIVISION**
New York, N.Y. 10017

Please turn page for Brief Summary

A more effective way to treat pediatric anxiety



Oral Suspension/Capsules
Dosage: Under six years, 50 mg. daily in divided doses. Over six years, 50-100 mg. daily in divided doses.

WHEN HYDROXYZINE HYDROCHLORIDE PARENTERAL SOLUTION IS ADMINISTERED INTRAVENOUSLY PARTICULAR ATTENTION SHOULD BE DIRECTED TO INSURE THAT THE DRUG IS INJECTED ONLY INTO THE VEIN (INCLUDING ASPIRATION AND PROPER ANATOMICAL SITE SELECTION) TO AVOID EITHER INTRA-ARTERIAL INJECTION OR EXTRAVASATION. The intravenous administration should be accomplished slowly, no faster than 25 mg. per minute, and not to exceed 100 mg. in any single dose. In order to help avoid possible adverse effects it is recommended that hydroxyzine parenteral solution be diluted to at least 50 cc. with sterile normal saline and administered over a period of four minutes or more preferably into the tubing of a running intravenous infusion.

Contraindications: Hypersensitivity to hydroxyzine. The parenteral solution, for intramuscular or intravenous use, *must not* be injected subcutaneously or intra-arterially.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: Hydroxyzine may potentiate the action of central nervous system depressants such as narcotics and barbiturates. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine parenteral solution for intramuscular use should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration should be done to help avoid intravascular injection. On reported intravenous injection a few instances of digital gangrene have occurred distal to the injection site, considered to be due to inadvertent intra-arterial injection or possibly periarterial extravasation. WHEN HYDROXYZINE HYDROCHLORIDE PARENTERAL SOLUTION IS ADMINISTERED INTRAVENOUSLY PARTICULAR ATTENTION SHOULD BE DIRECTED TO INSURE THAT THE DRUG IS INJECTED ONLY INTO THE VEIN (INCLUDING ASPIRATION AND PROPER ANATOMICAL SITE SELECTION) TO AVOID EITHER INTRA-ARTERIAL INJECTION OR EXTRAVASATION. Intravenous administration should be accomplished slowly, no faster than 25 mg. per minute, and not to exceed 100 mg. in any single dose. In order to help avoid possible adverse effects it is recommended that hydroxyzine parenteral solution be diluted to at least 50 cc. with sterile normal saline and administered over a period of four minutes or more, preferably into the tubing of a running intravenous infusion.

The intravenous administration of this drug is not recommended for children under 12 years of age.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

When this product is given intravenously undiluted, minimal amounts of intravascular hemolysis occur at the site of injection. Giving the maximum recommended intravenous dose (100 mg.) to adults results in immediate transient hemolysis with the liberation of a total of 2-3 grams of hemoglobin, which, in some individuals, can cause small amounts of hemoglobinuria. This compares with the normal red cell destruction from which approximately 8 Gm. of hemoglobin are liberated every 24 hours. If the hydroxyzine is diluted with 50 cc. of normal saline and given during a period of four minutes or more, this phenomenon does not occur.

Supply: Vistaril (hydroxyzine pamoate) Capsules: Equivalent to 25 mg., 50 mg., 100 mg. hydroxyzine HCl. Vistaril (hydroxyzine pamoate) Oral Suspension: Equivalent to 25 mg. hydroxyzine HCl per 5 cc. teaspoonful. Vistaril (hydroxyzine HCl) Parenteral Solution: 25 mg./cc.—10 cc. vial and 50 mg./cc.—2 cc. and 10 cc. vial; Isoject,® 25 and 50 mg. per cc., 1 cc. per unit, 100 mg./2 cc. unit.

Vistaril®
HYDROXYZINE

Pfizer
LABORATORIES DIVISION
New York, N.Y. 10017

More detailed professional information available on request.

[EXHIBIT 4]

[From Behavioral Neuropsychiatry, April 1969]

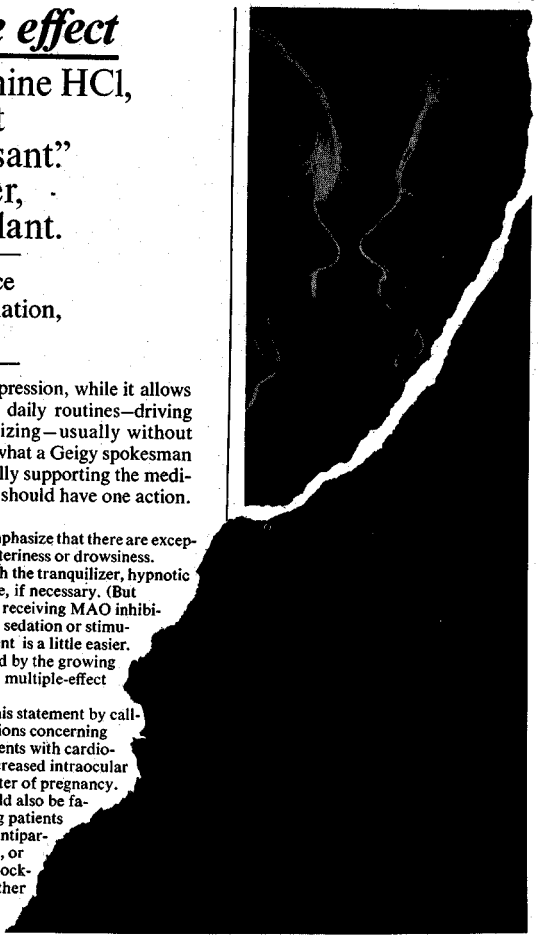
24

One drug, one effect

Tofranil®, imipramine HCl, therapeutic effect is "all antidepressant." Not a tranquilizer, not a CNS stimulant.

Surprise statement in face of trend towards combination, multiple-effect products.

— TOFRANIL can help relieve depression, while it allows most patients to go about their daily routines—driving the car, cleaning house, socializing—usually without drowsiness or jitteriness. That's what a Geigy spokesman said today, in a statement generally supporting the medical axiom that, ideally, one drug should have one action.



The Geigy spokesman was quick to emphasize that there are exceptions, patients who may experience jitteriness or drowsiness.

TOFRANIL can be used together with the tranquilizer, hypnotic or sedative of the psychiatrist's choice, if necessary. (But Tofranil is contraindicated in patients receiving MAO inhibitors.) And because there is little or no sedation or stimulation from Tofranil, dosage adjustment is a little easier.

The Geigy statement was prompted by the growing number of combination products, and multiple-effect claims for single agent preparations.

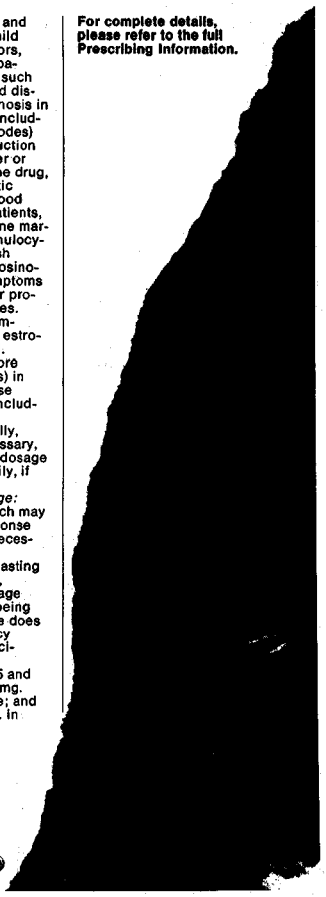
The Geigy spokesman concluded his statement by calling attention to the particular precautions concerning the use of Tofranil that pertain to patients with cardiovascular disease, hyperthyroidism, increased intraocular pressure, or who are in the first trimester of pregnancy. He pointed out that psychiatrists should also be familiar with the precautions concerning patients receiving anticholinergics (including antiparkinsonism agents), thyroid medication, or antihypertensive adrenergic neuron-blocking agents. All these precautions, together with complete prescribing details, are in the full Prescribing Information.

Tofrānil® imipramine hydrochloride

Is All Antidepressant
-Not a tranquilizer
-Not a CNS stimulant

Tofrānil®, imipramine hydrochloride
Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of this agent and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before this drug may be substituted. Initial dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, it should not be used during the first trimester of pregnancy. Cardiovascular complications, including myocardial infarction, strokes, and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy. Because of its anticholinergic effect, caution should be observed in prescribing the drug for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patients receiving thyroid medication when this compound was added to the regimen. Imipramine may block the pharmacologic activity of guanethidine and other related adrenergic neuron-blocking agents.
The drug is not recommended at the present time in patients under 12 years of age.
Adverse Reactions: Dryness of the mouth, tachycardia, constipation, disturbances of accommodation, sweating, dizziness, weight gain, urinary frequency or retention, nausea and vomiting, peripheral neuritis, mild parkinson-like syndrome, tremors, rare cases of falling in elderly patients, confusional states (with such symptoms as hallucinations and disorientation), activation of psychosis in schizophrenics and agitation (including hypomanic and manic episodes) which may require dosage reduction and/or addition of a tranquilizer or temporary discontinuation of the drug, epileptiform seizures, orthostatic hypotension and substantial blood pressure fall in hypertensive patients, purpura, transient jaundice, bone marrow depression including agranulocytosis, sensitization and skin rash including photosensitization, eosinophilia, and mild withdrawal symptoms on sudden discontinuation after prolonged treatment with high doses. Occasional hormonal effects (impotence, decreased libido, and estrogenic effects) may be observed. Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those using anticholinergic agents (including antiparkinsonism drugs).
Outpatient Adult Dosage: Initially, 75 mg. daily, increased, if necessary, to 150 or 200 mg. Maintenance dosage may be lower, 50 to 150 mg. daily, if possible.
Geriatric and Adolescent Dosage: Initially, 30 or 40 mg. daily, which may be increased according to response and tolerance. It is usually unnecessary to exceed 100 mg. daily.
A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
Availability: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg. for geriatric and adolescent use; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
(B)46-850-D

For complete details, please refer to the full Prescribing Information.



Geigy

Geigy Pharmaceuticals
Division of
Geigy Chemical Corporation
Ardsley, New York 10502

[EXHIBIT 5]

[From International Journal of Psychiatry, November 1967]

Before prescribing, please consult complete product information, a summary of which follows:
Contraindications: Infants, patients with history of convulsive disorders, glaucoma or known hypersensitivity to drug.
Warning: Not of value in the treatment of psychotic patients, and should not be employed in lieu of appropriate treatment.
Precautions: Limit dosage to smallest effective amount in elderly or debilitated patients (not more than 1 mg, one or two times daily initially) to preclude ataxia or oversedation, increasing gradually as needed or tolerated. As is true of all CNS-acting drugs, until correct maintenance dosage is established, advise patients against possibly hazardous procedures requiring complete mental alertness or physical coordination. Driving during therapy not recommended. In general, concurrent use with other psychotropic agents is not recommended. If such combination therapy is used, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, barbiturates, MAO inhibitors and other antidepressants. Advise patients against simultaneous ingestion of alcohol or other CNS depressants. Safe use in pregnancy not established. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Observe usual precautions in impaired renal or hepatic function. Periodic blood counts and liver function tests advisable in long-term use. Cease therapy gradually.
Side Effects: Side effects (usually dose-related) are fatigue, drowsiness and ataxia. Also reported: mild nausea, dizziness, blurred vision, diplopia, headache, incontinence, slurred speech, tremor and skin rash; paradoxical reactions (excitement, depression, stimulation, sleep disturbances, acute hyperexcited states, hallucinations); changes in EEG patterns during and after drug treatment. Abrupt cessation after prolonged overdosage may produce withdrawal symptoms (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating) similar to those seen with barbiturates, meprobamate and chlordiazepoxide HCl.
Dosage: *Adults:* Mild to moderate psychoneurotic reactions, 2 to 5 mg b.i.d. or t.i.d.; severe psychoneurotic reactions, 5 to 10 mg t.i.d. or q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; muscle spasm with cerebral palsy or athetosis, 2 to 10 mg t.i.d. or q.i.d. *Geriatric patients:* 1 or 2 mg/day initially, increase gradually as needed and tolerated. (See Precautions.)
Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 50 and 500.
Roche Laboratories, Division of
Hoffmann-La Roche Inc., Nutley, N.J. 07110

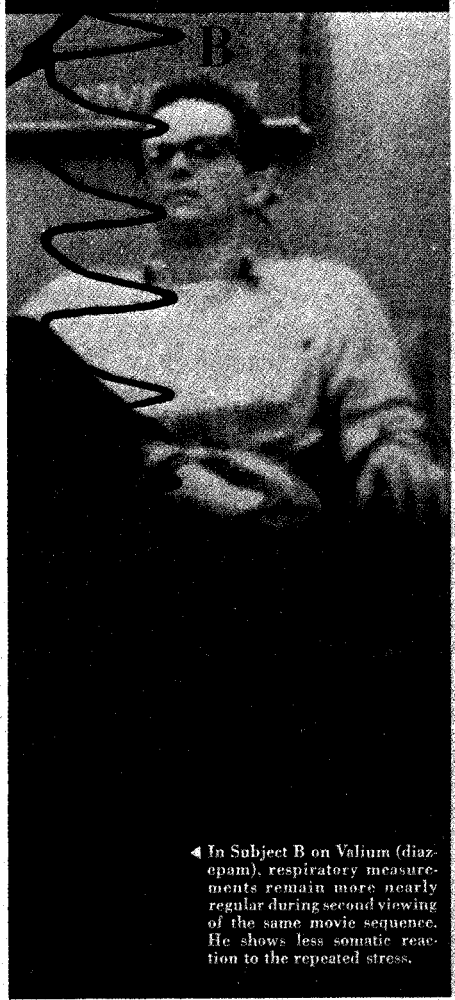
ROCHE

Both of these men are clinically diagnosed neurotic-anxious subjects...and both are facing the same laboratory-controlled stress a second time...



◀ Respiratory reactions for Subject A on placebo are very irregular during tense movie scene even during second viewing of film.

yet Subject A is overreacting to the repeated stressor... while Subject B shows less somatic reaction to the acute psychic stress.



◀ In Subject B on Valium (diazepam), respiratory measurements remain more nearly regular during second viewing of the same movie sequence. He shows less somatic reaction to the repeated stress.

Now: Valium (diazepam) effect in reducing certain somatic reactions to acute psychic stress measured quantitatively in double-blind study. Using a stress-provoking movie film, investigators at the Psychiatric and Psychosomatic Research Institute of Cedars-Sinai Medical Center in Los Angeles have demonstrated that certain somatic changes due to acute stress can be measured and statistically evaluated. In the course of these studies, nonanxious subjects appeared to *adapt* to repeated stress situations, while anxious subjects, interestingly, showed *reactivity* on second confrontation with the same stressor film. Using this difference as a yardstick, Valium (diazepam) was compared with placebo in 36 anxious subjects under double-blind control:

1. Measuring the somatic language of psychic stress. The use of "stressor films" offers a standardized and reproducible stimulus, simulating certain real-life situations in a laboratory-controlled setting. In this study, an adventure film showed four men fighting against seemingly insurmountable odds, in constant danger of death.

2. Four physiologic parameters recorded and correlated to give a composite score reflecting certain somatic manifestations of acute stress. Polygraph measurements were made simultaneously for each subject throughout the 100-minute film. These included EKG, GSR (galvanic skin resistance), respiratory excursions and finger pulse volume.

3. Objective data statistically measure certain somatic reactions to acute stress. Polygraph tracings of respiratory excursions shown at left reveal a clear difference between Valium (diazepam) and placebo response. The tracings of all four physiological parameters were quantified and analyzed statistically. After the second showing of the film one week later, analysis of the composite ANS|R scores showed a statistically significant difference (at the $t<0.001$ level) between subjects on Valium (diazepam) and those on placebo.

Of the scores for the four individual parameters measured, those for galvanic skin resistance (GSR) and respiratory excursions were statistically significant. Differences in cardiac activity and finger pulse volume were not significant. The only side effect reported was drowsiness in 13 subjects on Valium (diazepam) and in 7 on placebo.

4. The investigators concluded that in anxious-neurotic individuals Valium (diazepam) is effective in reducing certain autonomic nervous system reactions to acute stress.[1,2]

*In this text, **adaptation**, defined in psychodynamic terms, is "stimulus mastery"; **reactivity** signifies overreaction, from the norm, to a given stimulus.*

References: 1. Clemens, T. L., and Selesnick, S. T.: *Dis. Nerv. Syst.*, 28:98, 1967. 2. Selesnick, S. T., and Clemens, T. L.: From research film "Motion Picture Films in Psychosomatic Research," available from Roche Laboratories.

VALIUM®
(diazepam) Roche®

Senator NELSON. Mr. Gordon?

Mr. GORDON. Dr. Pillard, why hasn't there been more initiative on the part of the doctors to stop this type of promotion?

Dr. PILLARD. It has kind of come upon us insidiously over the years. As I say, psychopharmacology is a young field. I think many physicians now are very concerned. I think that our level of interest in this is now going to rise. Of course, there is also the possibility of such conflicts of interest—I noted with dismay that the editor of our professional journal, Dr. Francis Braceland, is also consulting editor for Medical World News. He is a distinguished physician, and I don't mean to criticize him, but I consider that a conflict of interest. Whether or not he is paid, his heart belongs to this journal, the American Journal of Psychiatry, the official journal of the American Psychiatric Association.

Senator NELSON. And what else was he?

Dr. PILLARD. Assistant editor on the editorial board of the Medical World News—the editorial advisory board.

Mr. GORDON. How can the individual doctor act along these lines? Wouldn't he have to be organized? Apparently the other organizations, the other existing medical organizations, don't seem to be doing anything about it. How do you think doctors can do this except to organize to achieve their objectives?

Dr. PILLARD. I think if they devote themselves strongly to the American Psychiatric Association or to their district medical societies something would be done. What dismays me is that we have so little voice—for example, in the American Medical Association there is no chance for the doctor even to vote on the delegates that he sends to the house of delegates. So I don't know what it is going to take to wake up those sleepwalkers.

Senator NELSON. I think you have made a number of excellent points. One of them, the objectivity of the editorial position of the magazine that is accepting drug advertising, I think, is demonstrated in a number of ways. We have not yet checked all the publications, but as was pointed out yesterday, the most comprehensive evaluation of prescription drugs ever done in the history of this country or any country was the National Academy of Sciences-National Research Council efficacy study under the 1962 statute, the Kefauver amendment. Save for the New England Journal, which is the only medical publication we have found thus far that has made a comprehensive presentation of the National Academy's recommendation on fixed combination antibiotics—they printed it in full—we noticed that the medical press simply makes reference to it. Yet, in some of these publications we find letters from doctors attacking extensively the report of the National Academy.

It seems to me that there isn't any question as to what is happening. They don't want to run criticisms of drugs which they carry in their advertising. As a matter of fact, after the National Academy made the recommendation that all these fixed combinations of antibiotics be taken off the market, the Journal of the American Medical Association has continued carrying an ad for Panalba.

It seems to me, on its face, it raises a serious question about the objectivity of the journal.

Dr. PILLARD. I think the editors are very honest and objective people as far as they can be. Dr. Inglefinger said in the symposium in Boston that he defended the practice of letting people run advertisements to present a different point of view. But I object to that. I don't see how you can inform people on page 22 and then misinform them on page 3.

Senator NELSON. I think another classic example is the drug that we went into here, chloramphenicol. All the journals were carrying ads promoting chloramphenicol. And all the testimony and all the experts said that it was being vastly misprescribed. It is clear to me, looking at the ads, that the ads simply were overwhelming vis-a-vis the editorial material that they occasionally ran—for example, an article by Dr. Dameshek in JAMA on the misuse of the drug. The fact is that it is being widely misprescribed. And it seems to me that they have the gravest responsibility, the entire medical profession in their journals and society meetings to raise the alarm about what was happening. But it didn't occur until it was given extensive publicity before this committee, and until after the FDA appeared before the committee and then sent letters to all the doctors in the country, and until there was extensive news coverage.

But it certainly raises doubts regarding the basis on which some of these drugs are being prescribed. My own conclusion is that the advertising is most effective.

Dr. PILLARD. We doctors value our independent judgment very highly. And I think one doctor may be reluctant to take editorial space to say what should or should not be done. But clearly there has to be more guidance and teaching from the senior members of the profession.

Mr. GORDON. In 1958 the Committee on Government Operations issued a report on false and misleading advertising of prescription tranquilizing drugs. It was the Blatnik subcommittee. Let me quote from it:

> The first study was made at the request of the Commissioner of Health of New York, because of the wide and indiscriminate use of these drugs outside, for the most part, of the psychiatric institutions, and because the kind and type of advertising had stimulated the use of these drugs in many, many situations where one did not think stimulation ought to point.

And then on another page, Dr. Stevenson of the University of Virginia is quoted. He says:

> Many of the advertisements for these drugs offer a strange mixture of the quasi-scientific presentation of data with a dramatic, frequently pictorial message. The word or pictures unfold a story of miserable suffering transformed into radiant happiness through, so they implied, the beneficent effect of the drugs advertised. Much of the advertising is pitched at a very low level of intelligence. It appeals directly to emotional syndromes, frequently unconscious, and bypasses the higher thought processes which should come into play in judging the effects of this drug.

Here it is 11 years later. Do you see any change in the advertising presentation of this type of drug?

Dr. PILLARD. I think the basic principle that they referred to is still operating. This is why I just don't think you can separate, as I said, the wheat from the chaff in advertising. I think that information should come from scientific presentation and scientific articles—dry as they may be to read, this is the way we learn things, not from

pictures and appeals of that sort. We go to school for years to be trained to understand these things, and this is the way we get our knowledge.

Mr. GORDON. Dr. Freedman, do you think there has been any improvement in the last 11 years?

Dr. FREEDMAN. I haven't seen any improvement. And don't forget, I am reluctant to be here, since, as chairman of the Drug Efficacy Panel on Psychiatric Drugs, we had to sit through several hundred of detailed examinations of what those package inserts claimed, and check them out. I am weary of it. There hasn't been any change. I think the only changes we have seen—and you picked it up—is that there is more compulsion to add the package insert with its contraindications and so forth printed along with the ad than there used to be.

There used to be not even that.

But—we will talk about it later—I have somewhat differing notions as to this advertising business. I think it is linked to so many different consequences. If that is correct, if we still are a competitive, free market, or whatever they want to call it, kind of society, the facts are that there is no other support for journals, no way to support the number of new journals—we have many new scientific journals in every field of science, and there are two or three or four new ones in each of the fields that you might be interested in coming out every year, or couple of years. There seems to be a need for information. If you follow the principle that where there is smoke there is fire, my question is—and I have no answer—what is this need among sub-specialists and sub-sub-specialists in the biological sciences, for more and more room to communicate their findings, and how do we confront that? And I think it is a complex question. We will need some way of underwriting the cost of all these journals—after all, students can't afford the real subscription fees, and I am not sure that academic doctors like Dr. Pillard and me can afford the fees that private practitioners can to buy the journals they want. All of these factors are involved here, and I am just saying I don't know yet how to adjudicate them.

Mr. GORDON. Dr. Freedman, you mentioned something about the free enterprise system. In the same report Dr. Harry Dowling is quoted as follows:

> But the techniques of merchandising which are familiar elsewhere have gradually taken over the field of the advertising drugs to the physician. This should not be so when we are dealing with something as important as good health, and the difference between living and dying. We are dealing with something different from shoes on the feet and trips to Bermuda.

Dr. FREEDMAN. Right, in the word "should" I agree.

Senator NELSON. Thank you very much, Dr. Pillard.

Our next witness will be Dr. Daniel Freedman, professor and chairman of the department of psychiatry, University of Chicago.

Dr. Freedman, we appreciate very much your taking the time to come here today to present your testimony on this very important subject. You will send us a biographical sketch which will be printed in the record prior to your statement.

(The document follows:)

CURRICULUM VITAE.—DANIEL X. FREEDMAN, M.D.

Born: LaFayette, Indiana, August 17, 1921; *Married:* Mary C. Neidigh, March 20, 1945. No Children. *Military Service:* 1942–1946, U.S. Army, Clinical Psychologist.

Education:

1935–1939: Lake Forest Academy and Crawfordsville High School, Indiana.
1939–42: Harvard College.
1946–47: B.A. *cum laude*, Social Relations, Harvard.
1947–51: M.D., Yale University School of Medicine (Keese Prize for Research).
1951–52: Internship: Grace-New Haven Community Hospital, Pediatrics.
1952–55: Residency: Psychiatry, Yale University School of Medicine.
1955–56: Chief Resident and Instructor, Yale University School of Medicine.
1958–66: Western New England Institute for Psychoanalysis, Graduate.

Present position:

1966—Professor and Chairman, Department of Psychiatry, the University of Chicago.
1969—Louis Block Professor of Biological Sciences, University of Chicago.

Previous positions:

1955–58: Instructor, Department of Psychiatry, Yale University School of Medicine
1958–66: Chief, Biological Sciences Section, Department of Psychiatry, Yale University; Director of Graduate Research Training Program in Psychiatry and Neurobehavioral Sciences, Yale; Attending Psychiatrist, Yale-New Haven Community Hospital; Consulting Psychiatrist: Veterans Administration Hospital, West Haven, Conn.; Fairfield Hills Hospital, Newton, Conn.; Connecticut Valley Hospital, Middletown, Conn.; Yale Psychiatric Institute.
1958–61: Assistant Professor of Psychiatry, Yale University School of Medicine
1961–64: Associate Professor of Psychiatry, Yale University School of Medicine
1964–66: Professor of Psychiatry, Yale University School of Medicine

Memberships:

Fellow: American Psychiatric Association, American College of Neuropsychopharmacology (President-Elect, 1969).
Member: Alpha Omega Alpha, American Association for the Advancement of Science, American Psychopathological Association, American Psychosomatic Society (Councillor, 1970–73), American Public Health Association, American Society for Pharmacology and Experimental Therapeutics, Chicago Psychoanalytic Society, Collegium Internationale Neuro-Psychopharmacologium (C.I.N.P.), Connecticut District APA (Counselor 1963–64), Group of the Advancement of Psychiatry, International Brain Research Organization (IBRO), New Haven-Middlesex Chapter APA (President 1965–66), Psychiatric Research Society, Sigma Xi, Society of Biological Psychiatry, Western New England Institute for Psychoanalysis, Western New England Psychoanalytic Society, Yale Medical Society (President 1962–63).

Consultantships and committees:

Past: Psychopharmacology Study Section, National Institutes of Health (1960–1965); U.S. Army Chemical Center (1965–1967); Psychopharmacology Research Training Conference, USPHS (1965); Advisory Board, Institute for Sex Research, Inc., Indiana University (1966–1968); Clinical Psychopharmacology Research Review Committee, National Institute of Mental Health (1965–1967; Chairman, 1967–1969); Panel on Psychiatric Drugs, National Academy of Sciences-National Research Council, Drug Efficacy Study (Chairman, 1966–1968); Ad Hoc Marihuana Advisory Committee, NIMH (1968).

Current: *Federal Government:* Psychotomimetic Advisory Committee, NIMH/Food & Drug Administration (1967–); National Research Council Committee on Brain Sciences (Liaison Representative—Social Science Research Council Commmittee on Biological Bases of Social Behavior); USPHS Mental Health Research Career Award Committee (Ad Hoc Member).

State and City: Connecticut State Department of Mental Health Academic Faculty (1966–); Professional Advisory Board, Mental Health Division, Chicago Board of Health (1966– ; Chairman, 1968–); The Illinois Psychiatric Advisory Council, State of Illinois (1966–); Departmental Research Committee, State of Illinois Department of Mental Health (1966–); Advisory Council, Stone-Brandel Center (1966–69); Narcotic Advisory Council, State of Illinois (1966–70).

Private: Committee on Biological Bases of Social Behavior, Social Science Research Council (1966–); Advisory Committee, Center for the Studies in Criminal Justice, University of Chicago (1967–); Board of Directors, Social Science Research Council (1967–); Board of Directors, Foundations' Fund for Research in Psychiatry (1969–72).

Editorial Advisory Boards:

Journal of Experimental Research in Personality (1965–69); Biochemical Pharmacology (1966–); Journal of Nervous and Mental Disease (1967–); The University of Chicago Press (1967–); Current Contents, Life Sciences (1968–); Communications in Behavioral Biology (1967–); Year Book of Psychiatry and Applied Mental Health (1969–).

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76. "The Psychopharmacology of Hallucinogenic Agents," *Annual Review of Medicine*, *20*:409–417, 1969, Freedman, D. X.
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84. "Psychiatric Therapies." In *Psychology Today: An Introduction*. Communications Research Machines, Inc. (in press, 1970), Freedman, D. X.

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2. *Handbook of Psychopharmacology*. Springer, 1969, edited by N. J. Giarman and D. X. Freedman.
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10. *The Borderline Syndrome*, Grinker, R., Sr., Werble, B. and Drye, R. (Eds.), (New York: Basic Books, 1968) : reviewed for *The Behavioral Science Book Service*, June 1968.

Senator NELSON. And you may present your statement however you desire, and extemporize it at any time.

STATEMENT OF DR. DANIEL X. FREEDMAN, PROFESSOR AND CHAIRMAN, DEPARTMENT OF PSYCHIATRY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

Dr. FREEDMAN. Thank you, Senator Nelson.

I think the hearings you have been holding bring into focus the consequence of advanced technology on our society. The question is whether we can take responsibility for the complexities—the mixed blessings—with which science and technology have endowed our network of health systems.

Our culture makes a distinction between the healer and the trained physician. The physician applies scientific principles in a specific instance—in the individual patient. This is the exercise of clinical judgment—a responsbility which, in its fundamentals, we cannot yet surrender to the computer. Yet, whatever trustworthiness and skill the physician delivers in his own person, both he and the patient, in fact, depend upon a wide range of resources. Weighing risks and gains, the physician "programs" a sequence of these. The components of such health systems range from educational institutions to paramedical skills, to biomedical research and technology, to a bewildering variety of information systems, as well as a number of informal and formal mechanisms establishing standards. As we examine components of this health network, we must appreciate its overall articulations; a piecemeal approach threatens unanticipated consequences to the total system.

Thus, I hope that this committee can foster a concerted review of the total drug related aspects of our health systems—with the aim of

recommending a sequence of steps leading to a reasonable adjudication of needs and resources. I would also like, before concluding, to offer two practical suggestions which could be immediately initiated without major disruption to our health systems.

Turning to the specific topic, I find the promotion of psychotropic drugs more offensive than consequential. A readily available antidote would involve programs in research and training designed to have an impact on medical practice. Advertising is an insult to the sensible practitioner who requires sound information on proven indications for a drug and an honest assessment of the general picture of the drug's safety, side effects toxicology and pharmacological rationale. More soundly referenced, rationalized and recommended dosage regimens are also useful.

But, apart from clearly proven dangers, information from pharmaceutical houses should not be legally binding on therapeutic or investigational practices. These matters are far more authentically controlled at the level of hospital and local practices. Indeed the appropriate distribution of relevant information entails far more than adequate drughouse data or compendia. It involves the fabric of formal and informal practices by which basic and continuing education in the best practice of medicine can be fostered.

Fortunately, the behavior of doctors and patients does not conform to the banal, trite, and sentimentalized fantasy world of the copywriter. Generally, both the doctor and the patient have the corrective feedback of reality. It is not that psychotropic drugs are always used sensibly and efficiently, nor that improvements in practice are not needed; rather, I see no data indicating widespread abuse of the scope that should cause undue alarm.

Self medication—properly structured (I do not refer to the TV pharmacy)—could conceivably be a useful social practice. We would still require better control of a variety of over-the-counter medications, combinations of which could be dangerous. Most societies also use drugs recreationally—for rituals of relaxation and escape from everyday reality. The most common are sedative antianxiety drugs such as alcohol, which is widely advertised. Our total attitude should be not to encourage widespread availability of stimulants and sedatives for these purposes. Nevertheless, used selectively and appropriately, the sedative antianxiety drugs can be useful to health and psychological integrity.

We should not equate unsavory advertising with the quality of pharmaceutical agents; with the value of pharmaceutical research and development; or with the significance of psychotropic drugs to public health and welfare. Similarly, commercial pressures undoubtedly have led to a wide number of "me too" compounds, which Dr. Pillard spoke about; but we must balance this against the flexibility they offer in finding the best drug for the individual patient.

On-going research may indicate that apparently similar drugs are differentially efficacious for specific clusters of symptoms in schizophrenia. There is also the luxury of selecting a drug with less side effects for a particular patient; but why individuals differ in the incidence of side effects is still unknown. We shall have to emerge from the era in which—simply for marketing advantages—industry pro-

motes similar and even identical drugs for quite different indications. It is as if one company promotes their brand of aspirin for headaches and another for fever, thereby implying that there really are specific differences. This sleight of hand fundamentally attacks the ethic underlying a scientifically informed system of medical care. I think Dr. Pillard showed examples of that.

The advent of the major tranquilizers—the anti-psychotic drugs—while not miraculous—brought a consequential step in the degree to which disabling mental disorders can be modified, and a significant impact on the extent to which effective and humane delivery of health services—called community mental health—might be organized. This does not obviate the problem of properly planning sequenced changes in our care of the mentally ill; the drugs nevertheless make such changes feasible. They also have a definite effect on preventing relapse which is of equal medical and social importance.

The so-called minor tranquilizers—the sedative anti-anxiety agents which have their greatest use in general medical practice—have probably enhanced the flexibility and efficiency through which the physician can offer effective treatment in a variety of medical contexts.

And here I would interpose, that I agree with Dr. Pillard's data on advertising these drugs for existential woes and griefs. One thing I think, what we do know in psychiatry, is that grief is very important to normal experience, and that stunted grief, stunted emotional working through of these problems, can lead to a serious psychiatric problem. In general we think in psychiatry that trying to meet the challenges, the ups and downs of life, are important to development.

In any event, in playing the game of what half dozen drugs to have on a desert island, I personally would include neither the sedative anti-anxiety drugs nor the antidepressants.

Mr. GORDON. I presume that you mean that we could get along without these. If we didn't have them, it wouldn't be a great loss, is that correct?

Dr. FREEDMAN. No, that isn't necessarily the way to put it. It depends on what you get accustomed to. In terms of, say, flexible medical practice, they are probably useful. I am just saying that if the bomb came and we had to start all over again, we can do without them.

Mr. GORDON. There is a question of priority.

Dr. FREEDMAN. I am not saying that somebody wouldn't learn how to brew, in such an awful world, how to brew something called mead or beer and use it in very much the same way that people do turn to drugs for some kind of relief.

Mr. GORDON. We have a scarcity of research resources, I think.

Dr. FREEDMAN. Yes.

Mr. GORDON. Now, from the standpoint of the welfare of our society, how far down in the scale of values would you allocate our resources—our scarce research resources into these particular fields, not from the commercial standpoint, but from the standpoint of the welfare of society.

Dr. FREEDMAN. You invite me to a nice megalomanic speculation. I never thought I could order priorities for society. Could I include TV and a few other of our luxuries?

Mr. GORDON. I am talking about how you would allocate our medical resources.

Dr. FREEDMAN. I don't know. I think we have to take this issue seriously. And in psychopharmacology I would say that one could seriously try to find drugs that, in terms of their molecular mode of action, might be more specific for certain kinds of severe, unrelenting anxiety. I think it might save you an awful lot of money that goes into psychotherapy, expensive psychotherapy, and not always effective psychotherapy. Perhaps psychosomatic disorders—public health problem—could eventually be helped. I can't throw the drugs out because they are around, you see. And this is the way with science. If it is there, you want to find out more so that you can do more with it. The major tranquilizers influence an enormous public health problem—half of our hospital beds.

So I am not willing to throw out the sedative anti-anxiety drugs as a banality. The fact that you and I both know that society can exist without them doesn't mean that either of us have assessed the cost in human suffering.

And that is all the further I can go.

A major consequence of all these drugs has been the astonishing advance in data on the chemical systems which regulate brain functions. With the support of the National Institutes with their programs in psychopharmacology and biobehavioral sciences, there have been genuinely new thrusts in psychiatry. Behavior cannot be explained solely by chemistry, but we are far readier to know what part hormones and chemicals may play in disordered behavior and when in a given disorder changes in brain chemistry may be important. Such data takes years to develop but can provide elegant control over the body's molecular systems and the possibility for a rational design of new molecular approaches, as well as understanding disease mechanisms. Such basic pharmacological research has been advanced in our field. Research has also been initiated into the causes of mental disorders and into more precise means of identifying different subpopulations of patients for whom such drugs might be specific.

If I could turn to the need for researchers, I would point out that the consequence has been an armamentarium of research techniques and a small cadre of knowledgeable experts who are advancing the edge of knowledge. This entails an interplay between research and its application, between laboratories and the clinic. It is exactly this interplay which leads to ever-increasing precision in treatment. Each study builds upon the next, leading, often slowly, but inexorably, to the goal of the right drug to be used rationally at the right time in the course of a mental disorder occurring in a specific person.

This not only takes time but an appropriate environment and something more than a medical degree. It requires the skill developed over the last 30 years in the general area of clinical investigations. With psychotropic drugs, it also involves the analysis of behavior and related social systems.

This area is known as clinical pharmacology and clinical psychopharmacology, which is intrinsically coupled to its basic research. This cadre of researchers is small and entirely inadequate to our needs.

There is no certainty that they can breed a larger generation of investigators needed to control man's bodily disfunctions and psychological disorganizations.

Basic and clinical researchers must not be working in total isolation either from each other or the scenes of education and clinical inquiry. If, so to speak, we wish to land a man on the brain—to have available the technology and know-how which could improve and safeguard our mental health—we will surely need firm and steady support. This, in turn, means a new appreciation of the vast range of activities which—together—make modern public health possible.

We are approaching a crisis in our approach to health systems in our concern about their faults. There is, for example, humanely justified clamor that we should focus on the application of medical expertise in order to deliver equally and cheaply the very best of medical practice for each and every citizen. Yet, we are all too likely to promise—not more than we can deliver—but more than we know how to deliver, and hence to stumble into cycles of confusion. To know how means to try—and to systematically evaluate—and that means research which is surely being devalued in the press for action. If we wish to strive for quality, we will have to organize to do so and take many small steps—to make a giant leap.

In every sector of our social life we see dismay with the complexities, with the disarticulated systems which have resulted in urban chaos, threaten the balance of population and food; and attack those institutions and heritages which bind and mark us as a civilized culture. As specialization grows, each of us becomes poignantly dependent on some other party who is essential to our life scheme—whether they are plumbers or scientists. A patient surrenders his fate to the expert with whom he collaborates in the "doctor patient relationship" only by exercising belief based on justified trust. Yet, as every segment of our society appears increasingly to fragment into selfish groups clamoring for recognition and power, the very vehicles of trust—traditions and values—have lost validity in establishing the basic rules of conduct. In a general retreat from complexity—in an understandable demand for relevance—the expert and the establishment have been equated and devalued.

We demand rather than inquire, and impose rather than negotiate. If we indict, rather than investigate, we may well further undermine the very roots of trust which make our social practices—if not satisfactory—at least barely tolerable.

My point is that those who seek information about psychoactive drugs must be prepared to search through a complex of facts; to not hear ready answers; to not be satisfied either with hastily publicized findings or hastily legislated solutions. We need only call to your attention the current flurry of drug abuse bills, some good and some bad, which are being pressed in these very halls.

So, the crisis is a matter of general trust and depreciation of inquiry. As applied to drugs and the health network, our only hope is to use our heads—our best heads—and after a review, to come up with a sequence of plans and programs which may have a chance of helping us to live with the consequences of technology and the problems of pharmaceutical industry and medical practice.

Accordingly, I suggest a blue ribbon panel, tapping men of good will and expertise from the various involved sectors, engaging in a 2-year commission or, preferably, by the National Academy of Sciences. Such a group would have to commission studies which could document clearly the variety of ways by which new drugs are developed with actual case histories. The Commission should explore: the imbalance between our almost infinite capacity to synthesize molecules and our restricted means of testing them.

Senator NELSON. What are you referring to as to the restricted means for testing them?

Dr. FREEDMAN. Two things. One is, there simply are not enough clinical investigators to take molecules that might be interesting or important and study them in man. It is the whole question of how you develop a drug before you get it to man. But behind that is the more important question to which I don't know the answer. If we can synthesize any number of molecules, it is insane to believe that we could or should test them all. The question is which ones do you test.

Senator NELSON. Why synthesize any if you don't test them?

Dr. FREEDMAN. First of all, you could test them in animals, or you could follow a hypothesis and say, this molecule looks interesting, it has certain effects in a biological system. Now, if we changed it and made it look something like a related molecule that had other effects and we linked them together, would this do something? If you are lucky and you know that this molecule affects a specific enzyme system, you think that enzyme system is related to disease, or you know it is, then you have a rational way of devising molecules aimed at a sequence of enzymes that might lead to change what happens in diseases. You test this in a variety of infrahuman biological systems.

Some of them may be toxic. And some won't get absorbed into the organ you want them to go into. So you have this capacity to make more potential drugs than you could possibly test in man. And, in between, you have to have the judgment of what drugs are worth testing, and on what basis. And I am saying case histories of what would be useful.

Senator NELSON. When you say testing, you are talking about drug testing?

Dr. FREEDMAN. Eventually you have to test them in man.

Senator NELSON. You are referring to that kind of testing, not some kind of laboratory testing?

Dr. FREEDMAN. Both. I am talking about the many steps before bringing the drug finally to man. And I have always been puzzled as to how people decide when to and why to.

Senator NELSON. Of course, that aspect of the drug industry which involves the company is one thing. NIH may be doing a test for one reason, and a scientist in his own university may be doing it for another reason, may he not?

Dr. FREEDMAN. Correct.

Senator NELSON. What about the present method of testing drugs by the companies? The issue of the adequacy of the present method of drug testing has been raised here many times—the fact that all testing presently rests with the control or management of the company seeking to market the drug. As a matter of fact, we are today introducing legis-

lation to provide for the establishment of a national drug testing and evaluation center which would be operated and maintained as a part of the FDA. You may have read the article in the New York Times yesterday——

Dr. FREEDMAN. The Times comes to Chicago a day late. Sorry.

Senator NELSON. I would commend it to your attention. It is a very long, detailed article involving this particular matter. But in any event, I wanted to ask you what your viewpoint was about the current method of testing and producing IND's and developing the drug?

Dr. FREEDMAN. I think it is confusing to everybody. One of the problems is adequate clinical investigators, adequate staff, and adequate adjudication of what that drug needs to have before it can get an IND. I would not want to be sitting in FDA deciding that. That is why I am proposing here that we really do some case histories involving the parties involved and find out how to make this process work more efficiently and smoothly. For example, there is no question in my mind that for psychotropic drugs it is hard to get new populations of patients to try these drugs.

It is a very difficult matter to get a drug to test. I wouldn't want to see any drug tested that was a "me too" drug—I would want to see something revolutionary and new. My question is, If you had something new and you had a good hunch, what would you have to go through and what would it cost? If you are a pharmaceutical researcher—and he is supported by the marketing and other departments—you are in fact working with fellow researchers, and you think they have discovered something, and you have at great expense tested it out in chemical tests and in animals; what does it now cost also to try that in man? What does it cost in terms of redtape, what does it cost in terms of very careful and honest adjudication of the safety of putting it ahead into clinical tests, let alone who tests it. That represents, as you have shown in testimony here, a maze of problems—including the choice of who tests it. How do you underwrite its financial support, and so forth? Over the years I have run into different segments (and different views) of this whole network of the drug establishment—I now really think people have got to sit down and iron this out. I don't know if they can come up with solutions for everything. But they have got to present the problems and see—if you play the role of a regulator, and I play the role of a manufacturer, and we turned it back and forth for a while, could we come out with some sensible solutions?

As it is right now, there is a great deal of discouragement, because most of the rules have been laid down by law and have not really been generated out of the interplay of real events. And that is what I am urging upon us. I think it can be done, and I think people want to do it in all these sectors of the drug "establishment," or preferably—the "drug network."

I never knew until a few years ago, when I consulted with one or two drug houses, how substantively you do develop a drug. So in all my medical education I never had any course on the development of a drug. I knew how Fleming approached penicillin. And there are some other romances. My ignorance cannot be unique.

Senator NELSON. He developed it by accident.

Dr. FREEDMAN. Right. I am sure a lot of that happens. That is what I am after. I am pointing really to the fact that I can't give you a balanced judgment. I just get tachistoscopic, partial view. You talk to pharmaceutical researchers and meet them at a society, and you hear them arguing about a new drug. I think we have got to hear from all these parties, and they have to hear from each other. And I think it would take a couple of years. I don't know of a scientific study (as in the Annals of Medicine of the New Yorker) a *real* account of what happens when you synthesize a molecule and then you have a hunch it might turn out to be a medically valuable drug. What are the sequences? What are the costs. And ultimately, what are the values?

Certainly in cancer chemotherapy I think you will find the network of drug practices related between the NIH and industry quite different than you would in another field.

Senator NELSON. We intended to have extensive hearings on exactly that point, examining all the sources of information of the companies, the scientists and all the rest, the FDA, what is the best method of approach, or how we can improve the current method. But you have to conclude the control tests at some stage, and then you have to put the drug on the market. You may find out after 10 years that it doesn't do what you wanted it to do, or that the side effects are more damaging than was thought, but you may not find that out until it is widely used in practice and you discover something about it that you could never discover in a well-controlled scientific test in any event.

Dr. FREEDMAN. This too can happen. That is why I would like to have documented case histories of drugs. And we can reach back in some fields, obviously, into the forties and fifties, and see if we can draw any general conclusions about this. I really don't know. It is not always just a matter of pure fate and chance. Some drugs have a certain logic and rationale behind them, and others don't. I have always insisted—I have talked to youngsters about LSD—I point out that you never know, it may take 20 years before you may find out certain things about certain drugs. Of course, this has led to strongly held viewpoints that we simply shouldn' have all these drugs; we should stop the whole operation of new drugs. And again, one could play that game. Let's figure it out; should we stop? And I would say, well, no. But if not, how do you sustain the expertise at the basic level of drug development? How do you sustain the expertise in clinical testing?

Do we need it?

And all this, I think, could be confronted. I would follow with interest the testimony you get here. I simply think that it is not going to be enough. I think the involved people are going to have to argue it out and arrange it into a very serious report. I don't know of such a report involving these various parties, not as self-interested parties, now, but saying: "Look, we have a serious national problem." It is correct that Congress play a role occasionally when the citizens themselves can do nothing, but I think we had better get the scientists and involved parties and the citizenry together on a panel that must work this out. This would represent just the evaluated information that you and I don't now have. Everybody has his own particular experience, bias, and anecdote. And that for me isn't enough.

Well, I did add in my meager remarks that I thought that the question of whether we should develop unprofitable compounds ought to be approached; what is the cost of that to society? And I think that any documentations and studies coming out of this blue ribbon commission should involve persons who had authentic knowledge and responsibility for the various steps along the line from drug development to patient care if we really wish to be informed rather than preached at. And by that I mean I really want to know from real experts. I have seen cases where a statement was not permitted, say, in a drug advertisement for a patient suffering from psoriasis. But the doctor who passed on that, the official of the FDA who passed on that, had never treated psoriasis—he had read it, but he didn't know really what happens to such a patient.

So to adjudicate these matters we want people—and they are easily available—who know something in the way of personal responsibility, personal experience, personal competence, and the areas that they are involved in. If we hear from drug houses—I would like to hear from very good researchers in drug houses who have been there for a while and have seen a lot happen.

Senator NELSON. Doesn't the experience of the NAS–NRC indicate a formula for bringing this kind of expertise to bear on the question of efficacy and relative efficacy and on the question of IND's?

Dr. FREEDMAN. Yes. I will tell you, somebody remarked that they didn't see any explicit statement in the psychiatric drug panel. My reason for not doing that is that I wanted to enlarge the community of people participating in that; that is, I wanted to see more experts that could have been tapped for that particular study, take a look at this problem. And through the American College of Neuropsychopharmacology that is being done. And I think that is a useful education for all of us too, to spread the network of involved people.

Senator NELSON. You were chairman of the NAS–NRC panel. What was the title of the panel?

Dr. FREEDMAN. "Psychiatric Drugs."

Senator NELSON. And your panel hasn't reported?

Dr. FREEDMAN. Oh, we reported. We simply made no general public statement as yet, because I would like to see more people participate in that.

Senator NELSON. So you haven't completed your recommendations yet?

Dr. FREEDMAN. Oh, yes. Each drug has been recommended. And we ourselves, for the FDA, have spoken to certain characteristic problems. We haven't published it as a white paper as yet.

Senator NELSON. So it has not been made public as of this date, is that what you are saying?

Dr. FREEDMAN. Any comments that we made to the FDA have not been extracted and put together as a paper. This is being done by many members of that panel now in collaboration with others who were not on the panel. So I think by November or December you will see something.

Senator NELSON. When the 1962 law was passed and it was decided that they would use the NAS–NRC to do the efficacy evaluations, what

is your view of this approach to this particular problem? In other words, is there a better way, or is this a good way?

Dr. FREEDMAN. It is an incomplete way. What is now needed—and I think there is a movement afoot—if we are concerned about efficacy, is further work on the criteria by which you establish efficacy. And once we do that, there will be an impact. Somebody out there is making drugs and needs to test them. Do they have the appropriate guidelines of what they need to do, from cost accounting to specialized personnel, to safeguards for clinical testing, the whole gamut—do they know how to proceed? Do the Government officials in FDA know precisely what to require, now that we have begun to look at criteria for efficacy?

Senator NELSON. You are talking about——

Dr. FREEDMAN. The consequences of beginning to make that a legal requirement.

Senator NELSON. Do I correctly understand that the requirement that was laid down with respect to the various panels of NAS–NRC was that there had to be presented well-controlled scientific studies that supported the claim for the drug?

Dr. FREEDMAN. Each claim, exactly.

Senator NELSON. Then in addition to that, do I understand correctly that the individual understanding, expertise and experience of the panel members was brought to bear on the question also?

Dr. FREEDMAN. Exactly. And they could call on any consultants outside the room that they wanted to represent either that or any other kind of expertise, correct.

Senator NELSON. And if a drug was not supported by an adequately controlled scientific test, it failed at that point forthwith, didn't it?

Dr. FREEDMAN. It certainly did.

Senator NELSON. Have you been raising the question as to whether or not the so-called well-controlled scientific tests are themselves adequate.

Dr. FREEDMAN. Yes. They have to be developed. In some areas they are adequate, they will be improved. In others we need improvement. You run into some problems that you don't know how to adjudicate in terms of objective tests. You run into the problem that there are in fact different modes of practice and you finally run into the business of regulating it. I think we did a good job; it was an awful job to have to do, because it is very hard to be the official person saying that this is veritably the truth. You can't program drug use, is what I am trying to say. So occasionally you will come into differences of opinion. And that was accommodated for in the study; you have a minority report and a majority report. I don't think our panel ran into that—we almost did once or twice, but we came to agreement. But you worry about being the arbiters of medical practice and patterns of medical practice. You don't know how the FDA is going to use your material.

Nor do we know if what we say is going to have standing in court. And all of this is what I mean by the health network. What statements of public bodies do indeed have adjudicative validity and will be used—or misused—as such in individual instances, such as malpractice suits or other kinds of instances? One should be very, very careful, as to the burden of an objective scrutiny of the data and assertions

about the state of the art as it is, if it has that kind of official stamp.

But that aside, the real issue of the 1962 act was, what guidelines do you need if you are going to develop a drug.

For drug efficacy, we have arrived at some notion of what the situation is at the moment for testing, for objective data, and for claims. But if somebody is developing a drug, what is it that they have to do? And this we haven't said. Criteria will and should shift with new knowledge.

And so it is in limbo. The drug house has to guess, or should have passionate people there that want to know all the facts or know how to develop them. But they had better have understanding when they come to FDA. And FDA has to be protected. That is, the people there may make an error. If they have so to function that they must never make an error, they may never make a ruling.

Senator NELSON. That happens in some bureaucracies.

Dr. FREEDMAN. Yes, sir.

Mr. DUFFY. Doctor, if I may interrupt you just a moment, I am curious and would like to explore a little bit into your comments, about the use of these NAS-NRC studies and your concern as to how they may effect future court actions, and so on. Are you in essence saying that perhaps regulation may interfere with the practice of one's profession and the ability to innovate in that practice?

Dr. FREEDMAN. You have said it. I tried to indicate what medical practice intrinsically was, without giving you a boring professional lecture on how in fact the physician operates with flexibility and innovation with certain drugs and with certain therapies. This was always a question during the drug efficacy review. Nobody knew whether this would be interfered with or not. And some of us asked that the FDA be sure to take our work as advisory. The burden was on them; here is the best we could come up with. And I assure you that we were highly critical. But we wanted to know what use will others make of what we say.

Mr. GORDON. Doctor, may I interrupt you. You are not saying, are you, that there is no such thing as a concept of good medical practice or bad medical practice?

Dr. FREEDMAN. In fact I am saying just that. There is a good medical practice. But you cannot arbitrarily legislate in good medical practice—I have seen revered teachers argue about the appropriate treatment of diabetes. The argument was instructive.

Mr. GORDON. Instructive?

Dr. FREEDMAN. Instructive. But you cannot program—you cannot make rules without reason—reasoning is more important than rule. I don't want to be the doctor telling people how they must use psychotropic drugs. I will tell them why I think they must use it in this way. And I would like to join an argument and a good scientific debate and see what we can learn. That is what good medical practice is all about.

But it means that there is a limit on the extent to which you can program what has to be done. Science works by improved consent among peers—not by fiat.

Now, if you have flaccid medical control and flaccid medical constraints and lack of initiative by isolated medical bodies on any one of these issues that you have looked at, then somebody has got to push

them to paying attention to things. This is exactly what is happening here in advertising. My point is that I think medical educators, scientists, industry, bureaucrats, legal and economic people, ought to get together and look at our health system as it is related to drugs. They ought to be encouraged to.

The other way to do it is to legislate components—and if you do that I don't know that you will always anticipate the consequences—like the consequences of the Kefauver Act certainly are that we are going to have to work together to develop guidelines as to what are the criteria for developing a drug. And if there were an expert that you could turn to and say, this man has been doing guidelines for 800 years (the pharmaceutical old man in the cave), and he could really tell you how to do it, fine. But that is not the name of the game.

Mr. GORDON. To be more specific, can you tell us how you came out with respect to the efficacy problem of the NAS-NRC report? Did you find many drugs that are inefficacious and shouldn't be on the market?

Dr. FREEDMAN. We found a good number. Most of them we found ineffective weren't marketed or aren't selling any more. These were drugs that came out since 1938. You see, you had various ratings from "effective," to "possibly effective," which puts the burden on the drug house. They now at some point are going to have to make that "possible," a "probable," or "effective." But in order to do that they have to do studies. I don't know that anybody has told them how costly it will be and how many drug trials they will have to do. If a number of "me-too" drugs fell into that category you would think a smart drug house would drop them.

Mr. GORDON. The statute calls for substantial evidence of efficacy, not "probable" or "possible" efficacy.

Dr. FREEDMAN. They have to be rated. And then it is up to FDA as to what they want to say to the drug companies as to what to do about that rating. Some very good drugs would need very little in the way of objective data to make them absolutely clean for the cleaned up claims we said they could claim.

Mr. GORDON. But you did find quite a few that were not effective?

Dr. FREEDMAN. We found quite a few that weren't in the "effective" category, quite a few that were "probably effective," and a large number that were "possibly."

Senator NELSON. Your ratings were "effective," "probably effective," and "possible effective"; is that correct?

Dr. FREEDMAN. The ratings were "effective," the second rating was "effective but." The drug is effective but; if the manufacturer's claim would remove this adjective, then it would be a clean statement. A third would be "probably effective." The bulk of evidence so far, so far as you can tell, certainly from the bulk of clinical practice, means that this is probably effective, but there are deficiencies in terms of objective studies.

Senator NELSON. When you reach the probably effective category, the FDA will make the judgment as to whether they will be required to submit additional controlled studies to prove effectiveness?

Dr. FREEDMAN. Right. But how all those things are going to be adjudicated I don't know. But, however it is done, there absolutely will be consequences for the whole health community.

I am repeating myself.

I might say that the healthy impact of this is that it will promote more research; people are going to have to investigate.

I think there is a problem of information dispersal that such a blue ribbon commission ought to look at. The uses of modern technology from TV to computers could be applied to these information problems. And I refer to doctors who are practicing. What kind of information do they really want? A doctor is in a small town, and there is a major medical center nearby. Has he any way other than one of those annual meetings (where I get up and lecture on psychotropic drugs and he meets me after the meeting to talk a little bit) has he any way to pick up the phone and say—as my friends do—I have a patient; here is the problem; how about a consultation? Which you can do informally with a friend.

Maybe these practices ought to be encouraged. And maybe they ought to be linked with our movements such as heart, cancer, and stroke centers. And maybe none of these things will be linked if you look at the whole public health picture and the bewildering variety of proposals. Our aim is the delivery of our specialties and our training and our consultation finally to the patient—but the articulation of these systems looks very chaotic to most of us at this juncture.

Put it this way, Senator, It is very hard to plan today if you are chairman of a department or dean of a medical school or faculty of a medical school trying to look ahead.

Since drugs teach us about disease and health, how should research into pharmacology and toxicology be advanced? And here I refer to the fact there are many toxicological problems. I am not at all convinced—I ran into most of these with LSD—but I am not at all convinced that the NIH is really equipped to knowledgeably fund the kind of toxicological studies the public seems to be interested in; somebody could look into that in any event.

What are our manpower needs in the entire chain from basic investigation to clinical practice? How can the development and use of pharmaceuticals be taught, inserted into high school science curriculums?

We are often asked to save our children from all of these street drugs. But if you look at high school science studies, the basics of pharmacology, even the history of penicillin is usually not there.

The whole problem of fads in our society are not taught in social science courses. Well, fads and drugs are very closely linked.

What curricular revolutions will we need in higher education without sacrificing quality in order to produce manpower? That means something has to be funded. If you want to try a different kind of medical education, that will be very expensive; but a block of money could fund it. We might see what a really inventive program of medical training could do. It is the most expensive training the world has ever known. And it gets longer and longer. And there should be some creative way of making it shorter. We are not going to find out soon enough to satisfy most of us who are interested unless we can fully fund a few major revolutionary studies in medical education.

All of this could be to the ultimate good of what bills are often passed for, namely, delivering services "now."

So I don't suggest we solely surrender the moment to a blue ribbon commission. An increase of funds to the NIMH psychopharmacology branch ought to be made available. This is a body of existing experts. They are organized to work together, which is an asset. And they can launch and underwrite programs of training and continuing education in psychotropic drugs directed both to the general practitioner and our medical institutions.

They should continue research on how practitioners in fact use drugs and how drugs are abused. The practitioner is not hapless or helpless; he can and should be involved in ongoing research in collaboration with experts, studying drug efficacy, as well as identifying the appropriate occasion and subpopulations for specific drug regimens. The scene should be in Washington and in those regional centers in which research and education must be visible for knowledge to advance. Support of varied and advanced careers in clinical and basic psychopharmacology and the essential laboratory equipment is also desirable. The NIH programs in clinical pharmacology could also be strengthened.

These are useful interim measures to offset current budgetary cutbacks and organizational problems. But if you ask, why could not such programs have been launched before? The answer is I believe, the increasingly shortsighted attacks over the past 6 years which can be simply translated: "we have enough research and enough investigators—let's put them to work." As if they were not working! At the same time, it is precisely research which critics call for whether they are concerned with the student abuse of drugs or with solutions for health delivery problems.

We cannot have it both ways. We do not have enough research, enough investigators, enough skilled personnel to teach and to generate a pattern of practice which could halfway deliver on the promises of quality for everyone. The need for medical manpower and applied technologies cannot be divorced from quality research and education. It is organic to the process of learning that "telling" is not enough; knowing and demonstrating better clinical practices by the researchers who value the attitude of inquiry are all important to medical practice and medical training.

I wonder if the Congress recognizes that the biological sciences in this country have advanced as perhaps nowhere else in history and have done so through the aid of the National Institutes. Our scientific community has had confidence in such agencies. The reason is that, during the 1950's, the grant givers and grant getters were continuously educating each other. Accordingly, policies tended to be in tune with the needs, and research and education was knowledgeably fostered. While there are complex issues in Federal underwriting of biomedical research and training, the facts are that many medical schools are on the brink of financial disaster. The most frequent solution is an invitation to become mass factories for the production of quality [sic] physicians.

These inconsistent goals and responses reflect the potential chaos facing the very guts of our health systems. Recent executive orders to the Department of Health, Education, and Welfare threaten to politicize the very scientific review procedures (by politically reviewed appointments to study groups) which, in the past, generated confidence in

government. Yet the potential still exists to advance psychopharmacology and clinical pharmacology if our Government is truly concerned about drug use and abuse.

The second area for immediate action might be a more creative relationship between the Food and Drug Administration with industry and the health sciences. Government employees cannot function wisely or effectively if they face misunderstandings or hysteria at every turn. Our expectations of this agency should be tempered so its officers can function in a real world rather than undertake the impossible roles which are frequently thrust upon them. I mean simply some understanding and restraint upon the part of government and the public in the extent to which they believe legal regulations can be the sole instrument in underwriting the quality and integrity of health practices or the avoiding of error. If the appropriate practice of medicine requires flexibility, then we cannot program regulations to the nth degree; many new and useful drugs could be lost by scientifically useless regulations.

FDA has recently received help from the drug efficacy study conducted by the NAS–NRC. Standards of medical practice should not be the primary function of either body. However, some kind of similar review and collaboration could continue in order to help establish guidelines and criteria for the testing of new drugs. To this end we should encourage constructive collaboration between industry, medicine, science, and FDA. Given the shortage of manpower, research sponsored by FDA might require closer collaboration, in terms of scientific review, between that agency and the national institutes.

And here it is my experience that in government they always say, "leave it to us, we will collaborate with each other." And I know what they mean. I too prefer informal relationships. But if you are in government you had better have the funds that are necessary for the informal collaboration, which means the top bosses of two agencies—or their super bosses in HEW had better agree.

In all these proposals we should appreciate the role of constraints which—however imperfect—do operate in our health systems—from the standards of the physician and his colleagues and hospital, to those of his local societies and governments. With help, our various medical journals, for example, can put constraints on advertising. Today, clinical investigations of drugs are increasingly undertaken in supervised settings which are subject to internal as well as external review. The best constraints, of course, derive from a not always evident "medical ethic" which should rest on humane compassion and regard for the rules of the scientific method. If organized medicine, the public, industry, and government should subscribe to these values—and act—all could gain. But I see little time left for hesitation.

Senator NELSON. Thank you very much, Doctor, for your fine presentation.

Mr. DUFFY. I just have one question. I noted on page 9 of your statement that you left out a sentence. Perhaps I could just ask you to clarify it for me. You say here:

We must be somewhat careful of impatiently demanding instant application of findings which, in fact, may not exist and which—in the absence of serious and sustained support a basic inquiry—may never exist.

I am a little puzzled by that.

Dr. FREEDMAN. You are sharp. I took that out of context from a paper I was writing on LSD abuse. And it is time to find out a lot. Some very good medical journals wrote editorials about "findings" of chromosomal damage which have been used to back up, I think, some very stupid bills on drug abuse. But if you establish genuine scientific criteria, all you can say is, gee, that is interesting. And maybe in 10 years we will know whether there is or isn't such damage; whether it is or isn't significant to health and reproduction—if truly scientific research is wanted and funded. As a doctor I am perfectly aware that a drug may have unanticipated consequences. So you weigh risks and gains. And so by scientific "findings"—I mean scientists and journalists can use their findings politically.

I don't want to be permitted to play God, and that tendency is what I am leery of. And I am pointing out that just because a report is in a good journal doesn't mean that it also carries biblical weight.

There is no substitute for data, for inquiry, and perspective. And science is full of the history of violent controversies and opinions. So I am simply saying, just because somebody gives you a scientific-looking paper, that isn't enough. You have to adjudicate; you have to find it out, you have to have a company of peers and equals who look at your data and may say yes or disagree or point to unanswered questions or unjustified premises.

Senator NELSON. I take it in speaking of LSD it is just accidental that you used the word "leery"?

Dr. FREEDMAN. Yes; I tripped up on that one, sorry.

Senator NELSON. I want to thank both of you for excellent presentations and very valuable contributions to the hearing record. We appreciate your taking the time to come here today.

We will now recess until next Thursday, August 7, at 9:30 o'clock.

(Whereupon, at 11:45 a.m., the subcommittee was adjourned, to reconvene at 9:30 a.m., Thursday, August 7, 1969.) [1]

[1] Testimony for Aug. 7, 1969, appears in pt. 14.

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

MONDAY, OCTOBER 27, 1969

UNITED STATES SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:05 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee), presiding.

Present: Senators Nelson, Javits, and Dole.

Also present: Chester H. Smith, staff director and general counsel; Benjamin Gordon, staff economist; Elaine C. Dye, clerical assistant; and James P. Duffy III, minority counsel.

Senator NELSON. The subcommittee will open its hearings. We are pleased today to welcome Dr. Margaret Mead. Senator Javits, Dr. Mead is a very distinguished constituent of yours, and I know that you wish to welcome her here today.

Senator JAVITS. Thank you, Mr. Chairman.

I just wish to note that we all know Dr. Mead as one of the most distinguished anthropologists in our country. New York has a very special interest in Dr. Mead as she is, I just wish to spread this on the record, the curator emeritus of ethnology, the Museum of Natural History which is in New York City. She is adjunct professor of anthropology at Columbia also of New York City, and chairman of the Department of Social Sciences at Fordham also New York City, and we naturally take great pride in her eminence and the tremendous contribution she makes to the Nation and the world through her scientific work in these very distinguished institutions. Thank you, Mr. Chairman.

Senator NELSON. Thank you, Senator Javits.

The committee welcomes you here today, Dr. Mead.

The question has been raised before this subcommittee by medical authorities that psychotropic drugs and especially tranquilizers are being overprescribed.

Dr. Fritz Freyhan of St. Vincent's Hospital of New York stated before this subcommittee that:

> It is, of course, no secret that overuse of drugs, not just psychoactive drugs, represents a perplexing problem in contemporary medicine. Depending on orientation, bias and vested-interests, the blame tends to be ascribed to our culture, to professional attitudes and to the promotional influence of the commercial interests of the pharmaceutical industry.

The highly authorative Medical Letter of October 3, 1969, in discussing two well-known tranquilizers stated that:

> . . . there are no reliable figures on the number that do take them, but it is known that few drugs of any class are prescribed more often. Many drugs are vastly over-prescribed and that a great number of persons are being led into unhealthy and costly drug dependence by physicians' too ready acceptance of the therapeutic advice given by a not-disinterested manufacturer.

Dr. Richard Pillard of Boston University stated that he sees advertising of these drugs as:

> . . . part of a trend to suggest the use, both of antidepressants and tranquilizers not only for specific mental illness, but to soothe life's ordinary woes.

He also asks the question whether it is healthy "for people to be reacting to or chemically protected from those emotions which are an inevitable part of a full and normal life."

Dr. Daniel Freedman of the University of Chicago told the subcommittee:

> One thing, I think, we do know in psychiatry is that grief is very important to normal experience, and that stunted emotional working through of these problems, can lead to a serious psychiatric problem. In general we think in psychiatry that trying to meet the challenges, the ups and downs of life, are important to development.

These are opinions of the possible effect of widespread use of psychotropic drugs on individuals. But how about the effect on our society and on our culture? Is there anything we can learn from the past or is this a new phenomenon?

I am sure that Dr. Mead, the world renowned anthropologist and student of comparative cultures, will make an important contribution to our thinking in this field.

Dr. Mead, we are very pleased that you have been willing to take the time from your very busy schedule to come down here and discuss your ideas about the area of interest in which this committee is now conducting hearings. Your statement, which is entitled "Excerpts From Testimony," will be printed in the record. You may proceed to make your observations by reading it or speaking extemporaneously, however you desire.

STATEMENT OF MARGARET MEAD, CURATOR EMERITUS OF ETHNOLOGY, THE AMERICAN MUSEUM OF NATURAL HISTORY AND ADJUNCT PROFESSOR OF ANTHROPOLOGY, COLUMBIA UNIVERSITY

Dr. MEAD. Well, Mr. Senator, I will state very briefly some of my specific competencies to talk about this problem. I have been for several years visiting professor of anthropology in the school of psychiatry at the Menninger Foundation, and I have been for the last 10 years, visiting professor of anthropology in the department of psychiatry of the University of Cincinnati College of Medicine, so I have been working quite closely with medical departments that were concerned with drugs, and specifically with the use of psychotropic drugs. I was president of the World Federation for Mental Health in 1956, and I was a member for 7 years of the group who evaluated research for the

National Institute of Mental Health. During World War II, as secretary of the Committee on Food Habits of the National Research Council, I developed the relationship between the human sciences and the field of nutrition. I have also had some experience with the field of the specific traning given to detail men, by pharmaceutical companies, and with the relationship between Government and industrial practice as chairman, 1967–69, of the Committee on Science in the Promotion of Human Welfare of the American Association for the Advance of Science, and as a member of the board of directors of the Scientists' Institute for Public Information.

Specifically, I have combined intensive anthropological research in eight different primitive cultures, with the study of our own culture, and I am assuming you have asked me here not to give detailed opinions about particular drugs, for instance, but to try to place the use of psychotropic drugs within the wider context of our society.

Senator NELSON. Yes.

Dr. MEAD. I think that our concern about psychotropic drugs, although it is part of our concern about any overuse—whether it is overuse that affects health or overuse that affects the budget of the consumer who has a limited amount of money to spend—crosses a great many other elements in our culture.

You will notice that in those excerpts that you read from previous testimony, what people were talking about were primarily moral problems, and moral problems related to health rather than specific side affects that affected, say, some organ of the body in a disadvantageous way. The overuse in addition to all the points that you have stressed here, disproportionate use of particular prescription drugs, is being questioned in terms of our moral and religious tradition and it has to be understood within this context.

If we look at the Christian tradition from which this country originally arose, we have two lines. We have the Roman Catholic tradition, and also Middle Eastern religions, this was a tradition of monasticism in which a few people did the abstaining for the entire community. There were hermits and anchorites, monks and nuns. They disciplined the flesh, they abstained from all indulgences, and their rigorous religious observances were believed to help the rest of the community who were allowed to have a good many festivals and live a rather different type of life, and the rest of the communities subsidized them. This was particularly characteristic of many countries that have remained relatively poor.

We also have, as part of our tradition, what is called the Puritan ethic, in which we democratically attempted to spread the practices of abstinence, sobriety and the postponement of all gratifications, hopefully to heaven or at least until a man got rich, throughout the entire population. The Puritan tradition, which has been a very important one in our country, was remarkably successful in promoting economic development and the Industrial Revolution, also includes a very strong bias against any chemical of any sort which alters mood, makes life seem less difficult than it is, puts one to sleep when one is kept awake by worries, relaxes one when one should stay tense, and so forth.

There are very many millions of people in this country who still believe that alcohol, tobacco, and the associated sins of dancing and card playing and things of this sort weaken the character, weaken the fiber of the Nation, and it should be disapproved of.

Now psychotropic drugs get involved in this Puritan tradition, and they also to some extent have gotten involved in the Catholic tradition because the Catholic Church in this country has still stood for facing grief whereas, on the whole, the Protestant and secularized community has abandoned grief or attempted to abandon any recognition of grief for quite a long time.

Additionally, within our religious and moral ethic in the past there has been a tremendous emphasis on self-control, on an individual being his own master, being in control of himself through will power, so that any drug that is regarded as addictive, and this includes alcohol—when one becomes what is called an alcoholic, which means holeplessly addicted—comes under reprobation not only for the other effects that it has on the personality but because of the weakening of the will and the loss of self-control.

These are traditions that came from Europe, they are still very important in Europe, and they are still a very important component of the criticism of this country made by Europeans, and especially by European theologians in many instances, and European psychiatrists who also share the same general cultural position.

But there is also a distinctively American emphasis that has developed out of the frontier and out of the demands that founding a new country made on Americans that is different. It contrasts with our European cultural roots. This is the general belief that if something is wrong you ought to fix it and as against the European notion that if something is wrong you should fix your character and bear it.

This was very well represented in conflicts between the Americans and British during World War II, where the Americans thought the British notion that you fixed your character, you just got a little more willpower and left everything exactly as it was, was ridiculous. The American idea was if this building isn't any good knock it down and build another one.

There is a general emphasis in this country upon finding external solutions to all problems; if you don't like where you are living move somewhere else; if you haven't got any land make it; if you have the wrong shaped nose get it fixed; if you have too big a nose and too small a chin take a piece of your nose and put it on your chin and don't complain that you are going to have to sing in the choir or as a spinster all your life. Right straight through our history we have adopted a policy that invention, technology, ingenuity, resources ought to be available to deal with anything that we want to have dealt with.

These three attitudes occur, in different mixtures in different constituencies, in different parts of the country and in different individuals, including the advertisers who advertise for the pharmaceutical industry and the detail men and the physicians who receive their ministrations. The practical desire to fix things comes into conflict with a belief that some measure of pain is part of man's lot in the world. If you carry that far enough you use no analgesics of any sort in childbrith because pain is what man was born to and woman was condemned to and she should continue to bear the pain.

If you carry the Protestant Puritan ethic far enough people take the attitude that everyone should develop enough character so that they never need anything to support them, except vitamins, and it is even doubtful if they should have too many of them because maybe if you depended on vitamins your character wouldn't develop properly. We have had all through this country since the 1960's emphasis on eating the right foods and which means changing your character, and somewhat of a questioning of these synthetic vitamins instead of exercising the moral choice of eating the right food.

All things come into play in the discussion of psychotropic drugs. We have drugs that can act as a sedative, that can relax, that can stimulate, that can energize, and that have enormously altered the population of our mental institutions. Some of these drugs have made it possible to treat people in outpatient situations, to send home very large numbers of people who would have had to stay in institutions and, at the same time, that these particular benefits are well known, we have the operation of these three ethics coming into play, questioning whether there ought to be drugs that make it possible for people not to worry as much or not to lie awake or not to be as tense as they would otherwise be.

And whenever the word "drug," of course, is used crosses over very dangerously in public opinion—and public opinon includes all of us also in our particular predispositions—it crosses over to the use of those drugs which we originally identified as hard drugs, and today, marihuana which is being linked with hard drugs by an act of cultural creation just as smoking cigarettes was once linked to prostitution as it was years ago when people knew that a woman who smoked a cigarette was either a prostitute or would become one. Obviously women who were not prostitutes and didn't want to become prostitutes, didn't smoke cigarettes and the first cigarette which someone persuaded a girl to take was a realistic introduction to a downward path. We put marihuana in the same situation.

Senator JAVITS. Dr. Mead, would you mind one question, if the Chair would allow it; just one?

Dr. MEAD. Any time.

Senator JAVITS. Just one question on marihuana because it happens to intrude in another committee of which I am the ranking minority member. You speak as if the scientific basis for discounting marihuana, according to what the kids say, as being nothing worse than alcohol or tobacco.

Dr. MEAD. Not nearly as bad.

Senator JAVITS. Perhaps even better. However, many people still leave it up in the air. It is not scientifically proved that maybe it is a threshold drug to addiction, et cetera. Would you care to substantiate your statement, which, if you stand by it, is very important, on that subject. Would you say there is not adequate scientific proof to dismiss marihuana as a threshold, addictive of similar drug comparable to hashish, heroin, and so on?

Dr. MEAD. Senator, I would separate hashish and heroin very sharply.

On the question of the use of *cannabis* in various forms we have cross-cultural evidence, we have cultures that have used it for a very long time. There is some evidence that if people use it to excess for 20 years, which mean that they spend their time smoking instead of

doing anything else, they showed some mental deterioration. You can find that with people who do nothing but eat for 20 years let alone people who only use alcohol, that is the excessive use of any piece of chemical intake, even bread and milk is not particularly good for you. We know that *cannabis* has been used for a very long period; we have accounts of the way in which it is used to energize during work and to relax after work. It is my considered opinion at present, and this is not proved because we haven't had instances of where we could follow children whose known situation was, well, authenticated into adult life where we could control all the other aspects of their lives so as to discuss this. But it is my considered opinion at present that marihuana is not harmful unless it is taken in enormous and excessive amounts. I believe that we are damaging this country, damaging our law, our whole law enforcement situation, damaging the trust between the older people and younger people by its prohibition, and this is far more serious than any damage that might be done to a few overusers, because you can get damage from any kind of overuse.

Senator JAVITS. Thank you very much. Thank you very much, Mr. Chairman.

Senator NELSON. It should be noted at this point in the record that the subject of marihuana is not under consideration by this subcommittee. As Senator Javits suggests, this subject is peripheral to the purpose of today's hearing dealing with the use of prescription psychotropic drugs. Please proceed, Dr. Mead.

Dr. MEAD. Now, I noticed in reading earlier testimony before this committee, that the question of side effects in terms of health damage to organs of the body or something of the sort still didn't play as important a role as this question of either the possibility of addiction, overdependence on drugs, which is related to addiction, and the whole moral question of whether it is right to help people escape. That is the reason that I have initially begun by raising these questions. You have discussed psychotropic drugs which are overprescribed, but so are a great many other drugs. When we talk about the side effects of psychotropic drugs we tend to be heavily influenced by the moral and religious and traditional issues involved. I would say at present that our general evidence of the good effects of psychotropic drugs is in the treatment of mental illness. This includes, if you take the hospitalized population a very large proportion of people in this country now who at some point or other are referred to a mental hospital because we have no other way of dealing with various forms of maladjustments. Instead of condemning hundreds of thousands of people to a life which permitted no recovery, these drugs have been exceedingly useful in permitting their treatment.

Senator NELSON. We have already had testimony, which I understand you have read, on the psychotropics. I cannot recall the statistics but they are very dramatic.

That is, we have cut the population of the mental hospitals by some dramatic figure, more than half, something like that, since the psychotropic drugs came into the marketplace sometime in the mid-1930's. I have forgotten the statistics but they are in the record. The testimony was that this has had a dramatic, positive, helpful effect upon the practice of psychiatry, that for the first time psychiatrists were able to get patients who were condemned to a lifetime within an institution out of the institution, so that they could be maintained in a reasonable

fashion within normal society, patients who would never otherwise make it without the drug.

Now, what about the person who does not have an emotional disturbance that would require institutionalizing? Apparently a massive number of people are users, who have prescribed for them psychotropic drugs and just continue to use them all their lives.

Do we know what effect it has upon their personality, their capacity to perform? Do we know how many of these people might be better off if they were off the drug and faced up to whatever problem was causing the tensions? Could they overcome it? Do we know very much about that aspect of the use of the drug by people who are not cases that would be hospitalized?

Dr. MEAD. Yes. You see, today the line between people who are hospitalized and the people who are not as definite as your question would suggest.

Most of the people under sufficient stress would be—would require some kind of help today. It isn't that there is such an increase in mental illness but we define it so differently that people who show minor symptoms of anxiety, worry, the girl who weeps into her typewriter every morning, who would have just been patted on the shoulder 25 years ago, all of these people who are not in mental institutions, and who are not going to psychiatrists would nevertheless if placed under more stress end up in mental hospitals. That is, we use our mental hospitals today in very different ways than we did when we only hospitalized psychotics.

So to make a line between the people who are in mental hospitals and the people who are not is not really something we can do today.

What we are moving toward is more and more treatment of those who appear to be primarily mentally upset in general hospitals or in outpatient departments, so they will never have to enter a regular mental hospital.

This picture of the absolutely sane man, you know, with a fine character who might be undermined by taking psychotropic drugs in contrast to the vulnerable fragile person who is mentally ill, is no longer the kind of distinction we would make.

We have, for example, instances of large numbers of men who, say, in civilian life, might never have broken down but under particular conditions of wartime will break down. Everybody has a breaking point, and psychotropic drugs are used to fend off breaking points.

I wouldn't want to let this pass without making one further comment, we are not certain that returning housewives to their families under the influence of psychotropic drugs which permit them to function at a low level, but nevertheless to function, is a completely good thing for the community. This is a question that has been raised by many psychiatrists. It has been raised in the deliberations of the World Federation for Mental Health, and I think when you are making this complete inquiry here this should be included. If we give *only* drug therapy we are in some instances returning zombies to the community. We have to consider whether it is a good idea for children to be reared by a zombie mother, whether this may be more dangerous than we have thought.

The drugs have made a tremendous difference in the accessibility of patients to psychotherapy but in many cases this is not followed up. There is often no other therapy used except drugs, and drug therapy

needs other sorts of therapy, some of which can be called facing your problems, and in which the ministerial professions have a large role, some of which may be called finding out what are particular anxieties, these patients need pedagogical psychotherapeutic, pastoral treatment, as well as drugs.

It is true that psychotropic drugs made inaccessible patients accessible, they have made wards filled with screaming disturbed people peaceful so that the patients who went there weren't more disturbed, they made it possible for us to begin discharging large numbers of patients from mental hospitals, and they made it possible for us to keep millions of others out. But they are not a panacea all by themselves and should be combined with better follow up, better care for patients in the community, halfway houses all sorts of services that we do not have today.

Senator NELSON. You referred to the individual who may very well get along adequately adjusted under the ordinary stresses of some civilian occupation who, transferred to the military or some other circumstance, may then break down.

Since you have made important studies of cultures all over the world including our own, I would like to ask whether or not the stresses, say, of the modern industrial traffic-jammed, smogged, noisy city are creating more emotional stresses causing more people to need some supportive help of one kind or another, whether it be psychotropic drugs or something else, than the person who lives in a more pastoral situation? In other words, are there higher percentages of people who break down in our metropolitan cultures than in the more quiet pastoral situations?

Dr. MEAD. As far as we know the rate of straight psychotic breakdown has not changed in this country in the last 100 years, that is individuals who would have to be hospitalized because the community is utterly unable to cope with them.

Senator NELSON. You mean the percentage of the population that breaks down?

Dr. MEAD. Psychotically.

Senator NELSON. Psychotically.

Dr. MEAD. And the studies we made in primitive societies (some of the best studies have been made in Taiwan) gave very much the same results that there were, the proportion of psychoses didn't change very much no matter what the community was.

Now, the people who are maladjusted but not psychotic are dealt with very differently in a small village community or remote farming or pastoral community than they can possibly be dealt with in a large city. Furthermore, we are no longer as tolerant of human suffering as we were. A large number of small breakdowns are still tolerated in any rural community, well removed from the pressures of the large cities. In these communities people have always tolerated small breakdowns. They would say, you know, those Jones, well they all had ticks. Old Grandmother Jones' face used to twitch all over the place, three of her daughters have ticks, and now her kids have ticks, and they would accept this.

Under the pressure of our large city of our modern concern which has increased enormously in the last 30 or 40 years we no longer tolerate these degrees of breakdown in the same way. So it is not so much that

there is so much more breakdown as we are less willing to let the breakdown occur, and less willing not to make an attempt to deal with it when it does occur.

There are undoubtedly new forms of stress in the city, noise, air pollution, constant relationships to strangers whose behavior you don't understand so that if you don't know whether they are drugged, crazy or going to murder you, as they reel toward you on the sidewalk, this is the kind of stress that one doesn't get in a small community. But in the small community feuds are carried down three and four generations and people live with organized hate that lasts from generation to generation. So that I think we have to say we have different stresses in our large cities and we have much more willingness to do something about the response to stress. Or you can say it the other way, less willingness to let the highly depressed person, for instance, operate within a business or professional context. But whether one is greater than the other we don't know.

Senator NELSON. Are you saying that there are all kinds of artificial or man-induced stresses in cities that don't exist outside the city, the items you have named, whether it is noise or traffic jams or frustrations of trying to get some place or doing something, that this does not have an effect, does not increase the number, the percentage, of people who live under nervous tensions. That these stresses do not increase the percentage who experience nervous tensions over what you might find in a smaller community?

Dr. MEAD. We don't know. You know, of course, when you make a study of a small community you find a tremendous amount of maladjustment and mental illness. This is partly because the small community does nothing about it, and the city insists on doing something about it in some cases. And it is different, but we don't know how different yet.

You know there are small communities where you think half the people in the village are witches who are intent on killing you. It is a lovely small community, you know everybody in it and everybody shares food unless they are afraid of being poisoned or sorcerized or bewitched. In prince and peasant and rural communities there are orders of stress that are very extreme, The really striking thing about these small communities is that no one did anything about small breakdowns and it is only with the modern mental health movement we have begun to think not only about the people who have been hospitalized but the people who are under too much stress in their daily lives.

Senator NELSON. Thank you.

Mr. GORDON. Dr. Mead, concerning the use of psychotropic drugs for the purpose of enhancing performance, as you know, athletes are not allowed to use psychotropic drugs. What do you think about that?

Dr. MEAD. I think it is more of the general position of which we can't decide whether an athlete is a racehorse or not. It is related to doping racehorses. This we have always felt was one of the wicked practices connected with horseracing which we should stop. You know our attitudes toward horseracing are mixed with our attitude toward gambling. There has been every source of misrepresentation involved. Good people knew horseracing was wicked, but at least one wicked thing we were not going to do, we were not going to dope the horses.

I think this is just one, another one, of these crossovers between traditional Puritanism, on the one hand, and attitudes toward athletic competition. We are not going to let athletes who have a spare chromosome compete. You know these are ways in which our attempt to deal with contests where we, on the one hand, claim that there is fair play and, on the other hand, do our best to have no new factors introduced, that is all. Whether you give antibiotics to chickens, there is a question not only of the effect on the people who eat the eggs or the chicken, but is it good for the chicken? Is it good for chickens to be raised in this sort of welfare state? These are traditional moral problems and they get very seriously raised.

I would like to, if I may, Mr. Chairman, to just lay on the table one other aspect of the whole question and that is the question of the whole health network, the galloping speed with which new drugs have been developed, the virtual breakdown in the country of orderly forms of communication which lead to physicians depending upon advertisements and drug companies promotions as after the only sources of information, very often they are able to handle. I would like to stress the need for a different type of medical education, and different orders of information conveyed to general practitioners. This is exceedingly important and we now have the means to do it if we will use our electronic background now to set up computer systems where real information can be conveyed to a physician.

But it isn't only the psychotropic drugs. We have a total breakdown now of physicians taking life histories of patients and they don't ask them what other drugs they take, and people go in and a doctor working with one part of the body prescribes a drug that if it was combined with a drug prescibed for another part may be lethal.

I know you have touched on these problems in your earlier hearings of psychotropic drugs. I am sure this has been touched upon in other parts of the testimony. I want to emphasize that the only conceivable answer to the population explosion and the drug explosion and the information explosion is using electronic retrieval and presentation methods, and so that a physician can get rapidly the information he needs about the incompatibility of a particular drug with previous disease states, with present drugs that are being prescribed by somebody else, with the other drugs the patient is buying at the drug store and self-prescribing. Each individual patient today is often in greater danger the more clinics or specialists he sees.

This is a very serious situation that needs resolution and it needs resolution in two ways. It needs a resolution in terms of how the information reaches the physician, not in the 2 minutes that the detail man gets into his office, but ways in which he can retrieve rapidly what he needs to know in terms of each patient. And, on the other hand, we urgently need some sort of health card for every person in the country on which it will be compulsory to punch drugs that are being prescribed for that patient, combined with information about allergies and sensitivities to penicillin and the fact that he is a diabetic and the whole series of things that are now being disregarded. In dealing with the drug explosion, I think we can compensate for the deficiencies of medical education by using the new inventions that have accompanied the

modern technological expansion. Unless we do, we have very little hope of keeping this thing in any kind of order.

Finally, I think that we have traditionally fragmented the roles of different parts of our society too deeply. We have looked on industry as looking for nothing but profit, on politicians as looking for nothing but power, and on do-good groups as doing nothing but doing special kinds of good. We have set them all in opposition to each other, and if we are going to build any kind of orderly attack on this tremendous problem of costs of medical care, of production of this great variety of drugs, the problem of testing the large numbers of drugs, and getting the information to physicians and patients, we are going to have to begin to cooperate in ways that we haven't before. We will have to invent some order of cooperation in which the pharmaceutical agencies and government and consumers and the medical profession can work together and assume that there is at least a modicum of good will that can be counted upon in each group if they were differently organized than the way we have organized them today.

Senator NELSON. You have presented the idea that everyone ought to have a health card. Would you elaborate on that a little bit and how would that be managed?

Dr. MEAD. It is managed on a very small scale now. The international health card which people carry around which shows when they had their last inoculations or immunizations in those things that are relevant to international travel. This is a standard card, it is completely set up so that it is possible to see when you had your last vaccination, if you need another booster for tetanus, etc. You can use that card anywhere in the world, where there is an epidemic or an attempt to revaccinate people or reimmunize them. This is on a small scale for those who go abroad, but we need something like this. We need it in a form that a technical assistant or a secretary can elicit the information, because no physician today has time to do even a perfunctory health history of any patient and, therefore, he is prescribing almost entirely in the dark. He may have the kind of skilled diagnostic hunch that this patient doesn't look as if he had something, but he doesn't ask them. Many of the best physicians in the country are not taking health histories that are worth anything in protecting patients from the flood of drugs that other physicians and clinics and pharmacists and their friends are prescribing for them.

Senator NELSON. With the vast number of drugs under trade names in the marketplace there really isn't any way for a physician to know how many of these trade names are actually the same drug.

Dr. MEAD. Well, they could put them on another retrieval system. When the physician encounters a patient who is taking a drug he has never heard of before, the physician ought to have a console in his office, he ought to be able to press a button and say what are the other drugs that are just like this one only have other names or what are the different components, what are the side effects, what are the drugs that are incompatible? This we do now. We can do such things at much less social cost than trying to handle these things that have been produced by our modern technological revolution in a nontechnological way.

The same thing should be done to locate foods that are incompatible with particular drugs.

Senator NELSON. I read a couple of excerpts in my brief opening remarks. One is from testimony by Dr. Daniel Freedman of the University of Chicago. He stated as follows:

> Most societies also use drugs recreationally for rituals, relaxation and escape from everyday reality. Most common are sedative anti-anxiety drugs. Our total attitude should not be not to encourage widespread availability of stimulants and sedatives for these purposes. One thing I think that we do know in psychiatry is that grief is very important to normal experience and that stunted grief, stunted emotional working through these problems, can lead to a serious psychiatric problem. Generally we think in psychiatry in trying to meet the challenge, the ups and downs of life are important to development.

Do you have any observation to make?

Dr. MEAD. I think here we have again the puritan ethic, people ought to meet all ups and downs without help, and the newer American ethic is that you shouldn't have to meet ups and downs that aren't necessary.

Senator NELSON. You are talking about unnecessary ups and downs.

Dr. MEAD. Yes! And we regard this standard American attitude, that differs from these older religious attitudes, is not in favor of a man going through the morning with a headache, which results in wrecked relationships to his colleagues or dictating all his letters incorrectly, he gets into a fight with somebody on the telephone, when he could take a couple of aspirins.

Now, I mean if you really follow these remarks of Dr. Freedman carefully it would be wrong to take aspirin for a headache, you should face the ups and downs of life and one of them is a headache and, on the whole, we think that is nonsense, and that people shouldn't do this. We do not believe as a people in unnecessary suffering, in unnecessary anxiety. It may be good for people to face the ups and downs of life when their children leave home and parents don't know where they are, but we are rather in favor of the children's sending telegrams saying they arrived safely. This argument that says that it is good for human beings to face the ups and downs of life, is then extended to include grief.

I agree that Americans were refusing to face grief. We were refusing to let people grieve, we gave up mourning, everybody was supposed to go back to work 3 days after the funeral and be cheerful. Everybody tried to cheer them up. If the bereaved was a widow they tried to remarry her at once, and standing around the grave people would say "I do hope she marries again." Now, this general denial of grief, the tendency to keep children completely away from any experience of death so that the first death they ever knew might be their parents at middle age, I think has been a bad element in American culture, and in British culture it has been just as bad.

This has changed somewhat in this country now, and we are more willing to deal truthfully with children about death, and we are more willing to permit the bereaved to grieve.

I do not think this point about grief should be tied to problems like anxiety, and relaxation, and the earlier quotation from Dr. Freedman that you read where he said most cultures have used some form of stimulant for relaxation.

With a very few exceptions, every culture we know has used whatever they can get. When they learned how to make a stronger stimu-

lant they used it, and if they then used it to excess they then developed countermeans to convert those that were using it to excess, to a life of abstinence.

We occasionally find a society that will reject anything that leads to any kind of ecstatic state or of people ever getting outside of themselves. This was the history of the Pueblo Indians in relation to peyote. When peyote started to spread they refused it and when alcohol started to spread they refused it. There are societies, usually very small ones, that can be organized around one temperamental emphasis of sobriety or excess. But in general man has sought for ways of changing his moods, of making it possible for him to work longer than he could, to stay up longer than he could, to get through a meeting or a tremendous bout of work better than he could have otherwise. When the work is over, whether it is plowing a field or taking a hazardous journey in a canoe or getting through a terrible board meeting, he very often uses the same drug as a relaxant, which suggests that the relationship between these mood changing drugs is not as simple as we have thought they are. In the West Indies, people smoke marihuana to get through a hard day's work and after they have done the hard day's work they smoke another bit of marihuana to relax and enjoy the evening. And there are many people who do this with cigarettes also, of course.

They smoke to keep working and then they smoke to relax, and all of these things fall under this general question of whether that man has any right to use natural or distilled or pharmaceutically produced aids to permit him to live the kind of life that he wants to live, and in most cases we find this combines work and relaxation or religion, work and relaxation.

Senator NELSON. I don't recall that I asked Dr. Freedman to elaborate on this rather sparse statement. It may very well be that he will agree with your elaboration, I don't know. As I read it, he may have been saying that the use of drugs to avoid almost all stresses in life is a serious matter and that he opposed that. You weren't suggesting that it would be healthy for people to avoid all the stresses.

Dr. MEAD. No; I think it is very unhealthy for them to avoid facing stresses of the order of death or even moving and separating from their friends. But I do believe it is worthwhile to avoid the stress that comes when the plumbing breaks down and both cars are broken and you can't find your husband to telephone him, and the child in nursery school, three children in nursery school, you were going to pick up 15 miles somewhere else, if a pill will permit you not to burst into tears under these circumstances but go next door and borrow another car, I think it is a good idea and I don't think we should confuse the inevitable stresses of the complexity of modern life with the great moments in man's existence which he has to face up to.

I think that a good deal of the testimony against psychotropic drugs, and particularly anxiety reducing drugs, is of this sort and confuses the issues.

Senator NELSON. I had the impression, although I have not reread the testimony, that some of the witnesses, at least, were saying about the same thing about the psychotropics as other witnesses have said

about other prescription drugs. We have had testimony from some distinguished doctors, pharmacologists, who have asserted as much as 50 or 60 percent of the drugs prescribed were unnecessarily prescribed or even, in many cases, prescribed for the wrong purpose.

Now, I have the impression that some of these witnesses on the psychotropics were simply saying, among other things, that a lot of people who are getting these drugs would, in fact, be better off without them. In other words, there is unnecessary prescribing of this type of drug also for many, many people.

Do you have any observations about that?

Dr. MEAD. I think it gets complicated. I agree with you, you know, that our evidence suggests that a great many drugs are prescribed that don't do any good, but I understand from Dr. Modell's analysis of the situation that nothing like the number of useless and poisonous drugs are used today that have been used in the past. That the whole history now of our scientific examination of drugs has been that we are to examine them with far more care, testing them more carefully, and developing drugs that have specific targets and eliminating drugs that are toxic, have dangerous cross effects or side effects, and that are useless.

Now, psychotropic drugs seem to fall in the same class as many other drugs where the purposes or efficacy attributed to them are not as great as it is believed to be, or is still claimed by advertisers at different levels after it has been demonstrated that it isn't useful.

That is a general position with all drugs as we develop and we find drugs we thought were useful are not useful or are dangerous, but if you look at the history of drug use, we are doing much better today than we have ever done before but we have just a large interconnected world with modern methods of diffusion of both the drug and the information so disasters loomed very large.

My only objection, or it isn't so much an objection as what I felt it was necessary to stress, is that in our evaluation of psychotropic drugs we are continually introducing moral judgments that are related to the fact that there is a large element in our culture that believes that whoever is in power, government or the church or a government that is controlled by a large majority of some church, should interfere with other peoples' lives and tell them how they should behave.

This has been going on since the beginning of our history. We passed laws that you couldn't kiss your wife on Sunday or couldn't take a bath in the bathtub in December, we have been systematically interfering with other peoples' lives, and where there is a difference of opinion in the country we have pressure groups which have intruded into wherever there was authoritative process.

I think the most dangerous thing where this has occurred, even more dangerous than prohibition, and prohibition began the breakdown of many of our urban controls of order, but even more than this is the breakdown over marihuana. In the past although the adults, a large number of adults, used certain things that were disapproved of by other members of the society, tea, coffee, tobacco, alcohol, and the children were not allowed to use them, nevertheless the children were told "When you grow up, when you are old enough, you can use them." The little boy who smoked corn silk tobacco in the barn and got a hiding for it or even got sent away to military school, nevertheless