

**Clinical Models of Response to Treatment**

**Historical Perspective**

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Diseases, including mental disorders, are certainly as old as mankind and so is the quest for their treatment and cure. My task is no less than to give you an historical overview of the many different ways in which patients and healers have dealt with the challenge of illness.

What were the models of treatment and response to it? How did these models change through the centuries? How did the models lead to definitions of the various concepts involved in these fundamental human problems?

### Definitions

Psychopharmacological Nosology is the theme of this afternoon's session. We need to stop here for a few definitions. Nosology is the pragmatically-oriented science of classifying diseases. This must be distinguished from pathology, which is the scientific study of the deviations in anatomical structures and physiological or psychological processes resulting from disease. Symptomatology, then, is the description of the various manifestations of diseases, based on empirical observation. Finally, phenomenology in the medical context, is the systematic description of patients' experiences and behavioral events as they reflect diseases.

And what is disease? Fundamentally, one may define disease in three ways: experientially, biomedically and socially.

The self-evident nature of disease is revealed by the patients' experience of feeling sick: "I feel sick".

The biomedical definition is based on more distinct and objective signs and symptoms of disease - such as fever, tumors, inflammation, convulsions, etc.

The social definition is open-ended and the most problematic, particularly in regards to psychiatric disease. Psychoses and major mood disorders are easily defined on the basis of social and behavioral criteria. But what about neuroses and personality disorders, the "worried well", the addictions and perversions?

The majority of psychiatric diseases fall into the first and third categories - the experiential and social - because there are no biological criteria for most of them. Few fall into the second, the biomedical category.

#### Descartes' Split and Pathology

In the 17th Century, René Descartes introduced the fateful split of body and mind, and with this split created the need for distinguishing between physiopathology and psychopathology. This distinction, in turn, called for different methods of treatment and judging the responses to treatment, in somatic and mental diseases.

In a very broad sense, mental or psychiatric illness may be divided into diseases that are symptomatic, associated with, or secondary to somatic illness, e.g., demonstrable brain lesions, and other mental, non-organic diseases to which we have referred traditionally as functional

or, following a recent suggestion by Ban (1), as sui generis disorders - which also have been referred to as endogenous. Within these two broad categories we have carved out a number of diagnostic classes, and sub-groups, the principal and major ones being psychoses and affective or mood disorders.

### Cure-seeking Behaviors

When certain signs, symptoms or other phenomena have indicated to an individual and his environment that (s)he is sick, the immediate response, in most cases, is an effort to reduce or eliminate all manifestations of the disease. We may call this general response help- or cure-seeking behavior. But sick persons do not really seek a cure of their disease. They want only relief of their suffering or their symptoms. It is the professional healer whose expertise is challenged to find a cure.

Modern physicians know that a true cure can only be accomplished if the cause of the disease is eliminated, and that means, in most cases, that the cause of the disease must first be known. In psychiatric diseases, more specifically in the psychoses and mood disorders, causes are only known for the so-called organic, or symptomatic, mental disorders. That, in turn, means that we cannot yet have cures for the functional disorders which comprise the major diseases, schizophrenia and unipolar as well as bipolar affective disorders, whose causes are still unknown.

However, even if we cannot cure these diseases yet, we are, at

least, able to treat them effectively by suppressing their symptoms.

Our current treatment methods, using psychopharmacological agents, can even reach beyond mere suppression of existing symptoms by preventing their recurrence, thus providing a kind of sustained stability for the patient.

On the other hand, once the physician has taken over the treatment of the patient, he may at times focus so narrowly on the symptoms, or on the treatment that he is convinced is indicated, that he loses sight of the patient's quality of life - or even his life itself. To illustrate the old adage that the cure is worse than the disease, we only have to think of the 17-18th Century practice of radical bloodletting and purging that physicians performed, which produced much suffering and at times definitely shortened the patient's life - or, in recent times certain forms of cancer chemo- and radio-therapy which often cruelly damage the patient's quality of life.

### Repertoire of Treatments

In the often-cited view of the World Health Organization, health is more than the absence of disease.

Let us take a rapid view of the historical sequence of treatments throughout the ages. There is only a limited repertoire of possible treatment approaches, just as there are only a handful of basic plots in fiction. There are first the tangible and the intangible treatments.

The tangible treatments comprise elimination of the assumed cause of the disease. Most surgery is of this type. There are prehistoric skulls that show the traces of trepanation, probably done to relieve the pressure of ill vapors in the brain. Many later medical treatments, such as bleeding and purging also aimed at elimination of the causative factor.

There are also tangible herbal and drug treatments, aimed at neutralizing or counteracting the effects of the noxious agent. Other treatments, such as burning, prolonged sleep or causing fevers and convulsions, are intended to activate the body's own natural powers of healing. In some way, the bizarre approaches of torturing the patient or even executing him, as in the medieval witch trials, must be counted among the concrete, if brutal, aberrations of the "furor therapeuticus". Other therapeutic approaches of the concrete type are exercise, rest, diet and spas which, if timed appropriately, are thought to re-establish the normal, natural rhythms and chemical equilibrium of the organism.

The intangible treatments range from religious rituals, exorcisms and magic incantations to therapy by animal magnetism (mesmerism), hypnotism and modern psychotherapy.

Among the many possible treatments, some are known to be specific, like an appendectomy for appendicitis, penicillin for pneumococcal pneumonia, nicotinic acid for pellagra - but this is only possible for diseases whose causes are known. Other treatments, like electroconvulsive therapy for depression, are unspecific, and still others, particularly in psychiatry, are partially specific, like

dopaminergic blockers for antipsychotic therapy.

### Historical Sequence of Treatment Models

The first great physician whose ethical principles still guide present-day medicine, was Hippocrates in the V Century B.C. We no longer believe in his Four Humors. The blood, the phlegm, the yellow and black bile, in their three stages of being crude, in coction or in crisis. But we are still guided by his strong belief in the absolute need for clinical observation, diet, exercise and the healing power of nature. It is noteworthy that Hippocrates also used medication frequently; no fewer than 265 different drugs have been mentioned in his works.

Seven hundred years later, Galen no longer concentrated on the mixture of humors in the body, but focused on the body states, such as being hot, cold, wet or dry, and aimed at procedures to contract or relax the body accordingly.

There followed a period, several centuries later, when the Arabs dominated medicine. One famous physician belonging to this era was the Jewish rabbi Maimonides. Perhaps the most important and fundamental contribution the Arabs made to medicine was their creation of the first pharmacopeia.

Western medieval medicine did not distinguish itself at that time except by some progress in surgery.

The most important figure in medicine of the Renaissance -

around 1500 - was Paracelsus, although he was still influenced by the secret traditions of alchemy. Paracelsus believed that if nature failed to cure the patient, a remedy that was antagonistic to the "spiritual seed" of the disease had to be given. These remedies or "arcana" were often characterized by their "signatures" - that is, their fortuitous resemblance to parts of the body. For example, a heart-shaped root of a plant might have been indicated for cardiac disease.

But Paracelsus also was an excellent clinician who abhorred dogma and introduced many new drugs, metallic preparations and the effective tincture opii into medicine.

The seventeenth century saw a controversy between the iatro-chemical vs the iatro-mechanical schools, which the great English clinician Sydenham overcame by integrating most careful clinical observation with dogma-free application of all effective treatments available at the time.

In the nineteenth century there was one more important, theoretical movement based on an intriguing concept. That was Hahnemann's theory of homoiopathy. His approach which is different from those given in the previously-described repertory was that diseases must be treated by extremely diluted substances that would, in large doses, produce the same symptoms as the disease - similia similibus curantur - similar things will be healed by similar things. Homoiopathy is still quite widely accepted, particularly in Europe. One might think that had Hahnemann been living today, he would have become an immunologist, because it is through the



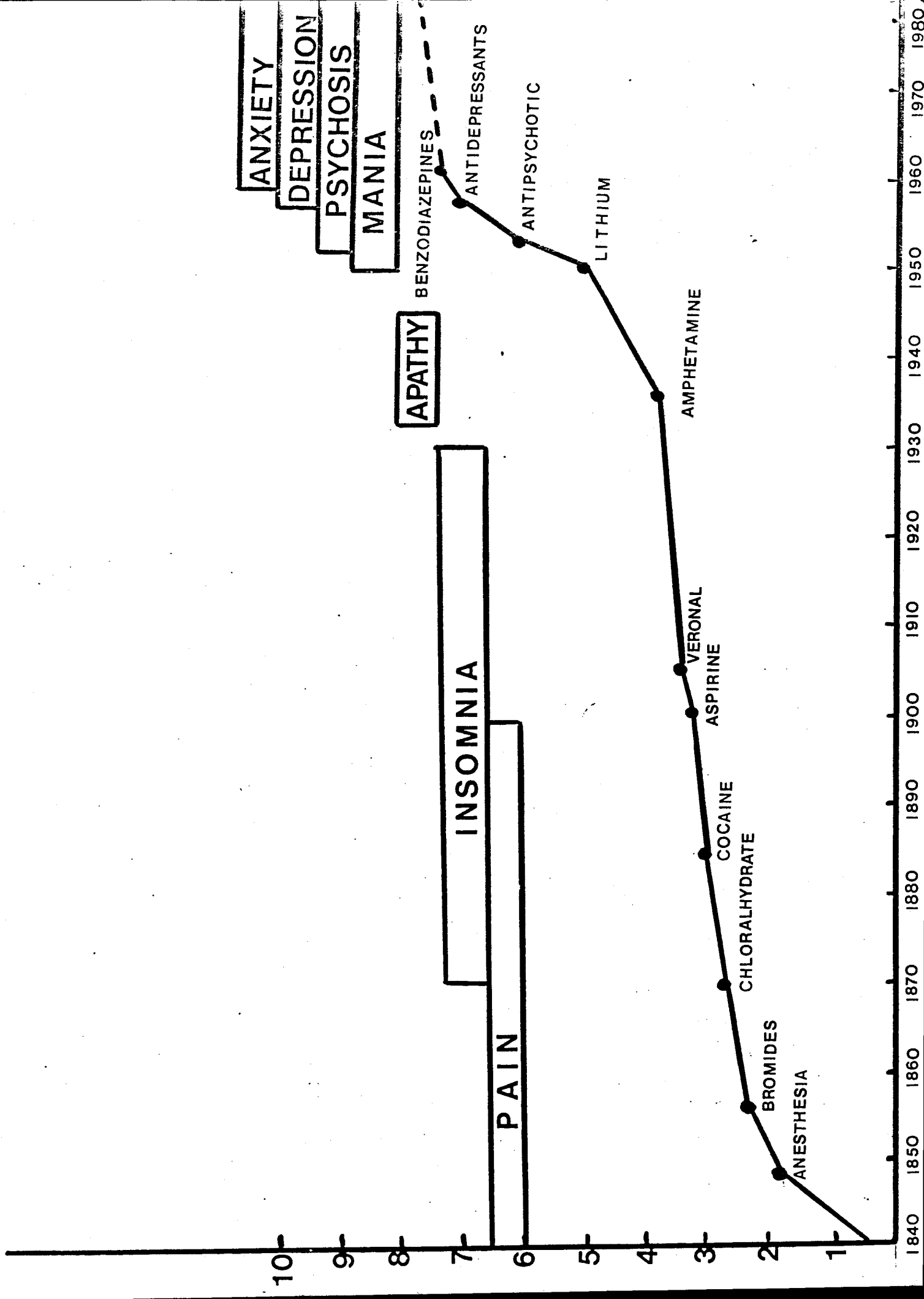
immune system that we today fight infectious diseases by inoculating the organism with very small amounts of the same substance, e.g. a weakened virus or bacterial toxin that would cause the disease, the model being that of antigen - antibody response. The same model had been successfully used before, by Jenner, for the vaccination against smallpox, although not on theoretical grounds but on an astute clinical hunch.

### History of Psychopharmacology

When in the past have we found innovative treatments in psychopharmacology? And where should we look in the future?

Some of the classic drugs of general medicine were found by systematic trial and error of many herbs and other plants in the past - e.g. digitalis, quinine and colchicine, for the treatment of heart disease, malaria and gout. On the other hand, much of the psychopharmacological development has come out of the laboratory. Figure 1 illustrates the growth of psychopharmacological treatment over the last 150 years. It actually started in 1803 when the alkaloid morphine was first isolated from opium by Serturmer. From then on an interesting pattern can be observed, which is characterized by periods in which psychological syndromes were attacked one by one. Sometimes the periods overlapped, but a definite progression over time can be noted. At first, pain was successfully conquered with the discovery of morphine, general anesthesia in the 1840's and local anesthesia in the 1880's. Next, and overlapping with the attack on pain came the search for treatment of insomnia and agitation. Solutions were found in the bromides, soon to be followed by the discovery of chloral-hydrate in the mid-19th Century and

# PSYCHOTHERAPEUTIC DRUGS



veronal, the first widely used barbiturate, in the first years of this century. Aspirin, still belonging to the attack on pain, also was produced in the early 1900's.

The next major psychopharmacological success came with the discovery of the amphetamines and their stimulating effects counteracting the inhibition-inertia syndrome. The disinhibiting effects of intravenously administered barbiturates were widely applied at about the same time. Then, from the 1950's on, there was a rapid succession of discoveries: the antimanic effects of lithium, the antipsychotic effects of the phenothiazines and butyrophenones, the antidepressant actions of MAO-inhibitors and of the tricyclics, quickly followed by the discovery of the anxiolytic benzodiazepines.

#### Focus on Target Syndromes

Unlike the drugs quinine and colchicine which are aimed at specific, diagnostically-defined diseases, all effective psychopharmacological drugs were targeted at syndromes rather than specific diagnostic entities. When I wrote my first paper on chlorpromazine in 1953, I referred to the drug as a new "inhibiting agent for psychomotor excitement" (2). The MAO-inhibitors were originally introduced into psychiatry as "energizing" drugs to overcome inertia and passivity, although their euphorizing effect had also been noted (3).

The antidepressant effect of imipramine was discovered by Kuhn by observing the drug's effects in a large group of schizophrenic patients (4). None of these three major breakthroughs in psychopharmacology

were in any way related to a systematic search for specific action in narrowly defined, homogeneous groups of psychiatric patients.

This raises the still unanswered question of whether the search for new psychopharmacological agents must be based on a search through ever more refined diagnostic efforts, or whether we should content ourselves with simply finding better drugs for the treatment of broadly defined syndromes, such as depression, psychosis, or anxiety, or for affecting wide-reaching physiological systems, such as the catecholaminergic, gabaergic, serotonergic or cholinergic ones.

#### Questioning Treatment Responses

Frequently, certain treatments that have been very effective for most patients apparently suffering from the same disease, prove unsuccessful for a certain number of patients. What are the reasons for such therapeutic failures? Possibly these patients belong to an as yet unidentified diagnostic subgroup for which the chosen treatment was not indicated; but there are other, more plausible explanations. Perhaps the patient is just in an unresponsive phase of his illness, or he or she might be treatment-resistant due to genetic-constitutional or special extraneous factors.

Many questions surround the response to treatment. For instance, how do we know that a treatment was effective? How effective has it been? When did it begin to work? How can we be sure that it is the treatment that was responsible for the patient's improvement? Strangely, few, if any, of these questions were ever seriously addressed

Strangely, few, if any, of these questions were ever seriously addressed before the 1940's. Until then a variety of questionable factors were taken as unquestionable assurance or evidence of a favorable response to a specific treatment. First, simply the patient's personal statement - "I feel better". Then, regardless of how the patient felt, the physician's personal opinion about the treatment response, and, last but not least, the physician's indoctrination by tradition and authority regarding treatment methods and how they work - or should work.

But then, a curious phenomenon occurred in 1946. The concept of the placebo and the procedure of using it which had existed in medicine for centuries in a rather subdued fashion, suddenly burst into methodological and experimental prominence with the explosive brilliance of a supernova. The recorded use of placebos in medicine dates back to 1787 when it was defined in Quincy's Lexicon as "a commonplace method of medicine" (5). In 1945, Pepper wrote a scholarly paper on the placebo because, as he pointed out, there had never been one written about it and no mention was made of the term in the Cumulative Index at that time. However, since the 19th and the beginning of the 20th century, the placebo had been freely prescribed and the word had been in daily use, Pepper suggested that "the giving of a placebo seems to be a function of the physician which, like certain functions of the body, is not to be mentioned in polite society" (6).

But at the Cornell Conference on Therapy in 1946, Gold (7) made a spirited case for the placebo and the double-blind control method of therapeutic agents, and almost over night the unmentionable placebo became a fashionable scientific gadget. It soon rose to the role of a status

symbol of the behavioral scientist. Today, the use of single-blind and double-blind placebo controls in experimental designs tends to distinguish the sophisticated white-collar investigator from the amateurish and unskilled experimenter.

One might argue that a radical innovation had been introduced when, in addition to the old clinical use of the placebo for therapeutic purposes, its important role for experiment and methodology was discovered. However, as early as 1912, the psychologist Hollingworth (8) took it for granted that a good investigator experimenting with drugs in human subjects employed placebos and double-blind procedures, although he did not use these terms which came into general use only after the Cornell Conference.

A disturbing methodological problem distinguishes most of clinical research in psychiatry from the rest of medicine, because, in the last analysis, almost all diagnostic criteria in psychiatry are derived from clinical judgments, due to the lack of objective, biological criteria.

There is today a strong tendency to apply strictly operational definitions to all problems and concepts in the behavioral sciences. This tendency stems from the realization that much of the success of the physical sciences in the last century has been the result of such strict operationism. The problem in the behavioral sciences is, however, different in that two factors which are of little or no significance in the physical sciences, play a dominant role in the behavioral sciences. These two factors are the *history* of the individual subjects and the

personal *meaning* the experimental and environmental conditions have for him. In contrast to this, a Z-particle (in a superconductor supercollider) which has a lifetime of much less than a billionth of a second, has not much of a history. Even geological specimen with a history of millions of years have still not acquired any personal meaning, and remain in an eternally valueless context.

### Objectivity - Reliability - Validity

In all clinical research, and most of all in psychiatry, methodology strives toward objectivity, reliability and validity. This applies, of course, also to the determination of treatment responses.

There are three main reasons which may determine the choice of an *objective* method in preference to others:

1. Results obtained by objective methods lend themselves more easily to intersubjective verification.
2. Objective methods sometimes enable the investigator to reveal basic mechanisms underlying the behavioral criteria.
3. Built-in checks and balances of objective methods tend to neutralize the comparative shortcomings of less experienced or less competent experimenters.

*Reliability* refers to the consistent recurrence of the same or closely related results on repeated testing or observation. Of the three factors, objectivity, reliability and validity, only reliability can be regularly and accurately quantified. Its measure can be expressed in

statistical terms. The reliability of a method is not of necessity positively related to its validity. In fact, in the behavioral sciences, we sometimes find a negative correlation between validity and reliability, as the validity of certain results often decreases when we try to control all experimental and environmental factors to such an extent that the test-retest and intertester reliability are raised to a maximum.

To *validate* a method is equivalent to establishing the meaning of its results beyond question. Whatever method is chosen to study a psychopharmaceutical problem, one of the basic difficulties is usually related to the question of valid criteria for the behavior under study. In psychology and psychiatry, we distinguish four types of validity: predictive validity, concurrent validity, content validity, and construct validity (9).

*Predictive* validity of a criterion makes it possible to predict the subject's future performance in the area characterized by the criterion, (e.g. in organic brain syndrome).

*Concurrent* validity is concerned with test items that sample a particular function or factor representative of a well-defined group of criteria, (e.g. in achievement tests, or DSM III diagnosis).

*Construct* validity is involved whenever a test is to be interpreted as a measure of some attribute or quality which is not operationally defined (in a wider sense, the search for new, e.g. more homogeneous diagnostic groupings).



Figure 2 illustrates how various instruments that serve to substitute for fully objective measures (of pointer-reading precision) have different trade-offs in the three areas objectivity, reliability and validity. I hasten to add, however, that this illustration is reflecting my personal view of this issue, a psychiatrist's view. I would not dare to show it to professional psychometricians who would, for example, never accept my potential dissociation of validity and reliability.

Most objective is, of course, the biological marker when it comes to measuring treatment response. It also has the highest reliability and validity - that is, if it is ideally specific. Otherwise, its validity may be very low, in spite of its high objectivity and reliability.

Next in objectivity are neuropsychological tests, but they are second to the structured interview in reliability and third to the free and structured interviews in validity.

Lowest in objectivity and reliability is the free interview, but, at least as I see it, it is highest in validity.

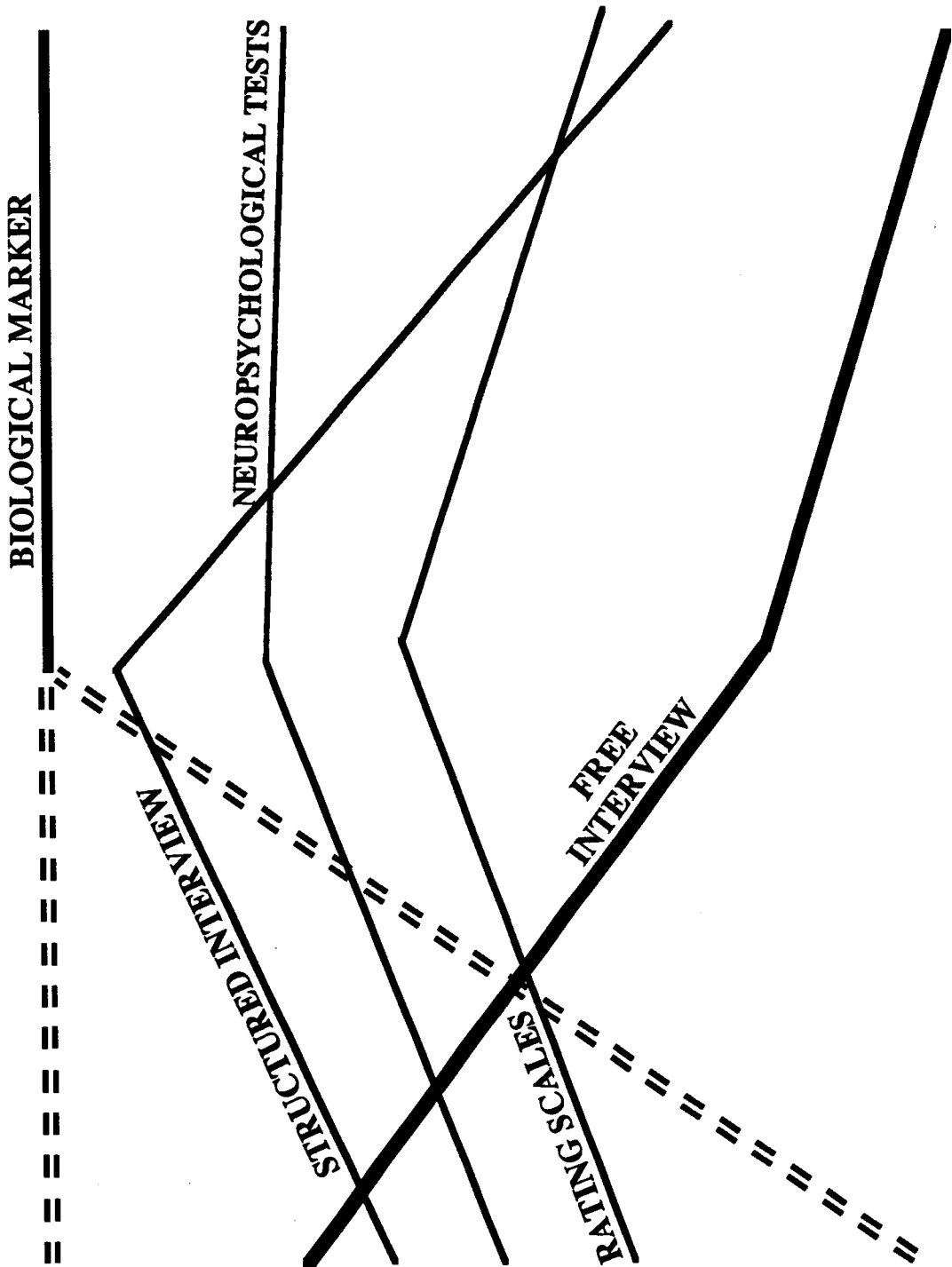
Rating scales are the most convenient of the objectifying instruments but are lower in all three factors when compared to neuropsychological tests and biological markers, while structured interviews probably strike the best compromise in the three areas.

Now, modern methodology for the establishment of the efficacy of any specific treatment does not depend on sophisticated technology. No

VALIDITY

RELIABILITY

OBJECTIVITY



electronics, no imaging, no chromatography, no molecular biology is required. The placebo was a factor well known for centuries to every clinician. The statistics Pascal had developed in the 17th Century to determine the probabilities of gambling, would have been adequate to evaluate random controlled clinical trials. One is moved to ask why double-blind, placebo-controlled trials were not undertaken one or two hundred years ago?

The answer may lie in the fact that the Galilean, detached approach to science did not entirely encompass medicine until well into the twentieth century. When treating human beings rather than inanimate objects, personal intuition, traditional conviction - even remnants of magic thinking - seemed to have maintained a shield of unscientific protection around patients - almost as though to guard them, from the intrusion of cold, scientific objectivity. Was such protection completely unjustified?

Today, medical research has moved on. It no longer depends entirely on clinical impressionism. The discovery progress of the neurosciences seems to be unstoppable, and psychiatry is facing greater promises than ever before for undreamed-of breakthroughs in basic research and sophisticated technology. We are applying appropriate, scientific methods to our data. We have made psychiatric history and are gaining constantly growing acceptance as members of equal scientific status in the medical community. But every gain also implies a loss, and psychiatry - the most humane discipline of medicine - must now guard against losing its human subjectivity and sensitivity altogether, in the overwhelming onrush of objective science.

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