Tranquilizing Drugs

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A SYMPOSIUM HELD UNDER THE AUSPICES OF THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE IN COOPERATION WITH THE AMERICAN PSYCHIATRIC ASSOCIATION AND THE AMERICAN PHYSIOLOGICAL SOCIETY AND PRESENTED AT THE ATLANTA GEORGIA, MEETING, DECEMBER 27–28, 1955

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Preface

One of the interesting features of the Atlanta meeting of the American Association for the Advancement of Science in late December, 1955, was a symposium on tranquilizing drugs. The meeting was co-sponsored by the American Psychiatric Association and the American Physiological Society represented by the undersigned and Fred A. Hitchcock respectively. Attendance was large and discussion spirited at the two sessions of the symposium, the first on pharmacological aspects of new tranquilizers, and the second on therapeutic factors relating to them.

This was merely a reflection of nation-wide concern over the possibilities of great improvement in psychiatric treatment by means of new chemicals. Promotion of better mental health was suggested by new drugs for the study of the causes and symptoms of the psychoses.

The Atlanta symposium on new tranquilizing drugs gave a chance for scientists from many different disciplines to discuss together pertinent ideas and findings. This cross fertilization between the different scientific and professional interests is a prime function of the American Association for the Advancement of Science. It was particularly gratifying that so many physicians, especially psychiatrists, participated in the sessions at Atlanta. It is warmly to be hoped that similar sessions can be arranged from time to time with regard to mood-altering drugs, so that all who are interested may have a chance to add to the rapidly growing concepts on mental disorder and ways of handling and preventing them. It really is not too much to hope, as *Life* has indicated, that a break-through may occur in regard to mental disease, so that better mental health and stability may be achieved for all of us.

Thanks are due to Dr. Chauncey D. Leake for facilitating the preparation of the volume for publication. One visible result of his work is the "Introductory Note." I also wish to thank my wife, Dr. W. A. Himwich, for preparing the Index.

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Introductory Note

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The Atlanta symposium dealt chiefly with new tranquilizing drugs, reserpine, chlorpromazine, azacyclonol, and meprobamate. There was, however, much related discussion on hallucinogenic drugs, such as lysergic acid diethylamide (LSD), mescaline, and adrenolutin. Indeed, one formal presentation, by Doctor Abram Hoffer, considered many aspects of adrenolutin action. There was also a formal report by Doctor Harold E. Himwich and Doctor Franco Rinaldi on the effect of benztropine methane sulfonate on parkinsonism.

The various new drugs being studied so vigorously in mental disorder deserve an effort at classification in order to avoid confusion. They may be classified most readily, at present, on the basis of overall action on humans, as (1) hallucinogens, (2) tranquilizers, and (3) central stimulants. Chemical classification may come later, when more data in regard to structure-action relations are available. It is interesting, however, to note at once that most of the hallucinogenic drugs are indoles, or contain indole radicals.

The hallucinogens include characteristically those chemicals which cause dissociation of usual neuronal association pathways. They break the overall nervous integration customary in a healthy person. A transitory psychotic-like state may be produced by their action, and this seems to be usually of a schizophrenic type. In general they are depressant agents and cause lassitude, muscle relaxation, lowered blood pressure, slow respiration, diminished heart action, and decreased speed of reaction time. In larger doses they may cause delirium.

Among the typical hallucinogens are mescaline, adrenolutin, bufotenine, lysergic acid diethylamide, harmaline, ibigaine, and yohimbine. Similar effects are caused by morphine and scopolamine. These drugs are related to the indoles. On the other hand, the same kind of effects can be caused by appropriate amounts of ethanol and cannabis, which are not chemically related to the indoles in any simple way. There may be different mechanisms of action for the differing chemical types. Indeed, ethanol may act, as suggested by Jordan and Speidel, by increasing the distance between synapses. The other hallucinogens seem rather to act on internal or cell-surface neuronal factors, which may interfere with synaptic transmission.

The tranquilizers are drugs which reduce anxiety, nervous and muscular tension, and acuity of awareness. They are mildly depressant, and induce muscular relaxation. They are not as intense nor as powerful in their action as the usual central depressants, whether the bromides, chloral hydrate, paraldehyde, or the depressant barbitals. They are not anticonvulsants; neither are they very close in action to alcohol. There are similarities, however, in the effects of all these kinds of drugs, as well as in the effects of some of the antihistaminics, the congestive analgesic such as the salicylates, and the morphines. The new tranquilizers are reserpine, chlorpormazine, meprobamate, and azacyclonol. There is little chemical similarity among these agents. Both reserpine and chlorpromazine, however, have indole-like radicals in their constitution.

The central stimulants are drugs which tend to cause increased alertness, increased respiratory and pulse rates, increased blood pressure and muscle tone, and increased speed of reaction, with exaggerated reflexes. They promote wakefulness and reduce the sense of fatigue. The common central stimulants again are a diverse chemical group. Some of them may cause convulsions in doses only slightly above those which induce increased alertness. These drugs include strychnine, metrazol, the xanthines such as caffeine, many alkyl amines as amphetamine, many tropines, cocaine, and other local anesthetics, and now the newer stimulants as pipradrol and methyl phenidryl acetate.

There is always an infectious enthusiasm in work in a new medical field. The promise of doing something worth while in promoting mental health and in handling mental disorder has stimulated much excitement and vigorous scientific and clinical effort. This was well reflected in the Atlanta symposium on the new tranquilizing drugs. It is sometimes helpful under such conditions to pause for reflection on what might have been done previously in regard to drugs like those now under such intensive study.

There is much to be gained, for instance, in quiet contemplation of the mass of material brought together on hallucinogens and related drugs by Lewis Lewin (1850–1929). His *Phantastica* (Berlin, 1924, with English translation in 1931 and 1934) contains many acute observations which might aid in orientation of current effort. Especially is he important for his notations on mescaline, which he investigated thoroughly. Similarly one should not neglect the clinical descriptions of mescal action given by Weir Mitchell (1829–1914) in 1896 or by Havelock Ellis (1859–1939) in 1897. It might be wise to go over carefully the immense amount of undigested factual information available on the action of morphine and alcohol. Much might be gained, as indicated by Doctor Henry Beecher, from a consideration of the vast information available from scientific study and clinical experience in anesthesia. Here great changes in central nervous system status and bodily function can be caused with amazing suddenness and with prompt control. Perhaps correlations can be made on an expanded time scale with some of the symptomology of mental disorder and with the effects produced by hallucinogens and tranquilizers.

For clarification of concepts in the new field of drugs affecting mood and behavior, it is wise for the alert investigator not only to recall what may have been found years ago, but also to look around at related green pastures in order to get ideas that might be helpful. Always is it pertinent to remember what functional activities may influence the situation. In the case of mood altering drugs there seem to be three that are significant. These are (1) the peripheral feedback from muscles and joints to the central

nervous system, (2) the functional variations in the blood-brain barrier, and (3) the endocrine conditions, especially those involving the thyroid.

Sensory feedback from muscles is a great factor in maintaining central nervous system alertness and wakefulness. Increased muscle tension seems to go with high nervous tension. Conversely muscle relaxation favors mental relaxation and sleep. Drugs that increase muscle tone tend to be central nervous system stimulants, and chemicals that relax muscles (excepting curarine compounds) are associated with more tranquil mental states. We need to devise methods for the quantitative estimation of muscle tone. Physicists are developing devices for measuring plasticity, and perhaps they can be adapted to muscle tension measurement.

Although there is no anatomical structure corresponding to the concept of a blood-brain barrier, there is clear evidence for a chemical gradient between the body circulation and the cells of the brain and brain stem. This may operate through various enzyme systems. It seems to be a protective mechanism to prevent certain kinds of chemicals from acting directly on the cells of the brain stem. Adrenalin or noradrenalin, released in the emergency reaction of the adrenal medulla prepares most vertebrates (excepting the opposum and armadillo, maybe) for "flight or fight," by increasing muscle tone and blood pressure, increasing blood sugar and blood coagulability, dilating the pupil, and opening the lungs. But if it is applied directly to the brain stem, as shown so clearly by Feldberg and Sherwood, it relaxes the muscles, and causes withdrawal phenomena, a sort of mild hypnosis or anesthesia, like the opossum often shows in the face of danger. The blood-brain barrier, possibly acting as a dehydrogenating mechanism, seems able to destroy adrenalin in most mammals before it reaches the brain stem. Related compounds which are not so readily dehydrogenated seem able to pass this barrier. What are the chemical factors involved in the mechanism of this important function of the blood-brain barrier? What enzyme systems are concerned? What competitive metabolic activities may be present? Under certain conditions can the blood-brain barrier act to produce adrenolutin from circulating

adrenalin? These questions deserve the frank asking in the hope of stimulating resourceful research that may help in giving answers which may aid further in understanding the etiology of mental disturbance.

Endocrine activity in relation to brain-stem function is little yet explored. However, it is well known that overactivity of the thyroid causes increased nervous and muscular tension, produces jitteriness, and brings insomnia and anxiety. What effect do depressant drugs have on endocrine function, or what action on the endocrines may come from the nervous stimulants? Here again are questions worth asking. It is already known that reserpine and chlorpromazine stimulate lactation and may affect menstruation.

The influence of factors such as these may be involved in many obscure aspects of findings derived solely from research pinpointed on the direct effect of mood-altering drugs on the brain and brain stem alone.

Electrophysiological Analysis of Tranquilizing Drug Action

An Electrophysiological Analysis of Drugs Useful in Psychotic States

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There are many approaches to experimental therapy that are attractive. One of the most attractive is, perhaps, the rational approach, and this, of course, means that a rationale or a reasonable facsimile thereof must be supplied as the basis for testing and experimentation. Our underlying hypothesis is built on the concept that disturbances in neural function can reflect themselves as mental disturbances and that abnormal modifications of neural function could indeed underlie mental disease.

In a sense, then, this is an inquiry into the premise that the operation of neural pathways, which constitute the substrate of the mind, is a function of the properties of the constituent units or neurons and that therefore abnormal patterns of activity must be based on abnormal changes in the properties of the neuron. More specifically, we wish to examine those properties that are involved in the functioning of the synapse, which has long been known to be one of the sites most vulnerable to many chemical influences.

For this purpose animal studies offer the opportunity of obtaining objective and quantifiable data. Nevertheless, the problem of interest is the analysis of mental disturbance and its possible therapeutic alteration in man. We plan, therefore, to carry out such studies in man and correlate the findings with the clinical picture. Before we can justifiably proceed with experiments of this type in man, we must work out as many facts and details of technique as possible in animals. Consequently, although we