CHAPTER 1

Chemistry of Psychotomimetics

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A. Introduction

A presentation and discussion of the psychotomimetic drugs in a handbook concerned with psychotropic agents must, at the onset, emphasize the several properties that make this class of materials unique.

Most psychotropic drugs are intended to be either curative or cosmetic. They may be used to reverse a pathologic mental state, or they may be intended to alleviate a persistent symptom which, in turn, might then allow some normal repair process to take effect. In either case, treatment is provided a patient who shows some psychological inadequacy with the intent of normalization. The psychotomimetics, on the other hand, are generally studied in subjects who have good psychological balance. To the extent that the effects are considered disruptive, the rationale of research is the generation of an intoxication that bears some superficial resemblance to a psychosis. When such a transient and reversible "model psychosis" is produced, biochemical and psychological changes can both be observed. But to the extent that the effects are considered constructive, there are benefits to be found in the areas of insight, changes of motivation, self-analysis, entertainment, and even simply escape. These results may be effected through a process of disorganization and reorganization, by a sensory elaboration such as visual or auditory enhancement, or by intense reverie or fantasy. There has been only limited experimentation with these drugs in the treatment of pathologic states, and so there has been little recognition of any potential medical utility. This limitation, along with a generalized abuse potential inherent in such drugs, has led to severe legal classifications which have, paradoxically, further restricted human experimentation. This latter point is exacerbated by another unique property. The effects that are observed such as changes in interpretation, in insight, and in communicability, can be assayed only in man. At the present time, no assays or behavioral tests in animals exist that allow satisfactory prediction of the qualitative nature of a new and unexplored psychotomimetic drug.

Thus, this group of drugs stands apart from the remainder of the psychotropic drugs and must be discussed in terms other than those of neuropathy, pathology, and related clinical presentations. Rather, a generalized chemical subdivision will be made predicated upon structure and grouped with reference to the principal neurotransmitters. Functional relationships with these endogenous factors are still controversial.

I. Terminology

A number of names are currently in use to identify this group of drugs. "Psychotomimetic," the adjective used in this chapter, literally means psychosis-imitating. In the
early work with these materials, it was believed that they led to an authentic psychotic state and might be of value in the search for endogenous psychotoxins or in biochemical unbalances that might he correlated with such mental states. To a clinician who interacts with mentally ill patients, these experiences might increase both understanding and compassion if he were to experience within himself the "psychotomimetic" syndrome. This concept fell into complete disrepute a decade ago, but today it has a balanced acceptability. The name remains neutral and medically unbiased and will be used in this chapter. The term "hallucinogen" is widely used, but it implies that the generation of hallucinations is a general property and, in fact, synthetic imagery of undocumentable origins is a rare property of these drugs. A third term, also widely used, is "psychedelic", which was coined in the mid-1960s to indicate mind-manifesting or mind-expanding properties. The term, however, has become associated with the broad and occasionally irresponsible popular use of these drugs. It is rarely seen in the medical and scientific literature due to the connotation of both condoning and encouraging paramedical use. The term "psychodysleptic" has been routinely employed in Europe for drugs of this classification to emphasize similarities to the psycholeptics (mood depressants) and psychoanaleptics (mood stimulators). A host of other terms proposed over the years (e.g., phantastica, delirients, schizogens, eidetikas, etc.) have historic interest but have never found wide acceptance.

II. Methods of Assay

Three broad areas of scientific discipline have been employed to rank and to attempt to explain the quantitative nature of the psychotomimetic drugs. The molecular structures of the active drugs themselves have been dissected and interpreted in completely physical terms; the materials have been titrated in animal models in a search for behavioral correlates that might relate to human activity; and most precisely, they have been studied in clinical experiments using humans.

The physical approach to explanations of biologic activity has been exclusively concerned with the geometry and measurable properties of the chemicals themselves. Intramolecular hydrogen bonding is a measurable property that can explain stabilization of unusual conformations (Smythes et al., 1970), and it is widely felt that in the case of bifunctional molecules, the establishment of parameters, such as the separation of charged sites, might allow some definition of sites of action (Kelley and Adamson, 1973). The natural molecular configuration of psychotomimetics can be determined using X-ray crystallography (Baker et al., 1973), but these data are obtained from solid samples, whereas these drugs are, by definition, only active in solution. Computer calculations of orbital charge densities and charge distributions (Snyder and Merrill, 1965) have been correlated with potency, as have empirical measurements such as partition coefficients (Barfknecht et al., 1975) and strengths of charge transfer complexes (Sung and Parker, 1972). Such properties are, in general, simple to measure or calculate precisely, but successful generalizations have been restricted to studies of small classes of closely related drugs. There has been no successful extrapolation to new chemicals.

Biologic titration in animal models has given a wider correlation, but one which still lacks behavioral logic. In vitro experiments have concentrated largely on interactions of selected psychotomimetics with neurotransmitters. Their agonist or antag-