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edited by Maxwell Gordon

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Edited by

MAXWELL GORDON

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A Series of Monographs

EDITED BY

GEORGE DESTEVENS

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TO MY WIFE

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Foreword

The many advances made in medicinal chemistry within the past quarter-century have done much to further our knowledge of the relationship between chemical structure and biological activity. This relationship has led to a tremendous collaborative effort between chemists and biologists, and this has been evidenced further by the considerable number of reviews which have appeared on various aspects of medicinal chemistry. For the most part, these have been confined to single chapters on selected topics. Of necessity, in such a format, it has been difficult to cover a particular area very broadly.

The purpose of this series is to present a series of monographs, each dealing with a specific field in medicinal chemistry. Thus, these edited or authored volumes will make available to the medicinal chemist and biologist an opportunity to review critically a topic; consequently, a broader perspective of a subject can be realized.

GEORGE DESTEVENS

Preface

The multidisciplinary nature of research on psychopharmacological agents, coupled with the rapid rate of growth of research in this area, has prompted us to make available a review on this topic. This book is written primarily for medicinal chemists and pharmacologists, but researchers in other disciplines such as clinical investigation, biochemistry, analytical chemistry, etc., may also find material of interest here.

The organization of this book is generally based on a treatment of the major classes of psychopharmacological agents in separate chapters. To the extent allowed by the diverse nature of the subject matter, each chapter covers the history, synthesis, pharmacological activity, *in vivo* distribution and metabolic fate, analytical methods, and, briefly, the clinical uses of each class of psychopharmacological agents. We feel that, by having these chapters written, in the main, by the discoverers or developers of each class of compounds, we have achieved an authoritative treatment of this complex subject. We hope that we have attained a successful balance in respect to the scientific disciplines involved, and we shall be grateful to our readers for pointing out any errors in fact or interpretation.

The disproportionate length of the phenothiazine review, relative to the other chapters, has resulted in this topic being put into a separate second volume. This arrangement was also deemed advisable because of the over-all size of the treatise; publication in a single volume would have resulted in too large a book. Volume I covers the literature up to 1963, with supplementary material made available in the appendix of Volume II.

It is our pleasure to acknowledge the valuable aid of many people in the preparation of these volumes. We are grateful to Dr. Charles E. Berkoff and Mr. R. F. McCandless for editorial assistance and to Mrs. Hilda Kihm and Miss Rita De Sanctis for excellent clerical assistance. We would like to thank Drs. S. Archer, A. Burger, L. Cook, P. N. Craig, R. B. Doughty, B. Douglas, M. Finklestein, H. Green, C. Kaiser, J. Laubach, B. Loev, R. McLean, R. F. Raffauf, L. J. Sternbach, G. deStevens, C. W. Scull, D. H. Tedeschi, R. E. Tedeschi, J. A. Weisbach, and C. L. Zirkle for reading various chapters.

We greatly appreciate the assistance of Mr. Paul Ackley of Smith Kline & French Laboratories in alphabetizing and tabulating the subject index by means of electronically sorted punched cards.

Philadelphia, Pennsylvania
June 1964

MAXWELL GORDON

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Introduction

MAXWELL GORDON

Smith Kline & French Laboratories, Philadelphia, Pennsylvania

This book starts with the assumption that psychopharmacology does have a basis in fact, that results from animal experimentation are transferable to man in some degree, and that conclusions can be reached from prior experience which will aid in the design of new drugs.

Our book is written by and for medicinal chemists and pharmacologists who are interested in the present state of the development of psychopharmacological agents. The drug-oriented clinician who is interested in psychopharmacology can find here the pharmacological basis for clinical trial of agents in man and some indication of their scope of application. He will not find here any detailed tract on the types of diagnoses that have responded to medicinal agents, nor will he find here any assistance in trying to decide where psychopharmacological agents may or may not have application to his practice of medicine. For answers to these questions, he must look elsewhere and we recommend the references on this subject given at the end of this chapter, as well as many original papers that are cited in the various chapters where appropriate. The books and papers listed at the end of this chapter also cover such subjects as the diagnosis of mental illness, the classification of mental illness, its treatment with drugs, etc.

The diagnosis of mental disease is a very complex art. Even the experts in the field do not always agree on a diagnosis for a certain set of symptoms. This being the case, it is not surprising that the layman, or even the nonspecialist scientist, is confused by this field. In discussing the use of chemical agents for the treatment of disease, it will be necessary to make a few statements about the diseases being treated, and here a vast oversimplification must be made. It is assumed, for the purposes of this book, that all persons with mental disease, either neurotics or psychotics, are either agitated above the "normal" level or depressed below the "normal" level of activity, or their symptomatology may present combinations of these. All other delusional, hallucinatory, paranoid, and other signs and symptoms of mental derangement must essentially be ignored in this discussion. To do otherwise would render this subject

too impossibly complicated to treat. Inasmuch as our treatment of the subject is in the main a chemical and pharmacological one, we rely only on the final assumption that the return of an agitated neurotic or psychotic patient to near-normal levels, or the elevation of a depressed patient to normal levels of activity is a therapeutic accomplishment. It is true that our therapy may do other things as well, and indeed often does, but for purposes of this book we cannot go beyond this point.

It must be recognized that there are many adherents of the psychoanalytic school who still maintain that the use of drugs in mental diseases is of no value, and that only psychoanalysis or psychotherapy can have any favorable effect in the area of the treatment of mental patients. We cannot attempt to resolve this difference of professional opinion, nor is this the proper place to make this resolution.

Historically, many sedative agents have been used to calm agitated mental patients. There are instances of the use of opiates mentioned in the literature; unfortunately, because of their potential addiction liability, the possible utility of opiates as psychopharmacological agents has not been established or disproved in modern medical practice (Carlson and Simpson, 1963).

The barbiturates have been used for many years to calm both agitated neurotics and psychotics. Unfortunately, the barbiturates and other similar hypnotics and sedatives have suffered from the limitation that either the sedative effects were inadequate or, if adequate, the patient was soporific or asleep. Thus the classical sedatives offer little opportunity to sedate patients without at the same time producing a hypnotic or stuporous state (cf. Berger, 1963). The main impact of the psychopharmacological agents has been to calm agitated patients to the point of making them tractable, without severely limiting their level of awareness. They are thus more amenable to psychotherapy and other rational treatment. Furthermore, prior to the discovery of the new antidepressant agents, classical stimulants have been only partially successful in the treatment of severe depressions.

Two agents are responsible for introducing the revolution in psychotherapy. These are reserpine, an alkaloid of *Rauwolfia serpentina*, and chlorpromazine, a synthetic drug related to the antihistamines. The introduction of *Rauwolfia* alkaloids (as the whole root) in western medicine began in 1953 and chlorpromazine was introduced in the following year.

Anyone who reads the old literature on the treatment of mental disease will find many approaches, among the more recent of which are electroshock, insulin shock, prefrontal lobotomy, etc., which were introduced with great fanfare and enthusiasm, followed by a gradual decrease in interest until the new therapy settled into its proper place in medicine, or disappeared from the scene. The relative undesirability of many of these treatments can be judged by the fact that in some mental hospitals they are no longer the treatment of choice.

The introduction of chlorpromazine and reserpine has resulted in an entirely new attitude toward mental disease. We have seen that most mental institutions have been converted from mere custodial establishments to true therapeutic hospitals. The staff of these institutions have likewise had their duty changed from that of custodian to that of modern therapist. It is particularly striking that in mental institutions today there is a marked absence of the noise, agitation, and confusion that have always been so evident in mental hospital wards. Also much less in evidence are the restraining devices, cold packs, etc., that belong in the middle ages.

It is quite interesting that one of the new psychopharmacological agents, reserpine, had a difficult time gaining acceptance in the Western hemisphere. The roots and leaves of several *Rauwolfia* species have been used since the middle ages in Indian medicine (this is the original Indian snakeroot).

In the 1930's, extensive chemical studies were carried out by Siddiqui (1939). The first isolation of reserpine was by Mueller *et al.* (1952). This work was quickly confirmed by a number of other groups in various countries.

The reported hypotensive effects of reserpine were received with considerable skepticism in the West. The hypotensive effect was difficult to demonstrate because of the delayed onset of hypotensive activity. Often treatment for several days or weeks was necessary to produce significant hypotensive effects. However, both the hypotensive and sedative effects are prolonged in nature, and both effects may be related to changes in brain and peripheral amine levels. The sedative effects of reserpine were responsible for its investigation as a psychotherapeutic agent. In more recent times, there has been medical emphasis mainly on its use in hypertension, since the larger doses required to produce sedation in mental patients often lead to an undesirable level of side effects.

Chlorpromazine was first used as a psychopharmacological agent at about the same time as reserpine. The former had its origin in the antihistaminic phenothiazines. It had been noted earlier that a number of these drugs produced sedation as one of their side effects. The potential therapeutic usefulness of a new structural series of central depressants caused French investigators to examine structure activity relationships in the phenothiazine antihistamines, and they thereby found structural changes which enhanced central nervous system effects—thus leading to chlorpromazine. It is a remarkable coincidence that two quite different drugs, from the standpoint of their origin, history, and structure, were introduced almost simultaneously to open the field of the drug treatment of mental disease.

To get some indication of the changes that have been brought about by the new psychopharmacological agents, it is of interest to look at the data from New York's twenty-seven State Hospitals. For many years the admission rate in these hospitals had been increasing at the rate of 2000 per year (Brill and Patton, 1959). However, starting in about 1956 there was a 19% increase in

discharges and a net drop in admissions. This trend has continued. It is believed that this improvement has been brought about because mentally disturbed patients are being treated earlier and more effectively with psychopharmacological agents. Many illnesses are being treated in early stages so that the patients do not require commitment. Not only do the patients become more manageable, and therefore more accessible to classical psychiatric treatment under the influence of tranquilizing drugs, but many are restored to useful function without the aid of any other treatment.

Thus, Goldman (1961) reports that recent improvements in functioning of psychiatric patients, as well as in constructive relationships between patient and physician, must be attributed in large part to newer drugs. Based on records of the Rochester State Hospital, Pollack (1962) reports that from 1955 to 1960 the number of hospitalized patients had decreased and the number of patients on convalescent or family care has increased.

Similarly, Ayd (1962) has reported that by the end of 1960 there were about 535,000 patients in state mental institutions, a reduction of more than 23,000 patients since 1955. Furthermore, the drop of 6614 patients between 1959 and 1960 was the largest annual reduction since 1956. In addition, in 1960 a new high of forty states reported decreases in mental hospital patient populations, as opposed to thirty states in 1959. Thus, the psychopharmacological agents have become quite well established in the treatment of psychoses, yet by no means is this application free from controversy.

Ayd (1963) has estimated that during the past 10 years 50 million patients throughout the world have received chlorpromazine, that 100,000 people have taken it for 1 year or longer, and that it has been the subject of, or mentioned in, 10,000 publications. Rothlin (1962) and Pichot (1963) have also published a review on 10 years of pharmacopsychotherapy.

In looking at the effect of pharmacotherapy on the population of mental hospitals, it should not be overlooked that it is the acute cases that are the most amenable to treatment. The hard core of patients in mental hospitals includes many congenital cases of mental retardation, patients with combined medical-psychiatric-social problems who are usually indigent, and victims of other chronic diseases in which the mental aberrations may be peripheral to their essentially medical problem.

In this connection, the contribution of chemotherapy in prior decades to the reduction in the number of syphilitics in mental hospitals who suffered from paresis, and the contributions of improved nutrition toward elimination of the psychoses resulting from pellagra (see Chapter 2, Volume II), should not be overlooked. Here we have instances of the solution to purely medical problems having the effect of eliminating, in time, one segment of the mental hospital population.

The availability of psychopharmacological agents for treating mental disease has resulted in many changes in the pattern of treatment of mental