MORPHINE & ALLIED DRUGS

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MORPHINE AND ALLIED DRUGS

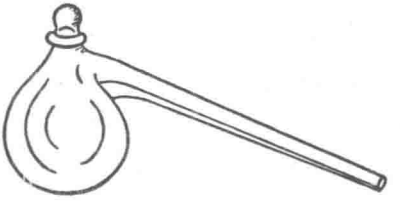
NATURAL COMPOUNDS

Morphine
Codeine
Thebaine
Papaverine
Narcotine
Minor Opium Alkaloids
and Others

SEMISYNTHETIC COMPOUNDS

Heroine
Dionine
Dilaudid
Metopon
Apomorphine
Nalorphine
and Others

SYNTHETIC COMPOUNDS



Meperidine
Methadone
Alphaprodine
Levorphan
Levallorphan
and Others

PREFACE

A CENTURY and a half after its isolation by Sertürner in 1803, the chemical structure of morphine has now been established. During the intervening period, the pharmacology of morphine and its derivatives has been the subject of an enormous amount of intensive research. During the last quarter of a century, an extensive program has been carried out in an attempt to reveal the true nature of addiction, and to develop, if possible, nonaddicting analgesic compounds possessing the clinically desirable properties of morphine. Until recently, this attempt has not been particularly fruitful. Now, however, several new synthetic compounds are available which, although still possessing varying degrees of addiction liability, appear to have certain advantages over morphine. Their development means that we are no longer dependent on opium and its constituents for analgesic agents of sufficient potency to relieve severe pain. The search for new and better analgesics, however, continues with undiminished zeal. Neither the clinician nor the research worker is content to accept a situation wherein relief from pain is secured at the risk or expense of provoking drug addiction. Even in cases of terminal illness, many clinicians hesitate to incur the additional distress which attends the development of physical and psychical dependence. It is not surprising, therefore, that an overwhelming volume of literature has appeared in this active field of research. It is fortunate, indeed, that from time to time various aspects of the subject—many quite broad—have been capably reviewed, and sincerest tribute is paid here to those who have laboured so conscientiously in this arduous work. Such reviews are most essential, in order to assemble the available material before the task is rendered hopeless by the volume of information and its ubiquitous distribution throughout medical literature. The exceptionally fine review of the alkaloids of opium by Drs. Krueger, Eddy, and Sumwalt of the United States Public Health Service is deserving of special mention. This outstanding monograph covers the literature in that field to 1941. Since that time,

numerous fine review articles of more limited scope have appeared. Notable are those by Drs. Harris Isbell and Abraham Wikler and their associates at the United States Public Health Service Hospital in Lexington, Kentucky. This group of workers has conducted extensive studies on the nature and treatment of narcotic addiction and on the addiction liabilities of new analgesic compounds. The fine contributions of Dr. Henry K. Beecher and his colleagues also call for special mention. These are but a few of the many excellent works available.

Recent years have seen many developments in this field, and this monograph is an attempt to bring together, in a single treatise, the pharmacology of morphine, its related alkaloids, derivatives, and newer substitutes. Although a rather extensive bibliography is included, it in no way represents an exhaustive survey of the voluminous literature on this subject. This is particularly true of the earlier literature which has been so admirably reviewed in the monumental work published by the United States Public Health Service, mentioned above. An effort has been made to bring this monograph as up to date as possible, but a treatise such as this can only hope to provide a useful source of factual information, point out the needs and trends of future research, and thus indicate the state of development of the subject. The rapid advances of current research, however, can almost revolutionize many of our existing concepts. Never before, perhaps, has this been so true as it is today, when fundamental research in the biological sciences is being conducted with unprecedented intensity.

Among the host of alkaloids which have been isolated from plants of the papaveraceous family, the alkaloids of opium are undoubtedly the most important. Although a vast amount of investigation has been carried out on these bases, the study of opium alkaloids still remains an active field of research. In comparison, the large number of alkaloids isolated from papaveraceous species, other than Papaver somniferum, have received very little attention, and surprisingly few of them have shown evidence of being potentially valuable therapeutic agents. Opium, and more particularly its chief alkaloid morphine, as well as its natural and synthetic derivatives, have a wide range of usefulness in the practice of medicine. The exceptional value of these drugs in the symptomatic therapy of certain conditions is well recognized. It is unfortunate, indeed, that such valuable drugs possess addiction liability. Moreover, tolerance develops with repeated administration, and progressively larger doses are required in order to obtain equivalent effects. The possession of addiction liability necessitates the exercise of strict control over their manufacture, sale, and distribution, which must conform with such regulations as the Harrison Narcotic

Law in the United States and the Opium and Narcotic Drug Law in Canada.

Probably few other classes of therapeutic agents have been more extensively studied than the analgesics. There are still many hiatuses in our knowledge of their pharmacology, and as is the case with most drugs, this is particularly true with regard to the underlying mechanisms involved. With respect to many of their effects, the site of action has been localized fairly discreetly, but the exact mode of action has yet to be established. The fundamental problems involved are complex and not likely to be resolved quickly. They are, however, under concerted attack by constantly improved methods of investigation. The employment of tracer techniques, for example, has been very valuable, particularly in the study of the distribution and metabolism of drugs. Advances in enzyme technology have also made important contributions to the elucidation of many problems. The extensive research program which has been carried out in an attempt to develop new and more useful analgesic agents has extended our knowledge of the relationship between pharmacological action and chemical structure in analgesic compounds. With the acquisition of further information concerning the nature of such phenomena as pain perception, analgesia, tolerance, and addiction, the synthesis of new and improved drugs for the relief of pain should be greatly facilitated.

It is a difficult task to present a concise picture of the pharmacology of these drugs, since the literature in this field is rife with controversy. Responsibility for Parts One, Two, and Five, with the exception of the material on metopon, must be borne by A. K. Reynolds. Wherever possible, a definite pattern has been followed in presenting the material. Each subject commences with a general discussion based on information which appears to be well established or which represents the bulk of available evidence. This is followed by more detailed information on the subject in which points of controversy are indicated. Since species variation is such a notable characteristic of the action of these drugs, the inclusion of material on the various animals studied is essential to an accurate and comprehensive presentation. This naturally makes the subject-matter much more voluminous than would otherwise be the case. Such drugs as codeine, heroine, dilaudid, and others have been treated separately in order to facilitate the location of desired information, and to maintain continuity in the discussion of each individual drug. Morphine, the most important alkaloid, has been presented in considerable detail. The remaining natural and semisynthetic derivatives have been treated in a more concise manner, their pharmacology being rounded out by frequent comparisons to morphine.

With the exception of the material on meperidine, responsibility for the preparation of Parts Three and Four was assumed entirely by Lowell O. Randall. These are devoted to a detailed discussion of the most important compounds developed thus far in the search for valuable new analgesic agents. Included also is the pharmacology of the better known analgesic antagonists and a discussion of theories of analgesia based on structure-activity relationships.

Several years have been devoted to the preparation of this monograph. If it serves nothing more than as a time saver to the host of busy research workers in this field, the authors will feel well rewarded. It is hoped, however, that it will prove to be not only a useful source of information but also a guide and stimulus to further reading.

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PART ONE

ALKALOIDS OF OPIUM

INTRODUCTION

OPIUM is obtained from the dried juice of the poppy plant, *Papaver somniferum*, which is cultivated chiefly in Asia Minor, India, China, Persia, and some Balkan countries. The milky juice is taken from the seed capsules just prior to ripening and then dried and powdered. Harvesting of opium dates back to very early times, and references to *meconion* may be found in the writings of Theophrastus, third century B.C. Opium has been used in medicine for centuries, and was extensively employed by Arabian physicians. The pure alkaloids, of course, were not known or utilized until early in the nineteenth century, but various preparations of the crude drug were compounded. Laudanum is said to have been developed by the great early physician Paracelsus, and tincture of opium remains an official preparation today. The preparation of paregoric is accredited to Le Mort of Leyden, and Sydenham's laudanum was prepared by Sydenham about the middle of the seventeenth century. "Brown mixture," a preparation of opium and licorice, was compounded about 1814 by Doctor Barton, a Philadelphia physician. Opium was introduced into the Orient by Arabian traders, and during the seventeenth century, opium abuse became wide-spread in China where the habit was exploited by the Portuguese and English. The Chinese government attempted to outlaw the sale and smoking of opium, and embargoes on its importation led to open conflict with England on more than one occasion. Narcotic abuse remains a serious social and economic problem to this day.

Powdered opium contains some twenty-five or more alkaloids which constitute about 25 per cent by weight of the opium and are responsible for its pharmacological activity. Morphine, codeine, thebaine, papaverine, narcotine, and narceine are the most important bases, many of the remaining alkaloids occurring only in traces. The quantities of the alkaloids present in opium vary widely with the specimen from which they are obtained, but the generally accepted average percentages are as follows: morphine, 10; codeine, 0.5; thebaine, 0.3; papaverine, 1; narcotine, 6; and narceine, 0.2. They exist in opium in

combination with acids, principally meconic. On the basis of their chemical configuration, the opium alkaloids fall into two distinct classes. The alkaloids of the phenanthrene group, as the name indicates, are derivatives of phenanthrene and are considerably more important from a therapeutic standpoint than the alkaloids of the benzylisoquinoline group with which they differ sharply in pharmacological properties. In addition to the alkaloids themselves, some of their better known derivatives are also discussed in the following sections. It should be borne in mind that the pharmacological actions of the opium alkaloids are not only complex but vary widely with species and dose. Generalizations are in many cases practically impossible, and hasty assumption that the effects observed in one species apply to another should be carefully avoided as such a practice may very often be entirely misleading.