

# Pharmacology: Clinical And Experimental



Hans H. Meyer and R. Gottlieb

# PHARMACOLOGY

## CLINICAL AND EXPERIMENTAL

A GROUNDWORK OF MEDICAL  
TREATMENT, BEING A TEXT-BOOK  
FOR STUDENTS AND PHYSICIANS

BY

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AND

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PROFESSORS OF PHARMACOLOGY

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*WITH 66 TEXT ILLUSTRATIONS, 7 IN COLOR*



PHILADELPHIA & LONDON  
J. B. LIPPINCOTT COMPANY

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## AUTHORS' PREFACE

Experimental pharmacology in its widest significance deals with the reactions of living organisms to various chemical agents or, otherwise expressed, with their behavior under chemically altered conditions of life. Consequently pharmacology is to be looked upon simply as one portion of biology.

Among the endless number of possible pharmacological reactions, there presents a special interest the study of which should aid the physician in practicing his healing art. This portion of pharmacology, "rational drug therapy," in a more restricted sense, forms the theoretical basis of drug treatment. If it is to serve its full usefulness in explaining the ways and means by which pathological conditions may be influenced by drugs, it must constantly keep in closest relations with general pathology, i. e., the study of the various disturbances which occur in disease. These two sciences working together must endeavor to explain how pathologically disturbed functions of the different organs may be influenced by drugs and be brought back to the norm. Here lies their significance for clinical teaching and medical practice.

Rational drug therapy, as presented by us, consequently is dealt with, in so far as possible, in connection with the physician's point of view as to the seat and cause of pathological conditions. For this reason we have divided the drugs into two classes, organotropic (those influencing organs or their functions), and catartropic (those acting on the causative agents of disease), and have thought it best to describe and analyze the organotropic pharmacological actions separately for each organ or functional system.

It appears to be not at all disadvantageous that this method of presentation requires that we frequently must hark back to a consideration of physiological basic principles, for in view of the fact that physiology has been displaced from among the first subjects in the examination for license, it became more important than ever that experimental pharmacologists should refresh and keep alive the knowledge of physiology in the consciousness of the candidate for license.

On the other hand, this necessitates the omission from this work of all mention of a number of important clinical facts, which, while they



possess value for the science of pharmacology, do not appear at present to be available as material for building the foundation of a scientific therapy.

While the different chapters, as shown in the table of contents, have been written by one or the other of us, still there has been a constant coöperation and collaboration between us, which leads us to hope that we have prepared for the reader a homogeneous work.

H. METER,  
R. GOTTLIEB.

## TRANSLATOR'S PREFACE

It has been the translator's aim to present a faithful rendition into English of the original work, and if in seeking to do this he has occasionally or frequently built up sentences which are unwieldy or un-English, he hopes that this will be borne in mind as extenuation therefor. Occasionally, where he has thought it would be of value, he has interpolated comments or additions, which are regularly indicated in the text.

J. T. H.

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\$ 353.91  
272.51

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# PHARMACOLOGY

## CLINICAL AND EXPERIMENTAL

### CHAPTER I

#### PHARMACOLOGY OF THE MOTOR NERVE-ENDINGS

WHILE all parts of the nervous system may be influenced by drugs, the nerve-endings and the nerve-centres are much more susceptible to such action than are the conducting paths. This is due partly to the scanty blood supply of the nerve-trunks, but chiefly to the fact that the medullated nerve-fibres are enclosed in sheaths and are thus protected from the action of the drugs, while the nerve-endings are not thus protected and are therefore more readily affected. However, this protection is not absolute, for, when exposed nerve-trunks are moistened with solutions of drugs or exposed to volatile gases, such as ether, chloroform, etc., which are soluble in the lipoids of the medullary portion of the nerve, stimulating or depressing actions result (*Joteyko u. Stephanowska, Sowton and Waller*).

#### DEPRESSION OF MOTOR NERVE-ENDINGS

Practically, however, pharmacological action on nerve-trunks is of importance only when a concentrated solution of a drug is applied to, or in the immediate neighborhood of, a nerve, as, for example, when cocaine is purposely so injected, or when a hypodermic of ether chances to reach a nerve-trunk, in which latter case most undesirable harmful effects may result.

After discussion of the pharmacology of the motor nerve-endings, that of the central nervous system, of the sensory nerve-endings, and finally that of the vegetative nervous system will be taken up in the order named.

CURARE and its readily analyzed actions form a good starting-point for the study of the pharmacology of the motor nerve-endings. Although little or not at all used in therapeutics, it should be useful as illustrating certain general conceptions of pharmacological action.

The South American arrow-poison, curare (woorari, urari), is obtained from various poisonous plants of the family of Loganiaceæ. Different explorers, notably Humboldt (1799-1804), have told how the Indians prepared this substance by evaporating aqueous extracts of various plants, often adding to it all kinds of other substances.

They also reported the enormous activity of the freshly prepared poison when it is introduced into wounds of men and animals.

Humboldt also noted that the flesh of animals thus poisoned could be ~~eaten~~ with impunity, and that wounds poisoned by curare could without danger be cleansed by sucking out the poison. Both of these observations indicated that when administered by the stomach it, as a rule, was inert.

**Active Principles.**—When brought to Europe, this poison immediately greatly interested physiologists, but, owing to the fact that its active principles readily undergo changes resulting in a diminution of their activity, it also proved far less powerful than the fresh curare.

The physiological activity of curare obtained from different sources has been found to differ not only quantitatively but also qualitatively. Böhm<sup>1</sup> showed that different alkaloids are contained in varying proportions in the three chief commercial varieties, tube curare, pot curare, and gourd curare, thus variously named from the different containers in which they are marketed. These alkaloids belong to two groups, the curines, possessing little or no true curare action, and the curarines, which produces the typical effects. The curine from tube curare is a cardiac depressant, and as, unfortunately, most of the commercial curare is of this variety, its unsatisfactory action is readily understood.

Curarine has not yet been obtained in crystalline form. Of the purest thus far prepared (Böhm<sup>1</sup>) 1/100–1/50 of a milligram produces typical paralysis in a frog. On the other hand, the curines, being heart poisons, do not produce true or typical curare effects but cause chiefly other disturbing effects. The more curarines and the less curine a curare contains, the more typical and uncomplicated by other effects is its action.

When an effective dose of curare is injected into a frog, it soon drops its head, abandons its normal crouching position, and lies on its belly. At first, irritation causes a powerful muscular response, but soon the movements become weaker. The frog no longer jumps, and the respiratory movements of the throat muscles are the only movements observed after irritation. Finally, the frog becomes entirely motionless and no reflex movements result from even the strongest stimuli. The frog, however, is not dead, for the heart continues to beat strongly. It is simply suffering from motor paralysis and, as the muscles still react readily to a direct stimulation, the cause of the paralysis must lie in some portion of the nervous system.

**Analysis of the Actions.**—In the middle of the last century, Claude Bernard<sup>1</sup> and Kölliker<sup>1</sup> both correctly analyzed these effects and determined that the paralysis was of peripheral causation. By ligature of the iliac artery or by tightly binding the whole of the upper thigh, exclusive of the sciatic nerve, one hind leg of a frog may be cut out from the circulation and the blood will no longer reach the periphery in this limb, although its innervation is not disturbed. If curare be injected into a frog so prepared, the rest of the frog soon becomes completely paralyzed, but movements occur spontaneously in this "isolated" leg and reflexly when the skin of any part of the body is irritated. Stimulation of the cord or of the exposed sciatic nerve causes muscular contractions in this leg but not in the other. It is thus shown that the poison does not act on the central nervous system, but must produce its effects by acting

in the motor in the periphery. That this action is not on the nerve system is proved by the fact that even after a nerve trunk has lain for some time in a curare solution its conductivity is not impaired in any way. Therefore, it is concluded that the drug paralyzes the motor nerve endings of voluntary muscles and does not produce any action on other organs.

It is of interest that Jackson (1915) lately failed to recognize that the sensory endings were one of the motor nerve endings. However, as at that time the influence of curare was not well known to physiologists, after examining the literature that this drug acted on the motor portion of the motor neuron, he described it and tested the motor action in the diaphragm.

The sensory nerve endings and the sensory nerve paths are not affected by curare, for, as mentioned above, in this experiment with the "isolated" frog irritation of any part of the body which had been exposed to the action of the drug caused reflex movements in the "isolated" frog which could never arise if the sensory nerve endings, nerve trunks, and the sensory tracts and the reflex mechanism in the spinal cord were still functionally intact.

The curare action, therefore, is limited to the motor end-organ, and the motor conduction paths remain, probably for a time, capable of conducting.

During the first few hours of the action of curare that the very delicate neuromuscular junctions do not lose their power of conduction was shown by Jackson in separate experiments. He succeeded in securing a muscle with two functionally independent parts and in stimulating the upper portion while the lower portion was paralyzed by a tightly sealed ligature. As before entering the subject the part which formed another branch to supply the two portions of the muscle, if the loss of "conduction or stimulus in both directions" were made under these conditions, it should be possible for a stimulation of the nerve trunk starting in the proximal part of the muscle to pass to those close to the severed trunk and thence down the branch leading to the paralyzed part of the muscle and to cause contraction of this part. As a matter of fact, in these experiments stimulation of the neuromuscular elements of the nerve in the proximal part strongly and repeatedly caused contraction in the paralyzed portion (Fig. 1).

The motor conduction paths are affected only after long continued exposure to curare solution (Kawano, Harada, & Suzuki), but this is of absolutely no importance except in the frog.

It thus appears that curare interferes in a particular manner at a point between the motor nerve fibers and their final terminal organs in the muscles, a transition which cannot be considered if the curare action be fully understood. During the motor stages of the action, they produce continuous movements until by a progressive tendency to fatigue of the motor nerve endings so that under rhythmic stimulus

(the contractions grow smaller and smaller at last) (Fig. 2).



FIG. 1. Frog, preparation of the neuromuscular junctions of the neuromuscular elements of the nerve in the proximal part of the muscle.

#### 4 PHARMACOLOGY OF MOTOR NERVE-ENDINGS

As is to be expected the results of the paralysis caused by curare differ materially in frogs and in warm-blooded animals. Curarized frogs can continue to live for days, for, even after all respiratory movements have ceased, the respiration through the skin can supply all the oxygen necessary for their metabolism. A satisfactory circulatory function is maintained and renal secretion continues and attends to the elimination of the poison. Curare poisoning may, therefore, be caused in a second frog by injecting the urine of a curarized one (*Jakabházy*).

Only much larger doses (30 times that necessary to cause paralysis) are fatal in frogs, these larger doses interfering with the circulation and thus preventing the secretion of the urine and the elimination of the poison. *Tillie* observed recovery from a paralysis which had been induced by smaller doses and had lasted 25 days.

In mammals the results of this primary action of curare are quite different, for in them the muscular paralysis causes asphyxia and death unless artificial respiration is instituted. However, the respiratory muscles are the last to be affected, so that, by administering the proper dose, it is possible to keep a rabbit alive for hours with all its muscles paralyzed except the diaphragm.

If artificial respiration is maintained and the curare be of good quality, both heart and vessels are entirely unaffected by any but very large doses, and, as the poison is excreted through the kidneys fairly rapidly, mammals too may recover after the paralysis passes off. Only after larger doses are other functions than those of the motor nerve-endings affected. Very large doses lower the blood-pressure by a depressing action on the peripheral vasoconstrictor mechanism (*Tillie*). When this action is fully developed, neither stimulation of the sciatic nor asphyxiation causes a rise in the blood-pressure. Large doses also weaken the cardio-inhibitory action of the vagus, but the motor mechanism of the heart is unaffected. The motor nerve-endings of smooth muscle are also but little affected (*Bidder*), the intestine remaining excitable and peristalsis continuing even after extremely large doses.

In connection with its use in physiological experiments, the question as to the nature of the action of curare on the central nervous system is of great interest. In Steiner's experiments with fishes, a narcosis of the cerebrum was apparently induced, but it is doubtful if the cerebrum of higher animals is appreciably affected by curare. The spinal cord is certainly not depressed. On the contrary, according to *Tillie*, larger doses cause an increase in its reflex excitability similar to that caused by strychnine. In mammals an increase in the excitability of the vasomotor centre occurs quite early (*Sollmann* and *Pölcher*).

The effects of curarization on the temperature and metabolism (*O. Frank* u. *F. Voit*) are to be considered simply as a result of the abolition of the



body of all vertebrate animals. Curare, which has been observed both in plants and in animals, after ingestion of curare is an immediate paralytic acting on all vertebrate animals. (Bridges?)

It has long been known that curare administered orally is entirely without action, whereas given in doses much larger than those which are fatal when given hypodermically. Formerly this lack of action when the drug was thus administered was explained by the assumption that the great gastric juice destroyed or changed the curare, although the acid of the gastric juice has a deleterious action on the most decomposed curare (5, 6, 7, 8, 9); this is not pronounced enough to explain the great difference between the action of the drug when given by mouth, and when injected subcutaneously. For it is due to its not being absorbed from the alimentary canal. Barrois<sup>10</sup> and Barrois<sup>11</sup> both showed that the comparatively slow absorption from the alimentary canal and the comparatively rapid excretion by the kidneys account for the lack of action when the drug is administered orally, but if the renal arteries be ligatured and the drug then introduced into the stomach, typical curare effects develop.

#### GENERAL FACTORS AND PRINCIPLES INVOLVED IN THE PHARMACOLOGICAL ACTION OF CURARE AND DRUGS

Before going farther, it seems advisable to bring forward certain general factors and principles involved in the pharmacological action of curare and drugs.

As to the action of a drug or poison to understand the agencies of the operations which it causes in the functions of the whole body, the action of curare is directed with unusual precision against a single kind of organ, the motor nerve-endings. This we call *selective action*. When injected subcutaneously, curare does not act on the subcutaneous tissue at the point of injection nor when given intravenously, does it act on the blood-vessels. It has thus no local action, but the motor nerve-endings in the whole body are acted upon wherever sufficient amounts of the drug are carried by the blood. This we call *systemic action*.

Just as the ordinary dose affects only the motor nerve-endings, so too the action of a dose many times larger is limited to these same organs, all other parts of the body being unaffected or nearly so.

With many other drugs having an elective systemic action, we find a somewhat different behavior; for example, with an increase in the minimal dose of atropine which diminishes glandular secretion, the pulse dilates and the pulse-rate increases, and, after a somewhat longer increase of the dose, still other functions are affected. Thus the dose effect is more affected by effects due to actions on other organs which with curare the selective action (acted with very large doses) is exerted on a single kind of organ, as it is in a very high dose of curare. Curare also illustrates well how the results of the