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

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AUTHORS' PREFACE

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. Meyer,
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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CONTENTS

CHAPTER I

CHAPTER II

CHAPTER III

CHAPTER IV

CHAPTER V

CHAPTER VI

ILLUSTRATIONS

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, choloroform, 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*[1] 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 produce 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*[1]) 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 curarine 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*[1] and *Kölliker*[1] 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

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 *Pilcher*).

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