

Referring to the mention of lantern slides Rudolph Raabe inquired whether the author would supply others than students of his school, the author replied he had the negatives and would have slides made, if request was made for them.

THE SEARCH FOR THE ACTIVE PRINCIPLES IN THE NARCOTIC SOLANUMS.*

BY FRED B. KILMER.

Through all races and peoples, among the most primitive and the barbaric, in widely separated lands, there is found an inherent belief of a mysterious power or essence in-dwelling in living plants.

In plants of the nightshade kind, there lay a power that would allay pain, intoxicate, kill. Through the ages, in the legends of the savage, in the lore of the peasant, there lives a story of the Mandrake, the Henbane, the Daturas, the Belladonna, and their peculiar power to stupefy, cure and poison.

The people of the ancient pagan world attributed these powers to superhuman agencies. From good spirits came the properties which were benign. Those which were destructive or harmful had their origin in spirits which were evil—devils. The wise man, the man of magic, the priest, crude forerunners of the scientist, believed that in his own person there was power to control these unseen dominions. Plants were poisonous or benign, according to his will.

Men skilled in so-called science through the centuries have continuously searched to find and to explain this hidden power.

Plato and Aristotle, held that these virtues were due to the varying preponderance of the elements—moist, dry, heat, cold. With Plato, the "harmonious love" between the elements instilled into plant life their beneficent virtues. From the "wanton love" of the elements arose their destructive power. Such classical writers upon *Materia Medica* as Dioscorides and Galen for the most part describe the properties and uses of vegetable drugs without attempting to explain the origin or cause of their power. It is notable, however, that in the case of certain poisonous drugs they at times inclined toward ascribing to them an occult power, perhaps a satanic influence, controllable by the use of charms, amulets and incantations. Of more than passing interest is the recognition by these writers of certain plant drugs which, through an identity or similarity of active principles, might be used interchangeably. Galen gives a table in which several of the solanums are so similar or equivalent in effect as to be interchangeable:

"Instead of dorycnium (belladonna)—the seed of henbane.

"Instead of halicacabus, the seed of strychnos.

"Instead of mandragora, dorycnium.

"Instead of the seed of henbane, the seed of sweet briar."

Here we have an inkling of our later discovery of identical active principles (alkaloids) in several of the narcotic solanums.

During the Middle Ages, Albertus Magnus taught that the active properties of plants were produced by the combination of five virtues: "that of the element which preponderates in the composition of the plant, the coöperating virtue of the

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other elements which are mixed with it, the virtue of the proportion in which they are mixed, the influence of the stars, and the virtue of the vegetable soul." "The virtue of the place (where the plant grows) and the virtue of the surrounding air are also effective."

The real work of alchemy, as defined by the alchemists themselves, was not to produce gold, but to prepare medicines. By a combination of the four elements (earth, fire, air and water) plus the trinity (mercury, salt, sulphur) the alchemists sought to produce the "universal medicine."

In drugs of manifest power, including poisonous substances, there was present an active principle, the "quintessence" of the alchemists. As defined by Paracelsus, "every substance is a compound of various elements among which one dominates the others, and impresses its own character upon the compound. This dominating element, disengaged, is the quintessence." If Paracelsus had been able to extract or separate from the henbane, stramonium, belladonna or from any of the narcotic nightshades the active principles which we call alkaloids, he would have attained the long-sought "quintessence."

THE OCCULT POWER OF THE NIGHTSHADES.

Through the centuries in medical annals we meet with the story of the "occult power" and the "occult virtues" of amulets, incantations, prayers, words, doings, stones, drugs and herbs. Arnold of Villanova, a 13th Century theologian and scientist, found in occult virtue "a property not immediately perceptible to the senses as are heat, light, cold, color, odor and taste, and also one whose existence cannot be learned by reason or experiment, but only by chance discovery." Occultism, in its inception, stood for a science born of "experiences" (experimental science) and from the beginning has been a science which investigates hidden things of nature. The occult power residing in the deadly nightshades is pictured in the records of ancient Babylon, and runs on through the "fathers" quite down to our own time. It is not easy to make anything out of the tangled mass. The noxious and malignant powers were in part intelligible, and in another part recondite and occult. Through some occult causes these plants varied in their power to react upon the body. Belladonna and stramoniums were always poisonous; the henbanes and the mandrake were rarely so classed. Through some occult principle, a small amount produced a poisonous effect; at other times a large amount showed no action. Our present knowledge leaves us still in the occult stage when we bury these varied actions under such terms as "immunity" and "idiosyncrasy." The great Galen taught that innocent qualities of such drugs as the narcotic solanums could through some occult power cause poisonous symptoms. Mathiolas wrote that the poisonous powers in the solanums "could act at the same time in a manifest and in an occult manner." Through some occult power certain parts of the noxious solanums were more active than other parts. With belladonna, the power of the berries was greater than the leaf or root. In stramonium, the seeds were the more active. With the mandrake, all power resided in the root. Possibly it is through tradition of the occult that makers of official standards adopt only certain parts of drug plants, and reject other parts, without regard to their content of active principles.

In the Middle Ages, the narcotic nightshades were carried into the cloister.

The power of the heathen gods and devils over them was exorcised by incantations and prayers. The mandrakes, henbanes and the daturas were cultivated in the monastic gardens and "purified" preparations made therefrom. At the close of the mediæval period came the printed volume. In the flood of herbals and pharmacopœia-like books the narcotic nightshades hold an exalted place, the mandrake generally filling the center of the stage. The potency of these drugs is made known. By reason of their poisonous power, at times they are banned from use in medicine. The mandrake is endowed with most marvelous attributes. The origin of their power was placed in the heavens, or they might be hell-born. They were controlled by gods and by devils. But the real source of their power had not been revealed to man. In the Seventeenth Century, a Wurtemberg physician, Matthias Faber, devoted ten years to the study of "Strychnos Manicum" (belladonna) and the allied solanums. In a monograph (issued 1677) he cites the authorities from the most ancient down to his own time, the whole forming a most complete study of the narcotic solanum group. Dramatically, and with poetic artistry, Faber places the origin of the occult power of the solanums "in the celestial channels of divinity—the stars." The powerful solanums were "born of the dread Saturn." Solanum "the companion of Mars" changed in form with every conjunction with the sun, Solanum "the comrade of Mercury" carrying implements of destruction. The varying phases of the placid Luna governed the solanum's maddening virus. Faber's views may be taken as representative of the orthodox beliefs of the latter half of the Seventeenth Century.

THE MYDRIATIC POWER.

In our day the most striking action of this group of narcotic solanums is their power to dilate the pupil of the eye. Yet this mydriatic action has been noted, lost and re-discovered more than a dozen times in the history of the plants. This action was known to Galen and other ancient authorities, but it was apparently looked upon as without importance. For many centuries, statements as to the action of these drugs upon the pupil of the eye are not recorded. The illustrious Boerhave, in the Seventeenth Century, as if to settle the question, states specifically that the juice of the belladonna had no action upon the eye. Faber, who, in the Seventeenth Century, devoted ten years to the study of the narcotic solanums, makes no citation in his abundant references as to the mydriatic action. In cases of poison which came under his own observation, he notes the "dimness of vision," but he attributes this phenomenon to the secondary action of the poison, and not to the mydriatic power of the drug. Nearly half a century after Faber, Sicelius (1724) reviewed the literature of belladonna and allied drugs, without making any note of their mydriatic action.

Fifty years after Sicelius, and a hundred years after Faber (1774), Peter John Andrew Daries, a Hamburg drug clerk, opened the way that led to the placing of this group of drugs in their rightful place as mydriatic agents. In making up a prescription, Daries spattered some of the juice of belladonna berries in his eye. Enlargement of the pupil and partial blindness followed. This accident led him to make an extended investigation of the action of the drug upon animals and birds, in which he was assisted by medical friends. This work clearly demonstrated the mydriatic action of the drug and suggested its practical use in operations upon the

eye. After forty years (1816) another drug clerk, Runge (famous for his work on aniline colors), spattered the juice of hyoscyamus in his eye. Enlargement of the pupil followed. With the spirit of a modern pharmacologist, Runge, assisted by colleagues and with the encouragement of the poet, Goethe, experimented with stramonium, belladonna and hyoscyamus, noting the mydriatic action upon animals, birds, etc. Runge produced an acid solution of the crude mydriatic bodies present in the drugs, which substance he called "koromegen" (Greek—Magnifier of the pupil). The labors of these two clerks clearly demonstrated the presence of mydriatic bodies in these solanums, and in the final outcome bestowed immeasurable blessings on the human race.

The early decades of the Nineteenth Century were notable in the history of the search for the vegetable alkaloids. Morphine, nicotine, quinine, caffeine, strychnine and emetine were among those definitely separated. Following the lead opened by the two drug clerks, Daries and Runge, many chemists had sought for the alkaloid we know as atropine. It was finally separated in 1833 by two German chemists, Greiger and Hess, and almost simultaneously by Mein, a German pharmacist. . . . From these years forward up to now, chemical and pharmaceutical workers have labored earnestly in an endeavor to establish the identity of the alkaloids found in the solanaceous group of plants. Their presence in the various species of the narcotic solanums has been investigated. Their presence in various parts of the plant structure and various periods of plant growth has been most fully studied. At the present time, the following alkaloids are classified as properly belonging to the group:

Apoatropine and belladonnine, $C_{17}H_{21}O_2N$
 Atropine and hyoscyamine, $C_{17}H_{23}O_3N$
 Norhyoscyamine and noratropine, $C_{18}H_{21}O_3N$
 Hyoscine (scopolamine), $C_{17}H_{21}O_4N$
 Tropacocaine, $C_{16}H_{19}O_2N$
 Meteloidine, $C_{13}H_{21}O_4N$

PHARMACY.

Consciously and unconsciously, pharmacy has ever taken into account the active principles residing in the narcotic solanums. Primitive man found that the fresh plant, bruised, and applied as a poultice or plaster, carried the anodyne (pain-quieting) power. Arab pharmacy produced from this a concentrated juice or "rob" in which the potent constituents were held in solution in the plant acids. In turn, pharmacy elaborated wines, vinegars and tinctures, each of which carried the active constituents of the drugs. Without any knowledge of the synergistic or the antagonistic action of drugs one upon another, polypharmacy produced mixtures of the narcotic solanums with a dozen or more drugs. As we look back upon these compounds, we wonder what became of the basic active constituents of the solanums. We can see that some of the added drugs might have increased their efficiency. With other additions it would seem that their power must have been modified. Historically notable was the mixture of the extracts of narcotic drugs, including the mandragora, hyoscyamus, opium, etc., used to produce narcosis through many centuries prior to the discovery of ether or chloroform. Here we have an

empirical exhibition of the active principles of these narcotic drugs acting one upon another: an anticipation of modern synergism: forerunner of our scopolamine morphine combinations to produce narcosis (twilight sleep).

When, in later centuries, pharmacy learned how to separate certain active constituents from the drug itself, the pendulum swung to the other extreme. Alkaloidal medication supplanted polypharmic mixtures. It was found, however, that these bodies did not, in all respects, represent the whole drug. With certain drugs there were constituents other than the so-called "alkaloids" which exerted an important influence upon the drug action. With many drugs, of which digitalis is a notable type, potency seemed to reside in a series of ill-defined substances called "glucosides." Thus, when, apparently, the long-sought "quintessence" had been found, it was realized that there was a "something" that was still needed.

In establishing pharmacopœial standards for the narcotic solanums, the pharmacopœial authorities have, in many instances, followed tradition and recognized a particular species of plant, or a certain part of the plant irrespective of the alkaloidal or pharmacological value of other species or other parts of the official drug. There are those who, with force, urge that in our pharmaceutical preparations we only exhibit one of the several active constituents. We are presenting only a fractional part of the whole drug. On the other hand, there are, undoubtedly, official mixtures wherein the essential active constituents are masked, neutralized, "buried" among many extraneous ingredients.

An episode in the search for the active principles of medicinal plants was of American origin. Following the discovery of the principles known as alkaloids, an attempt was made to separate certain resinous bodies, particularly those found in native American plants. The original process consisted of extracting resinous bodies from the plant substance by alcohol, obtaining a tincture, to which water was added, which separated the resinous bodies, the alcohol being recovered by distillation. They were confusedly termed "alkaloids," "resinoids," with similar designations. Out of the host of such preparations exploited, only a bare half-dozen remained in use. It was acknowledged that the term "alkaloids" was misapplied. In the main, the preparations were either crude drug resins or resinous products, together with a number of what were termed "unclassified concentrations."

Possibly pharmacy, even after all the centuries of study, has not yet succeeded in producing preparations containing the real "quintessence" of the solanaceous and other drugs. When we may be able to do this, medical practice may be induced to return to drugs. In the latter half of the Nineteenth Century the veil covering the constitution of the alkaloids began to be lifted. Out of extended research the following facts seem to have been established: The bases which are found in the same plants were found to possess, in general, not only analogous empirical formulas, but also a similar chemical constitution. Many alkaloids found in one and the same plant can be successfully converted one into the other. Thus, morphine into codeine, hyoscyamine into atropine, etc. Viewed from a chemical standpoint, the alkaloids were found to constitute a sharply defined class, inasmuch as they are all, or nearly all, derived from one and the same base, *viz.*, pyridine. Here arises a question: Is the pyridine or similar base the real active principle—the alkaloid—or must we seek further? Again, if we gain control of the base, can we produce the

alkaloidal bodies at will? In the laboratory we have produced synthetic alkaloids. In a few isolated instances the production of alkaloids in the plant has been stimulated. This is as far as we are able to go with our present knowledge.

WHY AN ALKALOID?

Primitive man classified plants according to their utility. The narcotic solanums were useless for forage or food. They gave no woody fibre for shelter or clothing. To him, in one sense, they were weeds, and in many ways they are still in this class. But the cave man found in these plants a power for good and for evil, and utilized this power. Through the centuries the narcotic solanums have held their place by reason of the medicinal power residing in their active principles, their alkaloids. Why are these bodies present in this group of plants? What is the function of alkaloidal bodies in plant life? After ages of study, we have no answer. Investigators have urged that these bodies are stored in the plant as protectives against animal enemies. This idea seems fallacious. The narcotic solanums are not food plants. By their odor and constituents they do not attract (in fact, they repel) food-seeking animals. Instances are recorded of animals feeding on these plants without harm. Birds eat their fruits. Worms and insects vigorously attack and destroy them. Their plant enemies seem to be immune to their poisonous power.

The alkaloidal bodies appear in all portions of the plant structure. At certain stages of the life history of the plant the proportions vary. In a slight degree, the proportions of the alkaloidal bodies are influenced by climate, soil and environment. Methods of cultivation have not resulted in securing any notable increase of alkaloidal content. It has been suggested that the presence of hyoscyamine, atropine, hyoscyne and like bodies in closely related species of the narcotic solanums may, in a measure, result in the influence of environment through the ages. There is much that is not yet clear as to the influence of environment upon plant life, and of plant life upon climate. That the alkaloidal bodies are formed somewhere during metabolic process of plant life is about as far as we have been able to go. In the life processes of the plant akin to what might be termed "digestion" the alkaloidal bodies seem to be elaborated. It has not been shown that the alkaloidal bodies formed in the narcotic solanums have any direct bearing upon the life processes. While it is true that the nitrogen in the alkaloids is an organic combination, it has not been found that they are in any way able to minister to the nutrition and growth of the plant. If the narcotic solanums were supplied with nitrogen solely through their alkaloids, they would starve.

Again, there comes the suggestion that these bodies are in the nature of excreta. A plant, in the ordinary sense, has no excreta. The matter deposited in the bark of trees and in leaves about to be shed may, however, be considered as dead matter—excreta. The narcotic solanums produce but little bark substance. In the plants of this group, the alkaloidal contents of the leaves disappear before they are shed. It is thus difficult to define the place and purpose of the alkaloids in the narcotic solanums. One hazy, perhaps untenable, suggestion might be offered. In some way they may act as catalytic agents, formed in the plant protoplasm, utilized by the plant in carrying out the processes necessary for life, growth and reproduction.

CONCLUSION.

Behind the veil in the Jimson Weed, the hyoscyamus, the belladonna and the mandrake, man found a power that would stupefy, blind, kill, cure. After decades of centuries we pick out a mysterious something which we name an "alkaloid" that will do the same thing, and exclaim "Eureka!" Then we begin to ponder as to why these untellable substances are found in these plants only, and why the elements which we call carbon, hydrogen, oxygen and nitrogen, form in certain nightshades these particular and peculiar alkaloids. Under our present knowledge, the active principles or alkaloids found in the narcotic solanums seem to be as follows:

NAME OF PLANT.	CONSTITUENTS.
<i>Atropa Belladonna</i>	Chiefly hyoscyamine
<i>Datura arborea</i>	Chiefly hyoscyamine with hyoscyamine
<i>Datura fastuosa</i>	Hyoscyamine alone or with hyoscyamine
<i>Datura meteloides</i>	Chiefly hyoscyamine: occasionally a little hyoscyamine or atropine
<i>Datura quercifolia</i>	Hyoscyamine and hyoscyamine
<i>Datura stramonium</i>	Chiefly hyoscyamine
<i>Duboisia myoporoides</i>	Hyoscyamine, hyoscyamine
<i>Hyoscyamus albus</i>	Hyoscyamine and hyoscyamine
<i>Hyoscyamus muticus</i>	Hyoscyamine
<i>Hyoscyamus niger</i>	Chiefly hyoscyamine with some hyoscyamine and atropine
<i>Hyoscyamus reticulatus</i>	Hyoscyamine and possibly other alkaloids
<i>Scopolia carniolica</i>	Hyoscyamine with hyoscyamine
<i>Scopolia japonica</i>	Hyoscyamine

In our every-day drugs there are still things beyond our vision. In many of them we find no "active principles," no alkaloid, the test tube reveals nothing measurable, and yet they carry great power.

"Beyond all that the eye may see, that the ear may hear, that the hands may feel, outside of taste, smell, outside of any native sense, there lies an unseen, unheard, unfelt universe, whose fringe we are just beginning to explore." (New Conceptions in Science.)

SUNLIGHT ON EPHEDRINE SOLUTIONS.

Edwin E. Moore and Marjorie B. Moore have reported that aqueous solutions of ephedrine hydrochloride and ephedrine sulphate in quartz or flint-glass containers were found to be resistant to the action of sunlight, whereas aqueous and oil solutions of the free base were quickly decomposed under the same conditions. Removal of oxygen from the solutions at least greatly retarded, if not completely prevented, the decomposition. The products formed varied with the conditions as temperature solvent, etc. Benzaldehyde, benzoic acid, benzal-ephedrine, amines, etc., have been identified. Certain dyes accelerated the decomposition, while others retarded it. Amber and some other colored glasses inhibited the action.—American Chemical Society.

DETECTION OF PHENACETIN.

By moistening a trace of phenacetin with acetone and 2 to 3 cc. of concentrated sulphuric acid, a red color will show, deepening in intensity when slowly heated on a water-bath with constant stirring, according to Charletti (*Giorn. di Ch.* through *Sept. Drug. Circ.*). When the mixture is diluted there will separate a brownish blue precipitate which dissolves in concentrated sulphuric acid with a red color. This seemingly depends upon formation of a condensation product of acetaldehyde and phenacetin. It is found that 1 mg. of phenacetin will give this reaction. Formaldehyde, trioxymethylene or hexamethylenetetramine will not produce this color.