what may be expected from consistent selection with the official belladonna. Further work of this nature, but leading to increased yield, together with a better understanding of soil and climatic condition is highly desirable. A similar series of investigations is suggested by the genus Datura. Here, however, the range of species is much greater and the variation in the nature of the alkaloids in the various species is such as to present problems of a different character, and which should lead to the use of some of these species for different specific purposes. The species Datura tatula has recently been shown to be equal to or better than Datura stramonium in the percentage of alkaloids. Both of these species have yielded to selection and hybridization in such a manner as to promise the early development of a much-improved strain. Turning to digitalis, we find a host of species and horticultural varieties of unknown therapeutic value which should furnish an abundance of material for the investigator. Many of these have been found to be extremely toxic, both in the flowering and nonflowering stages.

And so the discussion might be continued in detail for cannabis, conium, colchicum and any others that might be grown within the United States. Sufficient has been said, however, to draw attention to the many difficulties that may be encountered in attempting to grow medicinal plants upon a commercial scale, and of the opportunity and desirability for improvement. The beginner in this work should be advised to commence upon a small, experimental scale with a few of the most valuable drug-producing plants and enlarge his operations as results might indicate. The value of the work cannot be questioned, and while it is vitally important that medicinal plants be grown with the same care and consideration as in the case of corn, wheat or other economic forms, still the step from the wild plant to the highly developed variety of known constitution is a long one and cannot be accomplished in a few days.

It is hoped that nothing has been said which will tend to discourage the present widespread movement in drug cultivation. Rather, we would wish to encourage it but in such a manner as to lead to a fair understanding of the true state of affairs and to dispel the idea that large profits may be expected.

BOTANICAL DEPARTMENT, ELI LILLY & COMPANY, Indianapolis, April 8, 1915.

THREE INTERESTING INCOMPATIBILITIES.*

WILBUR L. SCOVILLE.

The first deals with the action of light and heat on the organic acid salts of the cinchona alkaloids.

In 1853, Pasteur found that on heating acid sulphate of cinchonine to 130° C. for several hours, a poisonous compound was formed which was isomeric with cinchonine. This for many years was regarded as one of the curiosities of cinchonine, possessing no practical interest, because in the use of cinchonine it never became necessary to heat it in this way, and consequently no change was expected. Hesse

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(1868, 1873 and 1875) studied the reaction several times in establishing the constitution of cinchonine, and Howard (1872) and Roques (1895) also studied it.

In 1805, Miller and Rhode found that on heating cinchonine with acetic acid at 100° C. for several hours, a similar compound was formed but which crystallized in a different form. Pasteur had called his product *cinchonicine,* and Miller and Rhode called theirs *cinchotoxin,* but in 1900, Brinner showed that the two substances were identical and that the body crystallizes in two forms.

In 1912, Prof. H. C. Biddle of the University of California, made a study of this reaction at temperatures of 100° C. and also at 36° C. with a view to learning whether this compound was likely to influence the therapeutic action of quinine or the other cinchona alkaloids.

Cinchonicine or cinchotoxin is an isomeric form of cinchonine, one hydroxyl group being changed to a ketone group. This change entirely destroys the febrifuge action of cinchonine and it becomes strongly poisonous. The new body resembles digitoxin in its action, inducing convulsions and death in sufficiently large doses. A similiar change occurs with quinine, but quinicine (or quinotoxin) is not as intense in its action as cinchonicine.

Biddle found that by heating either quinine or cinchonine in the presence of acetic, citric, tartaric, lactic, formic or malic acids, the alkaloids were completely converted to the poisonous isomer in from 24 to 48 hours at 100° C. Half of the conversion, he found, takes place in the first six hours. The change is shown by a darkening of the solution, and a lesser solubility of the product.

The color is a good indication of the change, the depth of color being proportionate to the amount of conversion. With sulphuric and hydrochloric acid there is no conversion, and when these acids are present in excess the change with organic acids is almost entirely prevented.

The change was also studied by Professor Biddle at 36° C,—approximately body temperature. As might be expected, it occurs much more slowly at this temperature, being less than 2% of conversion in 36 hours. But that it occurs at all at this temperature is significant, and stands as a warning for pharmaceutical combinations.

The change is induced by sunlight as well as by heat, and it has been shown that the brown color observed in bottles containing quinine, cinchonine, etc., and their salts, which have been exposed to light during long periods, is due to a small amount of these toxic compounds.

Pharmaceutically the change occurs most frequently in elixirs and syrups containing quinine in combination with iron citrate, such as Elixir of the Phosphates of Iron Quinine and Strychnine, Syrup of Iron Quinine and Strychnine Phosphates, etc.

These, as is well known, tend to darken on storage, especially if exposed to light, and the presence of ferric salts accelerates this action. This darkening is due in part to the change in the quinine by action of the organic acid present and promoted by heat or light. That an elixir or syrup so darkened is not only unsightly, but is also poisonous from the presence of quinotoxin, is the fact to be borne in mind. Doubtless some cases of "idiosyncrasy against quinine" are due to the presence of the isomeric and toxic body.

Such preparations should be stored in amber bottles, and should not be dispensed when a decided darkening has taken place.

Professor Biddle further cautions against the free eating of acid fruits when taking quinine as being liable to form enough of the toxic body to produce unpleasant results.

An interesting instance of the probable quinine combinations which may be made, and which need caution in storing is the following prescription which was recently brought to my attention:

℞ Aspirin.
Quininæ Sulph..... āā 3ss
M ft. capsul..... xii no.

This prescription was compounded and not called for. At the end of about a year the druggist found that the mixture had liquefied in the capsules, and asked for an explanation. It is probable that a series of reactions had occurred.

First, the water of crystallization in the quinine sulphate may have decomposed the aspirin, liberating salicylic and acetic acids. (The liquid in the capsules had an odor of acetic acid.)

Second, the acetic and salicylic acids converted a part of the quinine, forming quinotoxin, which is a liquid at ordinary temperatures.

Third, the quinotoxin, being a ketonic body, is likely to form an eutectic with salicylic acid, and if this eutectic melts at ordinary temperatures the liquid would thus be further accounted for.

There is some ground for this view, because a mixture of aspirin and quinine sulphate, when heated in a steam bath, soon liquefies and darkens. Quinotoxin is not as dark as cinchotoxin, but forms a brownish-yellow oil which does not crystallize easily. Hence, a slight darkening with quinine means more than with cinchonine. Quinine sulphate with acetic acid does not liquefy, but it does with salicylic acid.

Preparations containing quinine or other cinchona alkaloids, in combination with or in the presence of organic acids, should not be heated nor exposed to a strong light, and if stored for any length of time should be observed carefully. They are safer if a small proportion of free mineral acid is also present. This hinders the change, or may prevent it entirely.

The second incompatibility which I wish to discuss is that of ferric salts on organic acids induced by light.

A few years ago I was called on to explain why Wine of Beef and Iron, containing 20% of alcohol, persisted in fermenting. Sterilization and the presence of antiseptics did not prevent it, but it was noticed that the change, which closely resembled alcoholic fermentation in its physical aspects, and which gave off carbonic dioxide, seemed to be hastened by sunlight. Finally a sample, which showed a considerable pressure when the cork was removed, and which had all the appearance of active fermentation, was proved not only to be sterile itself but to be incapable of growing bacteria or yeasts which were added to it.

Sterile fermentation was certainly something new!

But that it could be anything but fermentation did not occur to me until its sterility was absolutely proved.

About this time abstracts of experiments upon the chemical action of light be-

gan to appear frequently in chemical literature, and this gave the clue to the true cause of decomposition.

Sunlight decomposes many organic compounds, and among the more sensitive are the organic acids, notably citric, tartaric, and lactic acids. This action is accelerated by ferric salts, which are thereby reduced.

Thus Wine of Beef and Iron, whether made from ferric citrate or tincture of citrochloride of iron, contains the iron in the ferric condition and also a citrate. It is furthermore acid in reaction. Hence, in the presence of strong light the iron is gradually reduced to the ferrous condition and the citric acid is completely oxidized to water and carbon dioxide. Like many other reactions, after once started it proceeds more vigorously, and may be energetic enough to burst the bottle.

Amber bottles, of course, inhibit this action. Neither does it occur in the presence of ferrous iron, at least not as vigorously.

In a diffused light the action is slow, yet I have had a bottle of tincture of citrochloride of iron develop considerable pressure while standing on a laboratory shelf where the direct rays from the sun never reached it, in the course of about two years. In direct sunlight this tincture will show an evolution of gas within a few hours.

The iron elixirs, bismuth elixirs, and most liquid ferric preparations are subject to this reaction. They should never be exposed to the direct rays of the sun and are much better preserved in bottles of amber glass.

The third incompatibility deals with combinations with boric acid. You are all doubtless aware of the fact that glycerin will decompose borax and change it from an alkaline to an acid reaction. This has usually been explained as first a combination in which the glycerin unites to form glyceryl borate and liberates sodium metaborate and water, then the water in turn decomposes glyceryl borate and liberates glycerin and boric acid. So the end products have been said to be sodium metaborate, glycerin, boric acid and water.

This reaction was very simple and satisfying—on paper—until in 1911 W. C. Duncan, Ph. C., of Edinburgh, in a paper published in the British Pharmaceutical Journal, pointed out these faults in the reaction. First, that compound esters are not easily formed in the presence of water; second, that such esters are hydrolyzed slowly, not instantaneously, by water; and third, that the liberated acid is much more active chemically than boric acid, for it causes vigorous effervescence with carbonates, whereas boric acid reacts sluggishly with carbonates. He found also that the amount of glycerin necessary to produce an acid reaction is two molecules of glycerin to one of borax, but if a permanent and active acidity is desired four molecules of glycerin must be used for each molecule of borax, or practically an equal weight, and this equation does not balance on the glycerylborate theory.

Mr. Duncan's explanation is that a new acid, glyceroboric acid, is formed which is analogous to glycerophosphoric acid, and is much more active chemically than boric acid.

Mr. Duncan attempted to prove this, but did not succeed in separating the pure substance from its excess of glycerin, and also failed to separate pure salts of lead, barium, calcium and magnesium which he prepared. But he did show that a number of reactions which occur with glycerylboric acid do not occur with ordinary boric acid, and the evidence is strong that the former acid is formed. Simi-

lar combinations occur with sucrose, glucose, and manitol, and with tartaric and citric acids.

Some time ago a complaint was made that an antiseptic tablet containing mercuric chloride, ammonium chloride, tartaric acid and boric acid did not keep well.

Examination showed that the tablets had a marked odor of hydrochloric acid, and subsequent experiments showed that the boric and tartaric acids had combined to form a borotartaric acid which was active enough to decompose ammonium chloride and liberate hydrochloric acid therefrom. Borotartaric acid was a somewhat familiar article in pharmacy fifty years ago, when its chief interest lay in the solubility, which is far greater than boric acid alone. But that the combination was powerful enough to liberate hydrochloric acid from ammonium chloride was not suspected.

Except for antiseptic washes and collyria, borax and boric acid are not prescribed often, but occasional combinations are found in which it is interesting to note that boric acid is not boric acid.

DISCUSSION.

In the discussion which followed, Mr. Mann stated that he had personally experienced very unpleasant results in a recent treatment of a hard cold, which he thought must have been due to taking rhinitis tablets (containing quinine sulphate) and aspirin at short intervals. A rash appeared which could not be accounted for in the normal course of the disease, and which was severe for a short time.

Mr. Seltzer stated that he had known of a number of cases of unpleasant results following the administration of quinine and aspirin in combination, and is now warning his physician-patrons of this incompatibility.

He thought that quinine and aspirin should not be administered together, or in sequence at short intervals.

Another interesting incompatibility which had recently come to his attention was the administration of hexamethylenamine in gelatin capsules. When these were taken into the stomach the gelatin softened and swelled, a small amount of the acid juices penetrated the capsule and started decomposition of the hexamethylenamine and the formaldehyde liberated acted immediately on the gelatin, rendering it insoluble and the capsules failed to dissolve. He cited one instance in which an active cathartic had resulted in a patient voiding a number of such capsules in an insoluble condition.

Mr. Scoville said that this is a particularly interesting case of incompatibility, gelatin being very sensitive to the action of formaldehyde, and such a condition as Mr. Seltzer had described was quite probable. Gelatin treated with formaldehyde has been recommended for enteric coatings, but while such a process was practical under proper conditions and adjustment, there was much danger of overdoing it and obtaining a wholly-insoluble instead of an enteric coating. The recommendation which had recently appeared in drug journals, to immerse gelatin capsules in a 10 percent formaldehyde solution for five minutes, then drying them and using for enteric capsules, should be condemned, because the result will be, not an enteric capsule but an insoluble one. Gelatin is so sensitive to the action of formaldehyde that minute traces show its effects.

The use of formaldehyde is more likely to result in an artificial leather than in an enteric coating.