# WHAT ABOUT DRUG EXTRACTION?*

BY WILBUR L. SCOVILLE.

*First*, what about the preliminary maceration, before packing and before percolation are started?

Up to the ninth revision of the Pharmacopœia drugs were moistened, packed in a percolator and saturated with the menstruum; then allowed to macerate for (usually) twenty-four to forty-eight hours before the flow was started. In the ninth revision the directions were changed to moisten, allow to stand six hours, then pack, etc.

Why the extra six hours? Is it to allow the drug to swell before packing? Is six hours necessary for swelling? If anybody has explained I have failed to hear.

I decided to ask a micrometer. I was not acquainted with one, but I could be introduced. A friendly carpenter kindly provided me with some little blocks of wood, planed to a smooth surface and measuring about 0.8 inch on the sides and about $^1/_8$ inch thick. A number of such blocks of soft pine and corresponding blocks of hard maple were furnished.

I measured each block for thickness at each of the four corners and also at the center, then placed it in water or in various strengths of alcohol, such as 24%, 49%, 77%, 87% and 95%. Each was then re-measured at intervals up to 48 or 72 hours of maceration.

From a series of more than 400 measurements averaging about 25 on each block, I learned how to use a micrometer and also that wood swells quite rapidly in water and in the weaker alcoholic liquids containing one-half or more water. The swelling was most rapid at the edge, slower at the center. The greater portion of swelling occurred within two hours in these liquids. Swelling occurred across, not with the grain.

The hard wood swelled about twice as much as the pine in most cases. The stronger alcohol swelling was less and was slower. In 87% alcohol swelling was slight and in 95% alcohol I found no swelling after soaking 72 hours.

Having practiced on smooth blocks, I then tried some drugs. I found it a different matter to measure irregular pieces and curved surfaces and only by marking each point for measurement could anything like concordant results be obtained.

The figures which follow give first the minimum, maximum and mean thicknesses in fractions of an inch of each piece. Not less than four measurements nor more than six—usually five measurements—were taken on each piece. The swelling is reported in fractions of an inch as the average of the four to six measurements after the stated interval of maceration.

The drugs selected represent barks, roots, seeds, buds, woods and leaves.

THE SWELLING OF DRUGS IN DIFFERENT MENSTRUA.

| | Measurements. | | | Increase. | | | |
|---|---|---|---|---|---|---|---|
| | Minimum. | Maximum. | Mean. | 1/2 to 2 hrs. | 3 to 6 hrs. | 24 hrs. | 48 to 72 hrs. |
| **Quassia Wood** | | | | | | | |
| Water | 0.070 | 0.098 | 0.078 | 0.004 | 0.005 | 0.005 | 0.005 |
| 49% Alcohol | 0.048 | 0.090 | 0.075 | 0.005 | 0.007 | 0.007 | 0.007 |
| 73% Alcohol | 0.104 | 0.130 | 0.118 | ... | 0.003 | 0.004 | 0.005 |
| 95% Alcohol | 0.097 | 0.102 | 0.101 | ... | 0.002 | 0.002 | 0.002 |

* Section on Practical Pharmacy and Dispensing, Toronto meeting, 1932.

| | Measurements. | | | Increase. | | | |
|---|---|---|---|---|---|---|---|
| | Minimum. | Maximum. | Mean. | ½ to 2 hrs. | 3 to 6 hrs. | 24 hrs. | 48 to 72 hrs. |
| **Sandalwood** | | | | | | | |
| Water | 0.114 | 0.167 | 0.141 | 0.006 | 0.007 | 0.007 | 0.007 |
| 49% Alcohol | 0.093 | 0.125 | 0.109 | 0.004 | 0.004 | 0.005 | 0.006 |
| 73% Alcohol | 0.118 | 0.172 | 0.160 | ... | 0.006 | 0.007 | 0.007 |
| 95% Alcohol | 0.093 | 0.151 | 0.100 | ... | 0.002 | 0.001 | 0.001 |
| **Cinchona Bark (U. S. P.)** | | | | | | | |
| Water | 0.114 | 0.126 | 0.118 | 0.005 | 0.008 | 0.015 | 0.010 |
| 49% Alcohol | 0.112 | 0.126 | 0.118 | 0.000 | 0.004 | 0.012 | 0.011 |
| 73% Alcohol | 0.121 | 0.125 | 0.123 | ... | 0.002 | 0.009 | 0.009 |
| 95% Alcohol | 0.105 | 0.116 | 0.111 | ... | 0.000 | 0.000 | 0.000 |
| **Cinchona Root Bark** | | | | | | | |
| Water | 0.098 | 0.157 | 0.121 | 0.014 | 0.013 | 0.018 | 0.018 |
| 49% Alcohol | 0.083 | 0.125 | 0.106 | 0.002 | 0.004 | 0.012 | 0.011 |
| 73% Alcohol | 0.093 | 0.112 | 0.098 | 0.002 | 0.005 | 0.016 | 0.015 |
| 95% Alcohol | 0.080 | 0.091 | 0.086 | ... | −0.002 | −0.002 | −0.002 |
| **Cascara Sagrada Bark** | | | | | | | |
| Water | 0.088 | 0.092 | 0.090 | 0.012 | 0.040 | 0.053 | 0.053 |
| 49% Alcohol | 0.090 | 0.095 | 0.092 | 0.005 | 0.017 | 0.025 | 0.029 |
| 73% Alcohol | 0.090 | 0.101 | 0.095 | ... | 0.014 | 0.016 | 0.017 |
| 95% Alcohol | 0.100 | 0.120 | 0.110 | −0.008 | −0.008 | 0.003 | 0.003 |
| **Wild Cherry Bark** | | | | | | | |
| Water | 0.046 | 0.074 | 0.052 | 0.009 | 0.004 | 0.013 | 0.014 |
| 49% Alcohol | 0.047 | 0.056 | 0.050 | 0.005 | 0.007 | 0.007 | 0.007 |
| 73% Alcohol | 0.069 | 0.077 | 0.072 | ... | 0.001 | 0.002 | 0.002 |
| 95% Alcohol | 0.056 | 0.095 | 0.075 | ... | 0.000 | 0.000 | 0.000 |
| **Aconite Root** | | | | | | | |
| Water | 0.170 | 0.208 | 0.189 | 0.036 | 0.072 | 0.075 | ... |
| 49% Alcohol | 0.186 | 0.220 | 0.205 | 0.028 | 0.040 | 0.038 | ... |
| 73% Alcohol | 0.124 | 0.178 | 0.148 | ... | 0.003 | 0.006 | 0.003 |
| 95% Alcohol | 0.186 | 0.253 | 0.213 | ... | −0.001 | −0.004 | −0.017 |
| **Gentian Root** | | | | | | | |
| Water | 0.104 | 0.130 | 0.118 | 0.016 | 0.039 | 0.047 | 0.047 |
| 49% Alcohol | 0.083 | 0.100 | 0.091 | 0.001 | 0.009 | 0.008 | 0.009 |
| 73% Alcohol | 0.078 | 0.090 | 0.089 | ... | 0.006 | 0.008 | 0.007 |
| 95% Alcohol | 0.100 | 0.127 | 0.106 | ... | 0.000 | 0.001 | 0.000 |
| **Licorice Root** | | | | | | | |
| Water | 0.082 | 0.100 | 0.094 | 0.015 | 0.018 | 0.018 | ... |
| 49% Alcohol | 0.085 | 0.108 | 0.094 | 0.008 | 0.008 | 0.009 | ... |
| 73% Alcohol | 0.091 | 0.097 | 0.094 | 0.005 | 0.008 | 0.008 | ... |
| 95% Alcohol | 0.067 | 0.088 | 0.076 | ... | −0.002 | 0.000 | −0.002 |
| **Stillingia Root** | | | | | | | |
| Water | 0.070 | 0.086 | 0.081 | 0.009 | 0.011 | 0.013 | 0.013 |
| 49% Alcohol | 0.072 | 0.089 | 0.078 | 0.005 | 0.007 | 0.007 | 0.007 |
| 73% Alcohol | 0.062 | 0.083 | 0.076 | 0.002 | 0.002 | 0.002 | 0.001 |
| 95% Alcohol | 0.069 | 0.092 | 0.082 | 0.000 | 0.000 | 0.000 | 0.000 |
| **Cacao Bean** | | | | | | | |
| Water | 0.328 | 0.351 | 0.340 | 0.023 | 0.041 | 0.050 | ... |
| 49% Alcohol | 0.290 | 0.320 | 0.307 | 0.011 | 0.018 | 0.017 | ... |
| 73% Alcohol | 0.335 | 0.380 | 0.361 | ... | ... | 0.022 | 0.021 |
| 95% Alcohol | 0.302 | 0.344 | 0.327 | ... | ... | −0.001 | −0.001 |

| | Measurements. | | | Increase. | | | |
|---|---|---|---|---|---|---|---|
| | Minimum. | Maximum. | Mean. | 1/2 to 2 hrs. | 3 to 6 hrs. | 24 hrs. | 48 to 72 hrs. |
| **Cocculus Indicus Seed** | | | | | | | |
| Water | 0.332 | 0.395 | 0.359 | 0.025 | 0.029 | 0.029 | ... |
| 49% Alcohol | 0.330 | 0.435 | 0.376 | 0.010 | 0.020 | 0.014 | ... |
| 73% Alcohol | 0.324 | 0.414 | 0.365 | ... | ... | 0.019 | 0.017 |
| 95% Alcohol | 0.353 | 0.429 | 0.391 | ... | ... | 0.001 | 0.006 |
| **Nux Vomica Seed** | | | | | | | |
| Water | 0.147 | 0.168 | 0.160 | 0.004 | ... | 0.017 | 0.039 |
| 49% Alcohol | 0.160 | 0.173 | 0.169 | 0.003 | 0.004 | 0.015 | 0.039 |
| 73% Alcohol | 0.204 | 0.226 | 0.215 | 0.002 | 0.002 | 0.014 | 0.026 |
| 95% Alcohol | 0.181 | 0.195 | 0.187 | 0.000 | −0.002 | 0.000 | 0.000 |
| **Pumpkin Seed** | | | | | | | |
| Water | 0.087 | 0.095 | 0.091 | 0.005 | 0.006 | 0.024 | 0.026 |
| 49% Alcohol | 0.070 | 0.088 | 0.077 | 0.002 | 0.003 | 0.027 | ... |
| 73% Alcohol | 0.078 | 0.085 | 0.080 | 0.005 | 0.009 | 0.008 | 0.010 |
| 95% Alcohol | 0.073 | 0.085 | 0.080 | 0.000 | 0.000 | 0.000 | 0.000 |
| **Balm of Gilead Buds** | | | | | | | |
| Water | 0.166 | 0.263 | 0.217 | 0.025 | 0.029 | 0.029 | ... |
| 49% Alcohol | 0.165 | 0.297 | 0.237 | 0.010 | 0.020 | 0.014 | ... |
| 73% Alcohol | 0.168 | 0.245 | 0.205 | ... | ... | −0.006 | −0.008 |
| 95% Alcohol | 0.148 | 0.248 | 0.204 | ... | ... | −0.013 | −0.021 |
| **Mullein Leaves** | | | | | | | |
| Water | 0.100 | 0.199 | 0.136 | 0.018 | 0.017 | 0.025 | ... |
| 49% Alcohol | 0.109 | 0.145 | 0.121 | 0.011 | 0.010 | 0.014 | ... |
| 73% Alcohol | 0.097 | 0.120 | 0.104 | ... | ... | 0.000 | 0.000 |
| 95% Alcohol | 0.098 | 0.131 | 0.109 | ... | ... | −0.003 | −0.011 |

These figures disclose some very glaring and annoying inconsistencies. For instance, quassia shows (by figures) a greater swelling in diluted alcohol than in water—and these figures were rechecked. Cascara shows first a shrinkage, then a swelling in 95% alcohol. And there are other very doubtful results. Also the lines are not directly comparative because different thicknesses of drugs were used in the individual tests.

A part of these seeming errors can be ascribed to lack of skill on the part of the operator, part to the real difficulty of measuring accurately any change in a material of irregular form where each measurement must be made on exactly the same spot where the surface is curved, and part to the difficulty of comparing measurements on a surface which is first firm and afterward soft and at varying intervals of time.

Aconite root and gentian became very soft—almost mushy—in water and in diluted alcohol, but remained hard in strong alcohol. Other drugs softened to a lesser extent in water—except perhaps mullein leaves—and all remained hard in alcohol. Whether alcohol actually shrinks the tissues or only hardens them is uncertain.

The question also remains whether the swelling or the softening effect is the greater factor in the extraction of drugs by the menstruum.

Another probable source of error in these measurements is the solvent power of the menstruum. With Balm of Gilead Buds, for instance, alcohol takes out considerable resinous material and by this method one does not know whether the reduced size of the buds is due to shrinkage of the tissues or to the extraction of resin or perhaps to both.

Several leaves were tried that are not reported because the normal thickness of the leaves—usually 0.005 to 0.007 inch—or on the midrib up to 0.012 inch—is too small to make a relative change certain, particularly when the tissues are softened. Mullein leaf is much thicker but it softens much in water and becomes brittle in alcohol, and the hairy surface makes an uncertain foundation for measurement. It is the only leaf tried that gave any comparable results, but these are not very satisfactory.

While the results are not very gratifying they do not show any need for long maceration before packing. They indicate that swelling takes place quite rapidly in water and that it diminishes as the alcoholic content becomes greater. This is what we would expect.

Roots and seeds appear to swell in larger measure than do barks and woods. The rate of swelling appears to be proportionate to that of penetration, hence swelling will be more rapid in a comminuted drug than when whole.

In water the greater part of swelling occurred in some cases within 15 minutes. Some of the measurements reported under "$^1/_2$ to 2 hours" were made after 15 minutes of immersion, some after about 30 minutes, 45 or 60 minutes, etc., as opportunity permitted. To save space and simplify the results they are all grouped as in the tabular report.

In alcoholic liquids swelling diminishes both in time and degree in some proportion to the alcohol present.

Taking the results as a whole I do not find justification for the preliminary six hours of maceration now directed. If the question relates to the rate of solubility of the active principles in the drug, and to time for osmosis, the maceration period after packing and saturation with the menstruum will take care of that.

My own most definite conclusion from the figures obtained is that this method for obtaining the facts is probably not the best that can be used. Another method was tried on gentian which shows a different angle on the subject.

Having a specially graduated cylinder at hand, of 25 cc. capacity and graduated so that tenths of a cubic centimeter could easily be read, this was used to measure the volume of ground gentian under the influence of different menstrua.

Five grams of the gentian, in about No. 30 powder, was placed in the cylinder, gently tapped down and the volume read. Then the menstruum was added, the mixture shaken until the drug was thoroughly wetted, the cylinder filled above the capacity with the liquid, again shaken well and then allowed to stand quietly about 20 hours. Then the volume of the drug was measured. Following are the results obtained.

5 Gm. dry = 14.2 cc., and 26.0 cc. in water = 183% expansion.
5 Gm. dry = 14.1 cc., and 21.6 cc. in 49% alcohol = 153% expansion.
5 Gm. dry = 14.1 cc., and 17.1 cc. in 73% alcohol = 121% expansion.
5 Gm. dry = 13.8 cc., and 14.6 cc. in 87% alcohol = 105% expansion.
5 Gm. dry = 14.1 cc., and 12.7 cc. in 95% alcohol = 90% of original.
5 Gm. dry = 13.8 cc., and 12.7 cc. in petroleum ether = 92% of original.

In these measurements the buoyancy of the liquid will affect the result and it will vary in the different cases. The results are not therefore accurately comparable. Perhaps a mixture of petroleum ether and carbon tetrachloride in proportions that will show the mixture to have the same specific gravity as the menstruum to be tested might provide a factor for correcting the buoyancy effect.

Or perhaps a different apparatus in which the liquid displaced by the swelling can be measured (or weighed) may be better.

Measurements involving the ground drug as it is used for extraction would correspond to the conditions of percolation and perhaps give us a better picture of what is taking place in actual operations.

## II.

### WHAT ABOUT THE RATE OF FLOW?

Both the Pharmacopœia and the National Formulary direct that drugs be percolated slowly in all cases. A uniform rate of ten to twenty drops of percolate per minute is directed for the fluidextracts and is inferred for tinctures. No differences are made for the various drugs, nor for the menstrua. But drugs differ in structure and in the ease with which they yield their constituents. Capsicum, for instance, has relatively large cells containing the oleoresin, and is very easily extracted. Cantharides, on the other hand, is especially difficult to extract. If drugs differ in structure and in the solubility of their active constituents, it is reasonable to expect that they should be treated differently.

The object of the Pharmacopœia seems to be that everything that is soluble in the menstruum should be completely extracted from the drug. On this basis a slow percolation insures the maximum of extracted matter.

On the other hand menstrua are selected because of what they exclude as well as for what they dissolve. If discrimination applies in the selection of menstrua, may it not also apply in methods of use?

Cinchona is a case in point. This drug contains alkaloids to which its medicinal value is due and it also contains a considerable amount of tannin which is chemically antagonistic to the alkaloids and which is the main cause of precipitation and deterioration in the preparations. Any menstruum which will extract the alkaloids will also dissolve the tannin. But if a proper acidulated menstruum be selected we find that it extracts the alkaloids rapidly and the tannin slowly. So if the drug be subjected to a relatively short preliminary maceration and then extracted rapidly, the alkaloids will all be taken out while the tannin, being more slowly soluble, is largely left behind. A more stable and entirely active preparation is obtained in this way.

Rhubarb is another instance. This drug contains anthraquinones, which exercise a cathartic action, and tannin which is astringent and therefore therapeutically antagonistic. And rhubarb preparations are notorious for precipitation.

I used to be told that rhubarb was the ideal drug for the treatment of diarrhea (witness the formerly popular Sun Cholera Mixture) because it first acted as a cathartic and removed offending matter from the bowels, then acted as an astringent. This sounded well until one questions how it may happen that tannin, which exercises its astringent action promptly on contact, can be induced to contradict its nature and do the Gaston-Alphonse stunt with a cathartic principle whose nature is to act slowly. Also, when we find that this astringent body is the part which hydrolyses in the preparation and then is deposited as a precipitate we have to conclude that this idealistic action is a delusion.

But we do find that the tannin in rhubarb is consistent in that it dissolves more slowly than does the anthraquinones and that by rapid extraction we secure actively

cathartic preparations which are more stable in that there is less precipitation or change.

This plan of rapid extraction to obtain better products—not merely to save time—is new and has been tried on but a few drugs. It seems that there may be considerable advantage in it for a number of drugs, particularly those that contain tannin but are not used primarily as astringents. Wild cherry and uva ursi, for instance.

## III.

### WHAT ABOUT THE SELECTION OF A MENSTRUUM?

If a selected menstruum dissolves the active principle of the drug and produces a liquid preparation which remains clear, it has been concluded that this menstruum is a proper one for that drug. The development of this plan has led to the use of some twenty or more different menstrua, many of which were selected without any relation to other mixtures in use or without adequate study of the drug. So many varieties of menstrua are unnecessary and illogical.

What are the factors that should govern the selection of a menstruum?

*First*, of course, the character and solubility of the active principle. It would appear that this has been almost the sole consideration in some cases.

*Second*, the character of the preparation. If it remains clear and presentable, that has been taken as evidence of the suitability of the menstruum. But that is not sufficient—as will be shown later.

*Third*, the effect of the menstruum upon other constituents of the drug. This is now noted in that we have different menstrua for pilular and for powdered extracts of the same drug, and frequently the menstruum for an extract is more strongly alcoholic than for the corresponding fluidextract. The stronger alcohol extracts less inert material and allows of a more concentrated product.

*Fourth*, the action of the menstruum upon the drug structure. This has been recognized rather vaguely in the size of powder directed, but this alone is not sufficient. An attempt to get some more fundamental information on this question is shown in the first section of this present paper.

As regards the first consideration—the solubility of the active principle—there is often too wide a range to be determinative. Tannin will dissolve in water, in alcohol or in any mixture of the two. So will alkaloids, as they exist in drugs.

Even resins appear to be slightly soluble in water though not enough to warrant any consideration of water as a menstruum for resinous drugs. But with resinous drugs while 95% alcohol would seem to be the ideal menstruum because of its solvent property we actually can extract more resin (soluble in 95% alcohol) with 87% alcohol, or in some cases with 77% alcohol than with 95% alcohol, under corresponding conditions. How can we account for that fact?

The second consideration, that of the appearance of the preparation, while often sound has yet led into error. Tincture of Krameria, for instance, remains a beautifully clear, deep red liquid on aging, but its tannin hydrolyzes within a few days, probably forming gallic acid which has a very different action. The only reliable official astringent preparation at the present time is Tincture of Nutgall which is made without water. All the rest are astringent only for a short period,

then the tannin is changed either into gallic acid which remains in solution or into phlobaphene, which precipitates.

Two of the most important galenical preparations in use to-day—Fluidextract of Ergot and Tincture of Digitalis—remain clear on aging but show a marked deterioration in activity. Probably there are others that lose in efficiency which we do not yet recognize as deteriorating.

An interesting question comes up in this line. Though the alkaloids of practically all the alkaloidal drugs can be extracted by means of acidulated water, experience has shown that more reliable results are obtained with quite strongly alcoholic menstrua—in the larger number of instances a 73% or 77% alcohol. An adequate answer to this question alone would probably throw considerable light on the subject of principles governing drug extraction.

The third consideration, that of rejecting an excess of inert material, is much simpler. As already noted it is now recognized in the manufacture of powdered extracts by extracting with strong alcohol. This does not dissolve any gums and it dissolves less sugars, and other inert material, so producing a more concentrated product.

Since it has been shown that the inert material in a drug modifies the action of the therapeutically active principles and thus is desirable, this exclusion must not be carried further than is necessary. We still use preparations of the drugs even in cases where the active principles are available in pure and economical form.

The fourth consideration—that of the action of the menstruum upon the drug structure—has had very little attention. This is concerned with the swelling and softening of the drug, the permeability of the cells, relative fineness of powders, dialysis, rate of solubility of the constituents, influence of constituents upon each other, both physical and chemical, etc.

Considering that drug extraction is fundamentally and distinctly a pharmaceutical operation of importance it is not creditable to our scientific standing that we know so little about these matters. We lack a scientific basis for the most distinctive pharmaceutical operation. We are helpless in the face of a new problem.

Consider Tincture of Digitalis as an instance. This drug contains glucosides which are soluble in dehydrated alcohol and are easily hydrolyzed by the presence of water. The drug is easily extracted by diluted alcohol, but a tincture made with that menstruum deteriorates rapidly and almost completely. Seventy-seven per cent alcohol makes a better preparation but this is also unstable. European workers have shown that dehydrated alcohol makes a stable and so a reliable tincture, but by our present method of extraction only about half the activity of digitalis can be extracted with that menstruum. Even 95 per cent alcohol takes out only about half the activity. This is not a question of solubility. Then why does not strong alcohol extract the glucosides? Obviously we do not know enough about the action of alcohol upon the drug structure or upon other constituents to intelligently tackle the problem.

Fluidextract of Ergot is another and similar instance. Recent investigations have established two alkaloids as responsible for the activity of ergot. These are soluble in alcohol but not in water, and are easily oxidized. The present fluidextract, made with diluted alcohol, is very unstable and not at all satisfactory. Again logic points to strong alcohol as a proper menstruum but again we find that alcohol

fails to extract the activity. In this instance we know that heat also destroys the activity so it seems reasonable to suspect that some other constituents of the drug may hinder the extraction of the active alkaloids, perhaps by coagulation. But we are entirely in the dark as to whether the difficulty lies in the drug structure or in interfering constituents.

If pharmacy is to claim any position in the scientific world it must place its most distinctive function on a more scientific basis. Pharmacy has contributed much to science which is not credited rightly because other branches have been accorded the credit. This cannot be altogether avoided, but advances which are so distinctively pharmaceutical that they cannot be miscredited are much needed and are too rare.

Our difficulties are our opportunities.

"Some ships sail east, and some sail west
though the selfsame wind doth blow;
It's the set of the sail, and not the gale
that decides where the ship shall go."

Scientific advancement lies in learning how to trim our sails of knowledge so as to overcome obstacles.

IV.

Finally, what about drug extraction as a problem? Is the study worth while? Aren't drugs—natural vegetable drugs—going out of use? Haven't we enough better and more scientific methods and means of treating disease to make natural drugs and their galenical preparations obsolete in a short time?

Well, what is the evidence? What do the modern developments indicate?

Fifty years ago natural drugs, mineral salts and a few animal drugs constituted most of the materia medica. The retail pharmacist of that day prided himself upon his ability to identify and select drugs and upon his personal skill in making tinctures, pills, plasters, elixirs and the various medicaments then in use.

Then synthetic chemistry invaded the field. Antipyretics came first, acetanilid leading and followed by a host of others, some synthetics, some mixtures, most of which have fallen by the way, but acetanilid, phenacetin, antipyrin and amidopyrine remain. These have greatly reduced the use of aconite but they have not replaced it. We just have a greater choice of antipyretics.

Then salicylates developed, giving us a synthetic oil of wintergreen and reducing the use of salicin and sodium salicylate by providing a variety of forms of salicylates with various advantages. Salicylate medication has increased because of the advantages, but the natural forms are still in use.

A later development has been that of hypnotics. We now have barbituric acid and derivatives thereof which possess a hypnotic action different from that of any natural drug. Again an increase in the variety of medicinal agents, but no natural drug displaced.

A long-continued attempt has been made to displace opium and coca by means of synthetic analgesics but with slight success. We have new analgesics which possess some advantages, but the natural drugs still occupy a firm position in materia medica. Chemists are still working to find products which may possess superior all-around advantages over these drugs, but without complete success thus far.

Anthelmintics have received attention from synthetic chemists more recently and carbon tetrachloride, tetrachlorethylene and thymol have come into use for this purpose. But nature's santonin, male fern and chenopodium still hold a strong place in worm treatment.

Anæsthetics have always been of the synthetic type but even these have not been able to run whisky out of use—to our political sorrow.

Synthetic products, then, have enlarged our materia medica and reduced our dependence upon natural drugs, but the latter still hold some advantages and show no signs of leaving the field.

A second important development of the half century is that of biological products: vaccines, serums, antitoxins, immunogens, etc. These have had much attention and have made a permanent place in treatment—less of disease than as preventives of disease. They are specific medicaments and while serums and antitoxins have a valuable place in the treatment of acute conditions in a limited number of diseases, the tendency of bacterio-biological products is more and more toward prophylactic uses. Their most important province is the prevention of disease. They function mostly before drugs are needed. They touch only the infectious types of disease and these are only a part of mankind's ills. They prevent much more than they cure—which is better but does not obliterate the need of drugs.

The most dramatic development of the later years has been that of the hormones—the active principles of the endocrine glands. This is a vicarious form of medication in that a normal gland of an animal is made to supply the need of the deficient gland in an individual. Since the endocrine glands are nature's factories for manufacturing hormones as needed, it follows that the hormonic effect is temporal and evanescent. They stimulate other organs to action. They supply impulse rather than action.

In many instances the hormones stimulate so promptly and powerfully as to be dramatic. Epinephrine, one of the first of the hormones to be employed, illustrates this. In cases of shock so severe as to cause heart action to cease, epinephrine has been injected into the heart muscle and the person who was seemingly dead has come to life. Such an effect is striking and naturally draws attention. The subsequent condition will depend upon natural recuperative powers, not on the initial action of epinephrine. For prolonged action it fails to meet the need. There are hundreds of persons with weak hearts who keep going, many of them at work, by the aid of digitalis who would succumb if they were dependent upon epinephrine. In an emergency the latter is the important agent; for steady and prolonged action digitalis is much superior.

Insulin is another instance. In this case no effective substitute has yet been found though plants are known which have an insulin-like action but not strong or dependable enough to take its place. Insulin supplies the impulse for assimilation of sugar in the diabetic. But its effect is all over in a few hours and the patient must take a fresh dose every day. It has no curative effect upon the disease. Hope still stays strong with plant chemists that some day a drug will be found which will not only supply the immediate needs of the diabetic but will be curative as well.

These two are typical of the general action of endocrine hormones. They are

peculiarly emergency agents. With the exception, perhaps, of the thyroid gland, they are in general not curative.

The pituitary body will come to the rescue of an exhausted mother, but ergot may prevent the exhaustion.

The dramatic effects which are sometimes obtained through the aid of these hormones has tended to raise unwarranted hopes as to their usefulness and blinded us to their ephemeral character. This is not a depreciation of the value of hormones in medicine; it is rather a new appreciation of old drugs.

Finally, consider the vitamins.

Fifteen years ago dieticians considered that when they understood the calorific value and digestibility of a food that was all that science could tell them about foods. To-day consideration of vitamins has almost obscured that of calories, and foods have become drugs. The leaven has become of more consequence than the bread. Wheat fields are giving way to spinach pastures. The fishes have been changed from brain-food to nose and throat remedies and also supplement the bone-food. The humble are beginning to inherit the earth.

And who knows whether we have yet discovered the real curative powers of vegetable drugs? They still hold a strong place in materia medica. They still baffle us to explain their effects in full. They maintain a mystic value, even with physicians.

I, for one, am not willing to concede that vegetable drugs are as yet threatened with obscurity. They are still worthy of pharmaceutical study.

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## AN EXPERIMENTAL STUDY OF THE DETERIORATION AND ASSAY OF SPIRIT OF ETHYL NITRITE.

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(*Continued from page 807, August 1932.*)

### STUDY OF THE EFFECT OF ADDED PRESERVATIVES.

The addition of some foreign substance intended to serve as a preservative has been one of the methods most frequently suggested for improving the keeping qualities of this preparation. The different substances which have been recommended for this purpose in the past are given in Table II. Of these, sodium bicarbonate, magnesium carbonate, potassium carbonate and glycerin have been most frequently mentioned and were therefore included among the substances selected for the experiments of this series.

In the first group of tests made, sodium bicarbonate and magnesium carbonate were used. In each case an amount equal to about 1 per cent of the spirit was added. Both salts had been used by other investigators as previously shown, and were used by them to neutralize the acid as rapidly as it was formed, as it was believed that the presence of acid was one of the principle causes of deterioration. A sample of the unaltered spirit was stored along with these two samples for comparison. The rate of deterioration of all three is shown in Tables IX, X and XI.

The second group of substances studied embraced glycerin and castor oil. Here again the amount added was about 1 per cent of the volume of the spirit.