

AGENTS AND MEANS EMPLOYED TO DISGUISE THE TASTE OF  
DRUGS AND METHODS FOR EVALUATING THE RELATIVE  
EFFICACY OF DISGUIISING AGENTS

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## INTRODUCTION

During the long era of medical ignorance and superstition, it was common belief that medicines should be repulsive in taste or mal-odorous in order to drive the "evil humours" from the body. The public of today, as a whole, is not as ignorant of medical matters as were its ancestors even as little as a century ago. This has been brought about to a large extent by health education in the public schools, news accounts of the latest discoveries in pharmaceutical chemistry and pharmacodynamics, feature articles by physicians and men in allied professions appearing in newspapers and magazines, and by public lectures and radio addresses. The combined effect has been to make the public conscious of the fact that a dose of medicine need not be bitter, acrid, or nauseating in order to be efficacious. Consequently, the physician who can prescribe effective therapeutic agents in palatable forms is more certain of success than one who has no regard for palatability. Disagreeably tasting substances are not relished by persons in good health and, surely, they should not be inflicted on ailing persons (for whom nausea and vomiting are not uncommon) if it is possible to avoid them.

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Note: Superscript numerals found in the text refer to articles or books listed in the section entitled "REFERENCES." Numerals enclosed by parentheses refer to articles or books listed in the section entitled "BIBLIOGRAPHY OF LITERATURE ON DISTASTEFUL DRUGS AND AGENTS USED FOR DISGUIISING THEM." Asterisks denote foot-notes.

Medicines which are administered in solid form present no serious problem with respect to taste. Provided they are not too bulky, they may easily be given in the form of cachets, capsules, coated pills or coated tablets, in which the taste of the medicament is entirely concealed. On the other hand, infants and most small children as well as some adults are unable to swallow such forms of medication, particularly cachets and large capsules. When such is the case, a liquid preparation must be given. Moreover, drugs in the liquid state are more quickly absorbed and, thereby, exhibit their therapeutic effects more promptly than solid forms of medication. Furthermore, there are a great number of drugs which are more conveniently dispensed in the liquid state. Many of these liquids are quite distasteful, solutions of iodides and bromides being notable examples.

This study was undertaken in an effort to devise a method for appraising the value of vehicles as disguising agents for distasteful drugs and then to use the method for evaluating some of the common pharmaceutical vehicles as agents to disguise certain unsavory medicaments. In order to approach this problem intelligently, it is first necessary to have a clear conception (as far as is known) of the nature of the taste sense itself. This is discussed in the section which follows, together with several theories pertaining to taste qualities and the mechanism of tasting.

### Physiology of Taste

A sapid body, in order to be tasted, must first be in solution. For example, if the tongue is dried with a towel

and a dry substance such as sodium chloride is immediately placed upon it, there will be no sensation of saltiness. The sensation will not be perceptible until some saliva has been secreted and has caused the salt to dissolve.

The sense of taste is made possible by sense organs called taste buds, which are located chiefly in the mucosa of the tongue. However, a few of these organs are found in the mucous membranes of the soft palate, the tonsils, the epiglottis and in certain portions of the fauces. In the tongue, the taste buds are primarily situated on the tip, edges and posterior third. They are contained in minute projections called papillae. These papillae are responsible for the rough appearance of the tongue. The taste bud is an oval bundle containing a number of elongated cells packed side by side, each of which terminates externally in a fine hair-like process extending through the central pore of the taste bud. The internal end of each cell is supplied with terminal filaments of the nerves of taste.

Regarding the identity and source of the nerves of taste, the glossopharyngeal, or ninth cranial, nerve is believed to send branches to the posterior third of the tongue. Considerable disagreement exists among authorities as to the origin of the nerve terminals in the anterior two-thirds of the tongue. Some authors believe they arise in the facial, or seventh cranial and others contend that they originate in the trigeminal (fifth cranial) nerve.

Very little is known concerning the cortical termination of the nerves of taste. The brain center for olfaction is located in the uncus and the anterior part of the hippocampal



convolution. The center for gustation is believed to be in close proximity and posterior to that for smell. When a sapid substance in solution is placed in the mouth, the hair-like projections in the taste buds presumably receive direct stimulation. This impulse is transmitted through the bodies of the cells, whence the sensation is picked up by the terminal arborizations of the nerves of taste and carried to the center for taste in the brain.

### Taste Qualities

Our taste organs are capable of distinguishing numerous sensations. Most authorities agree that there are only four primary or basic sensations of taste, namely: sweet, acid, salty and bitter. Some investigators, however, add alkaline, astringent and metallic sensations. All others are believed to be merely combinations of two or more of these fundamental sensations. Henning<sup>1</sup> argues that no experimenters in this field who have tested numerous materials can confine themselves to four distinct qualities of taste. He is of the opinion that all chemical substances have distinctive tastes of their own and that each can be distinguished from the others. Taste is analogous, he explains, to light, sound and odor phenomena. Just as each wave length of light produces a different color, each vibration a different tone, each aromatic a different odor, so each sapid substance produces a different taste. Salty, acid, sweet and bitter are merely the distinguishing points in taste continuity, analogous to red, yellow and blue which are points of distinction in the continuity of light.

In 1921, von Skramlik<sup>2</sup> was successful in imitating the tastes of various inorganic salts by admixture of two or more of four solutions in varying proportions. Each of his basic solutions possessed one of the four fundamental sensations of taste. The solutions employed contained sodium chloride, quinine, tartaric acid and glucose, which exhibited respectively salty, bitter, sour and sweet tastes. Baryscheva,<sup>3</sup> in 1926, claimed that the taste of any substance may be simulated by using solutions similar to those of von Skramlik. Naturally, olfactory and tactile sensations interfere with these duplications.

The fact that a complex taste sensation can be duplicated by mixing several primary sensations appears to support the view that there are only four primary taste sensations. If, on the other hand, Henning's theory were true, this duplication would be as impossible as the mixing of light of two widely different wave lengths to produce an intermediate wave length, or to mix two sound tones to produce an intermediate.

Alkaline taste, according to Henning, is a simple taste which he places in the continuity about half-way between sweet and bitter. The alkaline sensation is not, he explains, sweet and bitter as in a mixture of sugar and quinine. Regarding astringency, Kahlenberg<sup>4</sup> attributes this effect to the presence of hydrogen ions in about 0.0025 N. concentration. Ziehen<sup>5</sup> ascribes the astringent quality to a combination of elementary taste sensations and the sensation of feeling. With respect to the so-called metallic taste, Herlitzka,<sup>6</sup> von Frey<sup>7</sup> and Ziehen are of the opinion that odor, and not taste, is responsible for

the sensation. These workers believe that compounds which exhibit metallic taste are volatilized in the mouth and pass into the nasal cavity where they are perceived as odor sensations. On the contrary, Henning believes that the metallic taste is a true one and he places it in the neighborhood of sour taste.

Many so-called tastes are not produced entirely by the gustatory organs but are actually tastes combined with the senses of smell or feeling. In some instances, the "taste" of a substance can be wholly attributed to odor or common sensibility, i. e., the compound gives no taste sensation proper. For example, the "taste" of pepper is produced by the burning sensation which it causes, combined with a slight odor sensation; fixed oils are unpleasant in great measure because of their feel; fruit flavors, which are usually classified as tastes, are due to odor sensations. In contrast, the reactions obtained from certain volatile compounds which enter the mouth through the nasal passage and excite the organs of taste are designated as odors. As an example of this, the "odor" of chloroform is principally caused by its sweet taste.

It is interesting to note that tastes may be experienced without involvement of the taste buds.<sup>8</sup> In certain pathological conditions, sapid substances dissolved in the blood can stimulate the nerves of taste. In diabetes or jaundice, e. g., a sweet or bitter sensation, respectively, can be aroused by a high content of sugar in the blood or by the presence of bile in the blood. Furthermore, stimulation by chemical, electrical or mechanical means of the chorda tympani in the tympanic

cavity may excite sensations of taste.

All regions of the tongue's surface do not respond equally to the various kinds of taste stimuli. Moreover, there are many individual differences, i. e., the acuteness of the sense is not developed to a like degree in any two individuals.<sup>9</sup> In general, though, the posterior third of the tongue is most sensitive to bitter compounds, while at the tip of the tongue the bitter sense is less marked or may be entirely lacking. Sweet taste is well developed at the tip. This accounts for the fact that when certain substances are first taken into the mouth, they have a pleasantly sweet taste but, when later swallowed, a disagreeably bitter taste is produced. The sensation of saltiness, like that of sweetness, is best perceived at the tip of the tongue. The taste sense for sour substances is most acute at the sides of the tongue.

An interesting experiment was carried out by Öhrwall<sup>10</sup> in which he examined the reactivity of 125 fungiform papillae to bitter, sweet and acid solutions. These papillae were stimulated individually by application of drops of solutions of quinine, sugar and tartaric acid. His results were as follows:

60 papillae reacted to bitter, sweet and acid stimuli.

4 reacted to bitter and sweet.

7 reacted to bitter and acid.

12 reacted to sweet and acid.

3 reacted to sweet.

27 gave no taste reaction but were sensitive to pressure and temperature.

Lasareff<sup>11</sup> believes that there are four different kinds of papillae, each of which is capable of registering only one type

of stimulus. According to his conception, each type contains a taste-sensitive substance which is decomposed by the sapid compound to which it is sensitive. The decomposition product, he contends, is ionized and excites the nerve terminals. A sweet substance may affect bitter-, salt- or sour-sensitive papillae to a certain degree which lends shade or distinction to the taste.

While it is possible that only one kind of papilla and one type of nerve fiber may give rise to all the different qualities of taste depending on the chemical constitution of the substance being tasted, it appears much more probable that there are four distinctly different types of papillae and nerves, each of which produces only its own quality of sensation. To support this latter view, the following is offered: the fact that certain regions of the tongue's surface respond more readily than others to a particular stimulus, the fact that a chemically pure substance may show two different tastes when applied to two separate spots on the tongue, and the fact, as determined by Öhrwall, that a substance known to give rise to only one taste will do so when applied to some papillae and excites no taste sensation when applied to others.

#### Factors Which Influence Taste

There are a number of factors influencing taste, some of which are temperature, solubility, diffusion, chemical reactivity, adsorption, valency, ionization and colloidal state. The effects of these factors are discussed in the following paragraphs.

As early as 1847, Weber<sup>12</sup> observed that the nerves of taste

temporarily lose their ability to receive taste sensations when exposed to heat or cold. In 1869, Camerer<sup>13</sup> noticed that if the mouth was rinsed with a solution of common salt at various temperatures, the taste was most intense between 10° and 20° C. Kiesow,<sup>14</sup> in 1896, found that taste, in general, is more pronounced at higher than at lower temperatures.

In 1921, Komuro<sup>15</sup> undertook to determine whether or not the sense of taste has a coefficient of temperature. If the sense of taste, like that of smell, is a chemical sense and if, unlike sight or hearing, taste is conditioned by the chemical constitution of the stimuli acting upon it, and if the reactions which take place when substances in solution are tasted are of a purely chemical nature, then there should be a distinct temperature coefficient for these reactions since temperature directly affects the speed of chemical reactions. If, on the contrary, the reactions are colloido-chemical or physico-chemical, there should be no pronounced coefficient of temperature. Komuro performed a course of experiments with solutions of sodium chloride, sucrose, tartaric acid and quinine sulfate. The thresholds of taste of each of the substances employed were determined by several methods at 10°, 20°, 30° and 40° C. In all instances, the threshold values at 10° C. were just about twice the values of 20°. The effect of elevating the temperature from 20° to 30° was slight, lowering the taste limens only a trifle. At 40°, the values were not appreciably different from those at 30°. In general, the figures at 40° were identical with or very slightly lower than those for 30° although, in two cases, the threshold values for

the 40° temperature were somewhat higher than those for 30°. In other experiments, he determined taste limens for the four chemicals while the tongue was being stimulated mechanically (with a revolving brush) and while being stimulated chemically (with carbonated water). These accessory stimuli were found to raise considerably the taste thresholds of the four substances. From these results, Komuro concludes that the reactions taking place are not solely chemical and that there is no indication of the existence of a temperature coefficient of taste. The results do indicate, however, that the taste sense depends upon a physico-chemical or colloido-chemical process.

As stated previously, a substance must be soluble and in solution before it becomes gustable but the dissolved compound must have a fairly high rate of diffusion and must possess the property of reacting chemically with the protoplasm of the nerve terminal in the taste bud. According to Kahlenberg,<sup>4</sup> if the sapid compound fails to react chemically, it will be devoid of taste.

The taste system is regarded by Renqvist<sup>16</sup> as a heterogeneous one, the colloidal taste cells representing one phase and the sapid solution the other. The intensity of a taste sensation is governed by the quantity of adsorbed substance. The concentration of a salt necessary to induce taste, as stated by Renqvist, is inversely proportional to the rates of migration of the ions. Valency also plays a part, since the concentration of aluminum chloride required to produce a sensation is lower than that for either barium or calcium chlorides, whereas a maximum value is attained for salts of the alkali metals.

The chlorides, bromides and iodides of ammonium, sodium, potassium, lithium, rubidium and cesium have been studied by Kionka and Strätz<sup>17</sup> in an effort to establish a relationship between ions and taste and between molecular weight and taste. Their findings indicate that the intensity of taste is governed largely by the cation but that the anion appears to condition to some extent the character or quality of the taste. However, when these 18 salts were classified according to their molecular weights, it was found that bitter was the predominating taste in the 4 salts having the highest molecular weights; the next 6 shared bitter and salt tastes about equally; saltiness predominated in the 8 compounds having the lowest molecular weights, with the exception of cesium chloride in which bitterness prevailed.

Ostwald and Kuhn<sup>18</sup> have sought to establish a quantitative relation between sour taste and swelling of colloids by acids. They found, in general, that the greater the swelling action of an acid, the greater the concentration of hydrogen ions required to produce a sensation of sourness, or, to express it differently, strongly swelling acids taste less sour than weakly swelling acids having the same hydrogen ion concentration. They conclude that acid taste is a qualitative function of hydrogen ion concentration and that it is regulated quantitatively by the simultaneous swelling of tissue colloids, which swelling is not controlled by the hydrogen ion concentration.

Other workers<sup>17</sup> have investigated the influence of a colloid on the taste thresholds of salts. Threshold values for various salts were determined in aqueous solution and in a solution of



soluble starch. The difference, if any, was found to be insignificant.

A taste phenomenon which has been observed on a number of occasions is that of contrast. If the mouth is first rinsed with a salt solution and this is followed with pure water, a sweet sensation may be experienced for a short time after the entrance of the water. Henning<sup>1</sup> and Herlitzka<sup>6</sup> explain this occurrence by assuming that the dissolved salt causes colloid to be precipitated from the terminal taste apparatus, thereby producing a specific type of stimulation; following the application of water, the colloid again dissolves and gives rise to a different sort of stimulus. Contrast phenomenon may be noticed after tasting sour, salt or sweet compounds but not after bitter substances.

In a study employing 12 subjects, Henderson and Millet<sup>19</sup> have demonstrated that the pH of the saliva follows a regular daily rhythm. Their experiments show that the pH rises during meals and falls again shortly thereafter. A few years later, Blakeslee<sup>20</sup> determined taste thresholds for bitter, sour, sweet and salty substances on a group of 21 people. These same individuals were subjected to saliva pH determinations and it was concluded that the acidity of the saliva bears no close relation to acuity of taste. Salmon and Blakeslee<sup>21</sup> have since made a study of the variation in taste sensitivity of 7 persons to phenylthio-carbamide in a single day during which the subjects ate their three regular meals. This was accomplished by making threshold determinations on each individual at 15 minute intervals for about one hour after

meals and at least every hour during the remainder of the day. The variations observed were considerable but they appear to bear no connection to the rhythmic change in the pH of saliva as noted by Henderson and Millet.

While fatigue is quite noticeable in the case of olfactory sensations, the results obtained by Salmon and Blakeslee indicate that the factor of fatigue with respect to the taste organs is negligible. In like manner, the frequently repeated stimulation of the taste organs in no way intimates an increase in taste sensitivity.

Fluctuations in taste acuity, according to Barysheva,<sup>22</sup> may be attributed to various causes which either stimulate or depress the nervous system.

#### Means Used to Disguise Taste

The disagreeable taste of many remedies can be concealed either partially or completely by mixing them with or dissolving them in a pleasantly flavored vehicle or a blend of two or more vehicles. This procedure is, in all probability, employed more often than any other to disguise taste. The effectiveness of this method depends, in some cases, on how well the taste of the vehicle overpowers that of the medicament. In others, a repugnant drug may be blended with a vehicle to produce a palatable combination. For example, bitterness, which is usually regarded as disagreeable, can contribute to the palatability of certain flavors; bitter chocolate or the addition of bitters to alcoholic beverages serve as illustrations. The flavoring elixirs and syrups of the

United States Pharmacopoeia and of the National Formulary serve admirably for many drugs. Aromatic waters are used rather extensively but they are inferior to the syrups and elixirs as disguising agents. The principal virtue of aromatic waters lies not in their taste-disguising powers but in the fact that they are excellent solvents for many chemicals. A limited number of the official spirits and tinctures are frequently employed to impart their flavor to medicinal preparations. However, these tinctures and spirits are not intended to serve as pharmaceutical vehicles without dilution since they contain their respective flavoring agents in a relatively concentrated form and, in addition, they are highly alcoholic.

A very effective means in use to disguise the taste of drugs is that of mechanical coating of the tongue in order to render it impervious to the distasteful substance. Glycyrrhiza, eriodictyon and their preparations and other drugs to a lesser degree have long been in use to accomplish this end. These drugs have been employed in three ways. First, the cut drug may be chewed for a short period of time prior to the administration of the offensive-tasting medicament. Another method consists of painting the tongue with a tincture or fluidextract, made from the drug having taste-disguising properties, before giving the medicament. A third and, by far, the most popular method is to mix the distasteful drug directly with the mask or with a preparation of the mask. Roloff (88), in discussing the use of eriodictyon, favors the second of the above methods as being the most efficacious. In actual practice, however, neither of the first two is used to any appreciable

extent by reason of the inconvenience of these procedures. The drugs which fall into this class, in addition to furnishing a protective coating for the tongue, also impart a taste or flavor of their own which is considered to be pleasant by many individuals. Naturally, flavors which some people find agreeable may be regarded as unpleasant by others.

Stimulation of the tongue, either by mechanical or chemical means, is capable of elevating taste limens to a considerable extent. Komuro<sup>15</sup> found that taste thresholds for tartaric acid, sodium chloride, sucrose and quinine sulfate were higher than normal when the tongue was stimulated mechanically by means of a revolving brush. The thresholds for these same substances were raised to a greater degree through chemical stimulation, i. e., by administration in carbonic acid solution. This difference was most pronounced in the experiment with quinine sulfate, its threshold concentration in carbonated water being about five hundred times that of the salt in plain water. While mechanical stimulation, such as that performed by Komuro, is entirely impractical as a means for lessening the intensity of taste of medicines, carbon dioxide, on the other hand, is used extensively as a taste corrective for drugs, principally in the forms of granular effervescent salts and effervescent tablets. These preparations usually contain sodium bicarbonate and a mixture of citric and tartaric acids. When they are placed in water, they react to liberate carbon dioxide, thus carbonate the solution and thereby increase its palatability. An objection to preparations of this type is the fact that they do not keep very well. Each time the container in which they are stored is

opened, moisture from the atmosphere enters and serves as a medium for the reaction and premature liberation of carbon dioxide follows. The keeping qualities of the tablets are somewhat better than those of the granular salts because, in the tablets, a smaller proportion of surface is exposed to the action of atmospheric moisture. A recent patent<sup>23</sup> covers a process designed to stabilize these products. The premature escape of the gas is prevented by coating the solids separately with a fatty material containing lecithin. It appears to the writer that if this coating accomplishes the purpose for which it is intended, it will interfere when the reaction should take place. On rare occasions, ordinary carbonated water, the so-called "club soda," is used for the administration of medicines. This practise has not been extensive, probably because of the rapidity with which the water loses its carbonation after the bottle has been opened.

Several attempts have been made to counteract the unpleasantness of distasteful medicaments by means of local anesthesia. One trial referred to is that of Stevens (97) who employed elixir of coca and wine of coca in an effort to mask the bitterness of quinine. He had hoped that the coca would produce its anesthetic effect on the nerves of taste, thereby preventing the perception of bitterness. This proved to be rather unsuccessful and Stevens concluded that aromatic elixir of eriodictyon was the best disguising agent for quinine. *Gymnema silvestre* has been recommended as a taste corrective. (72). Extracts of the leaves of this tropical plant possess the peculiar property of destroying the sense of taste for sweet and bitter substances. (30). Howell<sup>24</sup> explains this phenomenon by assuming

that this *Gymnema* species exercises a selective action upon the taste terminals in the tongue, paralyzing only those for sweet and bitter materials. Should local anesthesia be selected as a method to disguise the taste of a particular drug, the anesthetic chosen should exert its effect instantaneously if it is expected to prevent or dull the taste of the drug with which it is administered. Its action should be of short duration so that it will not interfere aesthetically with the ingestion of food and, by no means, should it be a narcotic capable of causing addiction, such as coca or its alkaloids. It is highly probable that an anesthetic possessing the rapid action needed here will never be discovered. However, it appears that the method might be of value if the anesthetic were given prior to the administration of the medicament. This could be accomplished conveniently by preparing the anesthetic in the form of troches to be dissolved in the mouth and not swallowed as a tablet. In this way, the anesthetic would have an opportunity to exert its effect on the nerves of taste before any distasteful substance entered the mouth.

The taste of some chemicals can be altered and improved to a degree by the addition of other chemicals. This fact was known as long ago as 1907 when a British patent (39) was issued to protect a process for the manufacture of purgative lemonades containing magnesium sulfate. In this case, sodium sulfate is added to the epsom salt for the purpose of counteracting the bitter taste. More recently, Eschenbrenner (41) has recommended a mixture of monosodium phosphate and citric acid to lessen the disagreeable taste of urea solutions. He states, however, that

the whole should be given in carbonated water. Wilson\* has found that acid sodium phosphate considerably decreases the bitterness in a solution of magnesium sulfate. The mode of action of these chemicals which are added to increase palatability is not clear. The pH of the solutions is affected and, therefore, it appears that a buffer action is responsible.

The intensity of taste of certain drugs can be decreased to a marked degree or the taste may be entirely obliterated by transforming the drug into one that is less soluble than the original. For example, the bitterness of quinine is reduced greatly by converting the alkaloid into the tannate, a nearly insoluble salt. The drug need not be completely insoluble to be tasteless. If its solubility has been decreased to a point below its taste limen concentration, it will be tasteless.

As cited previously in the discussion of the effect of temperature on taste, the intensity of taste of a solution can be reduced by lowering its temperature. It is a well-known fact that milk which is very cold does not possess nearly as intense a taste as that which is warm. In this manner, then, distasteful solutions can be rendered more agreeable.

The taste of some drugs has been successfully masked by coating them, in powdered form, with some other substance which is either tasteless or possesses an agreeable taste. For example,

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\*Robert C. Wilson, Dean of the School of Pharmacy, The University of Georgia, conveyed this information to the writer. His solution is prepared by adding sufficient phosphoric acid to 4 drams of sodium phosphate to produce the acid salt, add 4 drams of magnesium sulfate and sufficient water to make 1 fluidounce of solution.

a patent was issued to Sartorius (90) in 1912 on a process for coating quinine. A few years later, Fantus (42) recommended the coating of calcium salicylate, senna, ipecac or digitalis, in a moderately coarse powder, with tolu and sugar in order to overcome the disagreeable taste of these agents. These coated powder particles may then be administered as such or they may be compressed into tablets. Unlike most tablets which are intended to be swallowed whole, these may be chewed as a confection by children who are unable to swallow the intact tablet.

Since the intensity of taste of any solution is directly proportional to the concentration, it follows that the repugnancy of a solution can be diminished by dilution. This practise has one disadvantage; it necessitates the giving of a relatively large volume of liquid in order to administer a single dose of medicine. As a result, it is rare for un-savory drugs to be prescribed in the form of a very dilute solution. On the other hand, advantage is taken of dilution in conjunction with another of the methods already discussed, e. g., physicians frequently prescribe distasteful drugs in a palatable vehicle and direct that a small quantity be taken in a glass of water.

The problem of masking taste can therefore be approached through a number of avenues. It is frequently advantageous to combine two or more of these means to conceal a particular medicament. For example, a drug may be dissolved in a palatable fruit syrup which in turn is mixed with cold carbonated water at the time of administration. This illustration involves the addition of a new taste (sweetness of the



sugar), a flavor (that of the fruit), chemical stimulation (carbon dioxide), dilution and cold.

Résumé of Literature on Distasteful Drugs and Agents  
Used for Disguising Them

It is frequently true that drugs which are referred to as distasteful are, in reality, malodorous. This has already been discussed under "Taste Qualities" and, for this reason, will not be taken up again. Since this thesis is confined to a study of the masking of the taste of drugs, any medicaments in which odor plays the major rôle have been purposely omitted from this résumé.

The review which follows is presented in tabular form to avoid undue duplication and to save space. More complete information concerning any of the articles cited can be found in the annotated bibliography under the numbers corresponding to those given in the tables. The opinions expressed in the columns captioned "Comment" are those of the authors cited and not those of this writer.

In Table I, no mention is made of particular distasteful drugs which the vehicles recommended are intended to mask; the vehicles, which are listed alphabetically, are suggested as general taste correctives. In Table II, specific mention is made of distasteful drugs and these appear in alphabetical sequence in the first column. When more than one reference to a particular drug is made, the vehicles or taste correctives suggested for that drug are then arranged alphabetically. In this way, these tables serve as a subject index for the bibliography.

Table I. - General Taste Correctives

| Vehicle or<br>Taste Corrective                                                           | Comment                                            | Bibli-<br>ography<br>Number |
|------------------------------------------------------------------------------------------|----------------------------------------------------|-----------------------------|
| Acacia Syrup                                                                             | :Value due to colloidal<br>:property               | : 92                        |
| Alkali Carbonate, Acid-<br>Reacting Substance,<br>Water-Soluble Gum,<br>Flavor & Perfume | :Addition of water yields<br>:palatable liquid     | : 79                        |
| Althea Syrup                                                                             | :Value due to colloidal<br>:property               | : 92                        |
| Aromatic Elixir                                                                          | :Good general vehicle                              | : 81                        |
| Aromatic Elixir                                                                          | :Inferior to Iso-Alcoholic<br>:Elixir              | : 50                        |
| Bumelia Dulcifica                                                                        | :Recommended                                       | : 72                        |
| Cacao Syrup, Prepared,<br>N.F.VI                                                         | :Good general vehicle                              | : 81                        |
| Cherry Syrup                                                                             | :Good all-purpose flavoring<br>:agent              | : 81                        |
| Cherry Syrup                                                                             | :Superior to Wild Cherry<br>:Syrup                 | : 46,<br>57                 |
| Chloroform                                                                               | :Use where sweetness of<br>:sugar is objectionable | : 4                         |
| Cocoa Syrup, N.F.V                                                                       | :Most palatable of 13<br>:vehicles tested          | : 108                       |
| Elixirs, Official                                                                        | :A discussion                                      | : 59                        |
| Eriodictyon                                                                              | :Disguises only basic bitter<br>:substances        | : 49                        |
| Eriodictyon                                                                              | :Paint tongue for best<br>:results                 | : 88                        |
| Eriodictyon Glutinosum                                                                   | :Recommended                                       | : 72                        |
| Eriodictyon Tincture                                                                     | :Suited for numerous<br>:substances                | : 23                        |
| Ether                                                                                    | :Frequently employed                               | : 4                         |
| Ethyl Acetate                                                                            | :Frequently employed                               | : 4                         |

Table I (Continued)

| Vehicle or<br>Taste Corrective     |    | Comment                                                             | Bibli-<br>ography<br>Number |
|------------------------------------|----|---------------------------------------------------------------------|-----------------------------|
| Ethyl Nitrite Spirit               |    | Frequently employed                                                 | 4                           |
| Grapefruit                         |    | Potential vehicle                                                   | 78                          |
| Gymnema Silvestre                  |    | Recommended                                                         | 72                          |
| Iso-Alcoholic Elixir               |    | Good general vehicle                                                | 81                          |
| Iso-Alcoholic Elixir               |    | Superior to Aromatic Elixir                                         | 50                          |
| Iso-Alcoholic Elixirs              |    | Alcohol content variable                                            | 43                          |
| Orange Syrup                       |    | Good general vehicle                                                | 81                          |
| Peppermint Oil                     | 30 | Recommended                                                         | 100                         |
| Clove Oil                          | 15 |                                                                     |                             |
| Abelmosk Seed Tincture<br>(1 : 10) | 5  |                                                                     |                             |
| Pepsin Compound Elixir             |    | Most frequently used<br>vehicle in St. Louis<br>prescription survey | 33                          |
| Phrynium Danielli                  |    | Recommended                                                         | 72                          |
| Raspberry Ether                    |    | Constituents paralyze<br>nerves of taste                            | 23                          |
| Raspberry Syrup                    |    | Good all-purpose flavoring<br>agent                                 | 81                          |
| Raspberry Syrup                    |    | Most palatable of 6<br>vehicles tested                              | 54                          |
| Sodium Biphosphate                 |    | Suited for numerous<br>substances                                   | 23                          |
| Sodium Phosphate                   |    | Suited for numerous<br>substances                                   | 23                          |

Table II. - Distasteful Drugs and Vehicles or Taste

## Correctives

| Distasteful Drug            | Vehicle or Taste Corrective                                                                                                     | Comment                    | Bibliography Number |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------|----------------------------|---------------------|
| Acid Acetyl-salicylic       | Glycerin, Sucrose & Lemon Tincture                                                                                              | Recommended                | 45                  |
| Acid Hydriodic Syrup        | Cherry Syrup                                                                                                                    | Recommended                | 44, 45              |
| Acid Hydrochloric Diluted   | Cherry Syrup                                                                                                                    | Recommended                | 57, 45              |
| Acid Hydrochloric Diluted   | Raspberry Syrup                                                                                                                 | Recommended                | 57, 44              |
| Acid Mandelic               | Althea Syrup                                                                                                                    | Satisfactory formula given | 92                  |
| Acid Mandelic               | Soluble Saccharin, Ammonium Chloride, Ammonium Carbonate, Sucrose, Anethol, Benzaldehyde, Fennel Oil & Glycyrrhiza Fluidextract | Recommended                | 58                  |
| Acid Taste                  | Glycyrrhiza Syrup                                                                                                               | Not suited                 | 56                  |
| Acids                       | Cherry Syrup                                                                                                                    | Buffer action              | 46                  |
| Acids                       | Cherry Syrup                                                                                                                    | Excellent vehicle          | 91                  |
| Acids                       | Cherry Syrup                                                                                                                    | Good disguise              | 92                  |
| Acids                       | Cherry Syrup                                                                                                                    | Ideal vehicle              | 81                  |
| Acids                       | Raspberry Syrup                                                                                                                 | Good mask                  | 81                  |
| Acids-see also "Sour Drugs" |                                                                                                                                 |                            |                     |
| Acrid Drugs                 | Acacia Syrup                                                                                                                    | Good vehicle               | 81                  |
| Acrid Drugs                 | Cherry Syrup                                                                                                                    | Recommended                | 46, 81              |
| Alkaline Mixtures           | Prepared Cacao Syrup                                                                                                            | Recommended                | 81                  |

Table II (Continued)

| Distasteful Drug             | Vehicle or Taste Corrective                 | Comment                            | Bibliography Number |
|------------------------------|---------------------------------------------|------------------------------------|---------------------|
| Alkaline Taste               | Glycyrrhiza Syrup                           | Best glycyrrhiza vehicle           | 56                  |
| Alkaloids                    | Cherry Syrup                                | Preferred to Wild Cherry Syrup     | 91                  |
| Alkaloids                    | Eriodictyon Aromatic Syrup                  | Superior to Glycyrrhiza Syrup      | 56                  |
| Alkaloids                    | Prepared Cacao Syrup                        | Recommended                        | 92                  |
| Alkaloids, Bitter            | Eriodictyon Aromatic Syrup                  | Best disguise                      | 81                  |
| Alkaloids, Bitter            | Eriodictyon Aromatic Syrup                  | Superior to Cherry Syrup           | 46                  |
| Alkaloids, Moderately Bitter | Cherry Syrup                                | Good disguise                      | 92                  |
| Alkaloids, Moderately Bitter | Cherry Syrup                                | Satisfactory                       | 46                  |
| Aloe                         | Glycyrrhiza Fluid-extract                   | Recommended                        | 63                  |
| Aloin                        | Eriodictyon Aromatic Syrup                  | Valueless                          | 56                  |
| Aloin                        | Glycyrrhiza Syrup                           | Valueless                          | 56                  |
| Aminopyrine                  | Eriodictyon Alkaline Elixir, Recipe Book II | Palatable                          | 44                  |
| Aminopyrine                  | Eriodictyon Alkaline Elixir                 | Resin adsorbs aminopyrine          | 51                  |
| Ammonium Carbonate           | Anise Syrup (Sugarless)                     | Superior to syrup containing sugar | 91                  |
| Ammonium Carbonate           | Diabetic Syrup (Sugarless)                  | Recommended                        | 92                  |

Table II (Continued)

| Distasteful<br>Drug   | Vehicle or<br>Taste Corrective | Comment                                       | Bibli-<br>ography<br>Number |
|-----------------------|--------------------------------|-----------------------------------------------|-----------------------------|
| Ammonium<br>Carbonate | :Orange Syrup<br>:(Sugarless)  | :Superior to<br>:syrup contain-<br>:ing sugar | : 91                        |
| Ammonium<br>Chloride  | :Cherry Syrup                  | :Good vehicle                                 | : 54                        |
| Ammonium<br>Chloride  | :Cinnamon Syrup                | :Best of 13<br>:vehicles tested:              | : 108                       |
| Ammonium<br>Chloride  | :Cinnamon Syrup                | :Excellent<br>:vehicle                        | : 81                        |
| Ammonium<br>Chloride  | :Citric Acid Syrup             | :Fair vehicle                                 | : 54                        |
| Ammonium<br>Chloride  | :Cranberry Syrup               | :Good vehicle                                 | : 54                        |
| Ammonium<br>Chloride  | :Glycyrrhiza Syrup             | :Recommended                                  | : 45                        |
| Ammonium<br>Chloride  | :Grape Syrup                   | :Recommended                                  | : 91,<br>92                 |
| Ammonium<br>Chloride  | :Orange Syrup                  | :Fair vehicle                                 | : 54                        |
| Ammonium<br>Chloride  | :Pineapple Syrup               | :Good disguise                                | : 91                        |
| Ammonium<br>Chloride  | :Pineapple Syrup               | :Recommended                                  | : 92                        |
| Ammonium<br>Chloride  | :Prepared Cacao Syrup          | :Recommended                                  | : 92                        |
| Ammonium<br>Chloride  | :Raspberry Syrup               | :Poor vehicle                                 | : 54                        |
| Ammonium<br>Chloride  | :Syrup (Simple)                | :Poor vehicle                                 | : 54                        |
| Antipyrine            | :Raspberry Syrup               | :Good mask                                    | : 81                        |
| Antipyrine            | :Raspberry Syrup               | :Recommended                                  | : 57                        |
| Atropine              | :Cherry Syrup                  | :Satisfactory                                 | : 46                        |

Table II (Continued)

| Distasteful Drug         | Vehicle or Taste Corrective     | Comment                                    | Bibliography Number |
|--------------------------|---------------------------------|--------------------------------------------|---------------------|
| Barbital                 | :Alcoholic Elixir,<br>:High     | :Recommended                               | : 47                |
| Barbital,<br>Soluble     | :Glycerin                       | :Recommended                               | : 45                |
| Barbital,<br>Soluble     | :Glycerin                       | :Superior to Low:<br>:Alcoholic<br>:Elixir | : 47                |
| Barbiturates,<br>Soluble | :Cherry Syrup                   | :Unsuited                                  | : 47                |
| Barbiturates,<br>Soluble | :Eriodictyon Aromatic<br>:Syrup | :Unsuited                                  | : 47                |
| Barbiturates,<br>Soluble | :Raspberry Syrup                | :Unsuited                                  | : 47                |
| Belladonna<br>Tincture   | :Iso-Alcoholic Elixir           | :Recommended                               | : 44                |
| Bitter Drugs             | :Acacia Syrup                   | :Good vehicle                              | : 81                |
| Bitter Drugs             | :Cherry Syrup                   | :Recommended                               | : 81                |
| Bitter Drugs             | :Cinnamon Syrup                 | :Fair disguise                             | : 92                |
| Bitter Drugs             | :Cinnamon Syrup                 | :Recommended                               | : 21                |
| Bitter Drugs             | :Cinnamon Water                 | :Recommended                               | : 21                |
| Bitter Drugs             | :Citric Acid Syrup              | :Recommended                               | : 81                |
| Bitter Drugs             | :Eriodictyon Aromatic<br>:Syrup | :Recommended                               | : 92                |
| Bitter Drugs             | :Glycyrrhiza Syrup              | :Fair disguise                             | : 92                |
| Bitter Drugs             | :Gymnema Sylvestre<br>:Leaves   | :Taste destroyed                           | : 30                |
| Bitter Drugs             | :Orange Syrup                   | :Recommended                               | : 21                |
| Bitter Drugs             | :Prepared Cacao Syrup           | :Recommended                               | : 81                |
| Bitter Drugs             | :Raspberry Syrup                | :Good disguise                             | : 92                |
| Bitter Drugs             | :Raspberry Syrup                | :Good mask                                 | : 81                |

Table II (Continued)

| Distasteful Drug      | Vehicle or Taste Corrective                                 | Comment                          | Bibliography Number |
|-----------------------|-------------------------------------------------------------|----------------------------------|---------------------|
| Bitter Drugs          | :Sarsaparilla<br>:Compound Syrup                            | :Fair disguise                   | : 92                |
| Bitter Drugs          | :Wild Cherry Syrup                                          | :Poor disguise                   | : 92                |
| Bromides              | :Aromatic Waters                                            | :Unsatisfactory                  | : 92                |
| Bromides              | :Elixirs                                                    | :Unsatisfactory                  | : 92                |
| Bromides              | :Glycyrrhiza Aromatic<br>:Syrup                             | :Splendid vehicle                | : 56                |
| Bromides              | :Glycyrrhiza Syrup                                          | :Best disguise                   | : 81                |
| Bromides              | :Raspberry Syrup                                            | :Good disguise                   | : 92                |
| Bromides              | :Saccharin Aromatic<br>:Elixir                              | :Superior to<br>:Aromatic Elixir | : 92                |
| Bromides              | :Soups                                                      | :Recommended                     | : 92                |
| Calcium Chloride      | :Acacia Syrup                                               | :Recommended                     | : 45                |
| Calcium Salicylate    | :Saccharinated Solu-<br>:tion of Tolu & White<br>:Fat Sugar | :Coating<br>:conceals taste      | : 42                |
| Cannabis Fluidextract | :Iso-Alcoholic Elixir                                       | :Recommended                     | : 44,<br>45         |
| Chloral Hydrate       | :Cherry Syrup                                               | :Poor vehicle                    | : 54                |
| Chloral Hydrate       | :Citric Acid Syrup                                          | :Good vehicle                    | : 54                |
| Chloral Hydrate       | :Cranberry Syrup                                            | :Good vehicle                    | : 54                |
| Chloral Hydrate       | :Glycyrrhiza<br>:Fluidextract                               | :Palatable                       | : 56                |
| Chloral Hydrate       | :Orange Syrup                                               | :Fair vehicle                    | : 54                |
| Chloral Hydrate       | :Raspberry Syrup                                            | :Poor vehicle                    | : 54                |
| Chloral Hydrate       | :Syrup (Simple)                                             | :Fair vehicle                    | : 54                |



Table II (Continued)

| Distasteful Drug            | Vehicle or Taste Corrective                  | Comment                                                                          | Bibliography Number |
|-----------------------------|----------------------------------------------|----------------------------------------------------------------------------------|---------------------|
| Chloral & Potassium Bromide | Eriodictyon Alkaline Elixir                  | Formula proposed to replace Compound Mixture of Chloral & Potassium Bromide N.F. | 53                  |
| Chlorides                   | Glycyrrhiza Syrup                            | Best disguise                                                                    | 81                  |
| Citrates                    | Prepared Cacao Syrup                         | Recommended                                                                      | 81                  |
| Codeine                     | Eriodictyon Aromatic Syrup                   | Recommended                                                                      | 92                  |
| Codeine Phosphate           | Cherry Syrup                                 | Recommended                                                                      | 57                  |
| Codeine Phosphate           | Eriodictyon Aromatic Syrup                   | Recommended                                                                      | 44,<br>45           |
| Codeine Salts               | Eriodictyon Aromatic Syrup                   | Bitterness concealed                                                             | 81                  |
| Digitalis                   | Saccharinated Solution of Tolu & Cacao Sugar | Coating conceals taste                                                           | 42                  |
| Digitalis Tincture          | Iso-Alcoholic Elixir                         | Recommended                                                                      | 44,<br>45           |
| Digitalis Tincture          | Raspberry Syrup                              | Best of 13 vehicles tested                                                       | 108                 |
| Digitalis Tincture          | Raspberry Syrup                              | Good disguise                                                                    | 92                  |
| Ephedrine                   | Cherry Syrup                                 | Recommended                                                                      | 81                  |
| Ephedrine                   | Cherry Syrup                                 | Satisfactory                                                                     | 46                  |
| Ephedrine Sulfate           | Cherry Syrup                                 | Recommended                                                                      | 45                  |
| Ergot Fluidextract          | Iso-Alcoholic Elixir                         | Recommended                                                                      | 45,<br>44           |
| Ethyl Carbamate             | Cherry Syrup                                 | Recommended                                                                      | 46                  |

Table II (Continued)

| Distasteful Drug         | Vehicle or Taste Corrective                        | Comment                                              | Bibliography Number |
|--------------------------|----------------------------------------------------|------------------------------------------------------|---------------------|
| Ethyl Carbamate          | Cinnamon Syrup                                     | Recommended                                          | 45                  |
| Halides                  | Glycyrrhiza Syrup                                  | Superior to Simple Syrup or Glycyrrhiza Fluidextract | 56                  |
| Iodides                  | Glycyrrhiza Syrup                                  | Best disguise                                        | 81                  |
| Iodides                  | Sarsaparilla Compound Syrup                        | Recommended                                          | 81                  |
| Ipecac                   | Saccharinated Solution of Tolu & Cacao Sugar       | Coating conceals taste                               | 42                  |
| Iron & Ammonium Citrates | Cherry Syrup                                       | Recommended                                          | 57                  |
| Iron & Ammonium Citrates | Cinnamon Syrup                                     | Recommended                                          | 44, 45              |
| Iron Salts               | Cherry Syrup                                       | Good vehicle                                         | 81                  |
| Iron Salts               | Cherry Syrup                                       | No tannin                                            | 46                  |
| Iron Salts               | Cherry Syrup                                       | Preferred to Wild Cherry Syrup                       | 91                  |
| Iron Salts               | Cinnamon Syrup                                     | Excellent vehicle                                    | 81                  |
| Iron Salts               | Cinnamon Syrup                                     | No tannin                                            | 54                  |
| Magnesium Sulfate        | Acid Citric, Cardamom Compound Tincture & Glycerin | Palatable                                            | 35                  |
| Magnesium Sulfate        | Acid Citric & Sarsaparilla Compound Syrup          | Palatable                                            | 35                  |
| Magnesium Sulfate        | Acid Sulfuric Aromatic & Glycerin                  | Palatable                                            | 35                  |

Table II (Continued)

| Distasteful Drug       | Vehicle or Taste Corrective                                                                          | Comment                                          | Bibliography Number |
|------------------------|------------------------------------------------------------------------------------------------------|--------------------------------------------------|---------------------|
| Magnesium Sulfate      | :Alcohol, Cardamom<br>:Compound Fluidex-<br>:tract, Coffee, Glyc-<br>:erin, Garantose &<br>:Vanillin | :Palatable                                       | : 35                |
| Magnesium Sulfate      | :Glycerin & Orange<br>:Juice                                                                         | :Palatable                                       | : 35                |
| Magnesium Sulfate      | :Mint Essence                                                                                        | :Taste completely<br>:masked                     | : 9                 |
| Magnesium Sulfate      | :Peppermint Oil                                                                                      | :Recommended                                     | : 8                 |
| Magnesium Sulfate      | :Raspberry Syrup                                                                                     | :Palatable                                       | : 73                |
| Magnesium Sulfate      | :Sodium Sulfate &<br>:Lemonade                                                                       | :Sodium Sulfate<br>:counteracts bit-<br>:terness | : 39                |
| Mercuric Salts         | :Sarsaparilla<br>:Compound Syrup                                                                     | :Good disguise                                   | : 92                |
| Methenamine            | :Grape Syrup                                                                                         | :Recommended                                     | : 91,<br>92         |
| Methenamine            | :Pineapple Syrup                                                                                     | :Good disguise                                   | : 91                |
| Methenamine            | :Pineapple Syrup                                                                                     | :Recommended                                     | : 92                |
| Morphine Tartrate      | :Water                                                                                               | :1-2000 dilution<br>:is bitter                   | : 17                |
| Phenobarbital          | :Alcoholic Elixir,<br>:High                                                                          | :Recommended                                     | : 47                |
| Phenobarbital          | :Elixir formula given                                                                                | :About 30% alco-<br>:hol prevents<br>:bitterness | : 51                |
| Phenobarbital          | :Eriodictyon                                                                                         | :Unsuited                                        | : 49                |
| Phenobarbital          | :Iso-Alcoholic Elixir                                                                                | :Recommended                                     | : 44                |
| Phenobarbital, Soluble | : Glycerin                                                                                           | :Most palatable<br>:liquid form                  | : 47                |

Table II (Continued)

| Distasteful<br>Drug       | Vehicle or<br>Taste Corrective     | Comment                                    | Bibli-<br>ography<br>Number |
|---------------------------|------------------------------------|--------------------------------------------|-----------------------------|
| Phenobarbital,<br>Soluble | Glycerin & Sacchar-<br>in, Soluble | Recommended                                | 45                          |
| Potassium<br>Acetate      | Anise Syrup<br>(Sugarless)         | Superior to<br>syrup contain-<br>ing sugar | 91                          |
| Potassium<br>Acetate      | Cherry Syrup                       | Poor vehicle                               | 54                          |
| Potassium<br>Acetate      | Citric Acid Syrup                  | Good vehicle                               | 54                          |
| Potassium<br>Acetate      | Cranberry Syrup                    | Good vehicle                               | 54                          |
| Potassium<br>Acetate      | Diabetic Syrup<br>(Sugarless)      | Recommended                                | 92                          |
| Potassium<br>Acetate      | Orange Syrup                       | Good vehicle                               | 54                          |
| Potassium<br>Acetate      | Orange Syrup<br>(Sugarless)        | Superior to<br>syrup contain-<br>ing sugar | 91                          |
| Potassium<br>Acetate      | Raspberry Syrup                    | Fair vehicle                               | 54                          |
| Potassium<br>Acetate      | Syrup (Simple)                     | Poor vehicle                               | 54                          |
| Potassium<br>Bromide      | Alkaline Carbonated<br>Waters      | Taste very much<br>masked                  | 10                          |
| Potassium<br>Bromide      | Glycyrrhiza Syrup                  | Recommended                                | 44,<br>45                   |
| Potassium<br>Bromide      | Vinegar                            | Good taste<br>corrective                   | 31                          |
| Potassium<br>Citrate      | Anise Syrup<br>(Sugarless)         | Superior to<br>syrup contain-<br>ing sugar | 91                          |
| Potassium<br>Citrate      | Diabetic Syrup<br>(Sugarless)      | Recommended                                | 92                          |

Table II (Continued)

| Distasteful Drug            | Vehicle or Taste Corrective | Comment                                           | Bibliography Number |
|-----------------------------|-----------------------------|---------------------------------------------------|---------------------|
| Potassium Citrate           | Grape Syrup                 | Recommended                                       | 91, 92              |
| Potassium Citrate           | Orange Syrup (Sugarless)    | Superior to syrup containing sugar                | 91                  |
| Potassium Citrate           | Pineapple Syrup             | Good disguise                                     | 91                  |
| Potassium Citrate           | Pineapple Syrup             | Good vehicle                                      | 48                  |
| Potassium Citrate           | Pineapple Syrup             | Recommended                                       | 92                  |
| Potassium Guaiacolsulfonate | Eriodictyon Aromatic Syrup  | Most palatable of 7 vehicles tested               | 96                  |
| Potassium Iodide            | Acid Mineral Water          | Recommended                                       | 99                  |
| Potassium Iodide            | Alkaline Carbonated Waters  | Taste very much masked                            | 10                  |
| Potassium Iodide            | Anise Syrup (Sugarless)     | Superior to syrup containing sugar                | 91                  |
| Potassium Iodide            | Blackthorn Berry Syrup      | Recommended                                       | 19                  |
| Potassium Iodide            | Blackthorn Berry Syrup      | Tannin present prevents taste of potassium iodide | 60                  |
| Potassium Iodide            | Cherry Syrup                | Fair vehicle                                      | 54                  |
| Potassium Iodide            | Citric Acid Syrup           | Poor vehicle                                      | 54                  |
| Potassium Iodide            | Cranberry Syrup             | Poor vehicle                                      | 54                  |
| Potassium Iodide            | Diabetic Syrup (Sugarless)  | Recommended                                       | 92                  |

Table II (Continued)

| Distasteful<br>Drug | Vehicle or<br>Taste Corrective         | Comment                                       | Bibli-<br>ography<br>Number |
|---------------------|----------------------------------------|-----------------------------------------------|-----------------------------|
| Potassium<br>Iodide | :Glycyrrhiza Extract                   | :Taste disguised                              | : 14                        |
| Potassium<br>Iodide | :Glycyrrhiza Syrup &<br>:Acacia Syrup  | :Recommended                                  | : 45                        |
| Potassium<br>Iodide | :Gooseberry Syrup                      | :Excellent ve-<br>:hicle                      | : 11                        |
| Potassium<br>Iodide | :Grape Syrup                           | :Recommended                                  | : 91,<br>: 92               |
| Potassium<br>Iodide | :Milk                                  | :Palatable                                    | : 70                        |
| Potassium<br>Iodide | :Milk                                  | :Poor vehicle                                 | : 19                        |
| Potassium<br>Iodide | :Milk                                  | :Slight metallic<br>:after-taste              | : 69                        |
| Potassium<br>Iodide | :Orange Syrup                          | :Fair vehicle                                 | : 54                        |
| Potassium<br>Iodide | :Orange Syrup<br>:(Sugarless)          | :Superior to<br>:syrup contain-<br>:ing sugar | : 91                        |
| Potassium<br>Iodide | :Raspberry Syrup                       | :Good vehicle                                 | : 54                        |
| Potassium<br>Iodide | :Syrup (Simple)                        | :Good vehicle                                 | : 54                        |
| Quinidine           | :Saccharin, Syrup &<br>:Orange Essence | :Tasteless chill-<br>:tonic                   | : 38                        |
| Quinine             | :Acid Citric                           | :Taste improved                               | : 21                        |
| Quinine             | :Acid Diglycolic                       | :Tasteless es-<br>:ters formed                | : 27                        |
| Quinine             | :Acid Tannic                           | :Bitterless                                   | : 64                        |
| Quinine             | :Acid Tannic                           | :Tasteless                                    | : 110                       |
| Quinine             | :Acid Tannic                           |                                               | : 61                        |

Table II (Continued)

| Distasteful Drug | Vehicle or Taste Corrective                          | Comment                            | Bibliography Number |
|------------------|------------------------------------------------------|------------------------------------|---------------------|
| Quinine          | :Almond Oil & Sodium Bicarbonate                     | :No unpleasant after-taste         | : 109               |
| Quinine          | :Anise                                               | :Bitterness masked                 | : 37                |
| Quinine          | :Anise Extract, Star                                 | :Taste improved                    | : 21                |
| Quinine          | :Beef Extract, Liquid                                | :Taste improved                    | : 36                |
| Quinine          | :Cacao Syrup, Prepared                               | :Recommended                       | : 81                |
| Quinine          | :Cardamom Extract                                    | :Taste improved                    | : 21                |
| Quinine          | :Chloroform                                          | :Bitterness decreased at least 2/3 | : 4                 |
| Quinine          | :Chocolate Syrup                                     | :Taste disguised perfectly         | : 68                |
| Quinine          | :Clove Extract                                       | :Taste improved                    | : 21                |
| Quinine          | :Coffee, Black Alcoholic                             | :Best means of administration      | : 71                |
| Quinine          | :Coffee & Lemon Juice                                | :Taste disguised satisfactorily    | : 34                |
| Quinine          | :Cognac & Lemon Juice                                | :Bitterness masked                 | : 93                |
| Quinine          | :Coriander Extract                                   | :Taste improved                    | : 21                |
| Quinine          | :Eriodictyon Aromatic Elixir                         | :Best vehicle tested               | : 97                |
| Quinine          | :Eriodictyon Aromatic Syrup                          | :Recommended                       | : 21, 92            |
| Quinine          | :Eriodictyon, Glycyrrhiza & Chocolate Compound Syrup | :Recommended                       | : 21                |
| Quinine          | :Eriodictyon Syrup                                   | :Tasteless                         | : 89                |
| Quinine          | :Fennel                                              | :Bitterness masked                 | : 37                |

Table II (Continued)

| Distasteful Drug | Vehicle or Taste Corrective                                        | Comment                    | Bibliography Number |
|------------------|--------------------------------------------------------------------|----------------------------|---------------------|
| Quinine          | Fruit, Sour (Apple)                                                | Bitterness masked          | 93                  |
| Quinine          | Fruit, Sour (Apple or Pear)                                        | Bitterness removed         | 5                   |
| Quinine          | Glycyrrhiza Aromatic Elixir                                        | Taste masked               | 66, 106             |
| Quinine          | Glycyrrhiza Aromatic Honey                                         | Taste masked               | 66                  |
| Quinine          | Glycyrrhiza Aromatic Powder                                        | Taste masked               | 106                 |
| Quinine          | Glycyrrhiza Aromatic Syrup                                         | Taste concealed completely | 22                  |
| Quinine          | Glycyrrhiza Aromatic Syrup                                         | Taste masked               | 66                  |
| Quinine          | Glycyrrhiza Extract                                                | Recommended                | 94                  |
| Quinine          | Glycyrrhiza Extract                                                | Unsatisfactory             | 63                  |
| Quinine          | Glycyrrhiza Extract                                                | Useful corrective          | 40                  |
| Quinine          | Glycyrrhiza Fluidextract                                           | Taste concealed completely | 63                  |
| Quinine          | Glycyrrhiza Fluidextract                                           | Taste masked               | 106                 |
| Quinine          | Glycyrrhiza Fluidextract, Taraxacum Fluidextract & Aromatic Elixir | Taste disguised            | 7                   |
| Quinine          | Lemon Juice                                                        | Taste disguised            | 109                 |
| Quinine          | Orange Peel Extract                                                | Taste improved             | 21                  |
| Quinine          | Pralines                                                           | Suggested for children     | 94                  |
| Quinine          | Saccharin                                                          | Good taste corrective      | 12                  |



Table II (Continued)

| Distasteful Drug               | Vehicle or Taste Corrective                                                           | Comment                                | Bibliography Number |
|--------------------------------|---------------------------------------------------------------------------------------|----------------------------------------|---------------------|
| Quinine                        | Taraxacum Compound<br>Elixir                                                          | Taste masked<br>completely             | 29                  |
| Quinine                        | Tea & Lemon Juice                                                                     | Taste disguised<br>satisfactorily      | 34                  |
| Quinine                        | Whisky & Lemon Juice                                                                  | Bitterness<br>masked                   | 93                  |
| Quinine                        | Whisky or other<br>Hydro-Alcoholic<br>Solution                                        | Taste disguised<br>satisfactorily      | 34                  |
| Quinine<br>Bisulfate           | Acid Tannic                                                                           | Tasteless                              | 13                  |
| Quinine<br>Bisulfate           | Acid Tannic                                                                           | 1/3 Quinine                            | 95                  |
| Quinine<br>Bisulfate           | Cocoa Syrup, N.F.V                                                                    | Best of 13<br>vehicles tested          | 108                 |
| Quinine<br>Derivatives         |                                                                                       | Tasteless                              | 75,<br>76           |
| Quinine<br>Ethylcarbon-<br>ate | Eriodictyon Aromatic<br>Syrup                                                         | Recommended                            | 44,<br>45,<br>81    |
| Quinine<br>Hydrochloride       | Acid Citric, Acid<br>Tannic, Ammonium<br>Chloride, Sodium<br>Saccharate &<br>Glycerin | Taste masked                           | 80                  |
| Quinine<br>Hydrochloride       | Eriodictyon<br>Fluidextract                                                           | After-taste<br>eliminated              | 21                  |
| Quinine<br>Hydrochloride       | Tolu Balsam &<br>Gelatin                                                              | Rendered taste-<br>less by coating     | 90                  |
| Quinine Salt                   | Cacao Butter & Milk                                                                   | Taste masked                           | 87                  |
| Quinine Salt                   | 2,3-Dihydroxynaph-<br>thalene-O-Monoacetic<br>Acid                                    | Nearly<br>tasteless<br>compound formed | 65,<br>83           |
| Quinine Salt                   | Elm Mucilage                                                                          | Taste concealed                        | 3                   |

Table II (Continued)

| Distasteful Drug     | Vehicle or Taste Corrective             | Comment                         | Bibliography Number |
|----------------------|-----------------------------------------|---------------------------------|---------------------|
| Quinine Salts        | :Coffee                                 | :Recommended                    | : 101               |
| Quinine Salts        | :Coffee Extract or<br>:Infusion         | :Good taste<br>:correctives     | : 20                |
| Quinine Salts        | :Coffee Infusion &<br>:Chloroform Syrup | :Effective taste<br>:corrective | : 102               |
| Quinine Salts        | :Cognac                                 | :Recommended                    | : 101               |
| Quinine Salts        | :Eriodictyon Syrup                      | :Effective taste<br>:corrective | : 102               |
| Quinine Salts        | :Eriodictyon Syrup                      | :Good taste<br>:corrective      | : 20                |
| Quinine Salts        | :Glycyrrhiza Extract                    | :Good taste<br>:corrective      | : 20                |
| Quinine Salts        | :Glycyrrhizin,<br>:Ammoniated           | :Bitterness<br>:masked          | : 32,<br>62         |
| Quinine Salts        | :Glycyrrhizin,<br>:Ammoniated           | :Good taste<br>:corrective      | : 20                |
| Quinine Salts        | :Lemon Juice                            | :Recommended                    | : 101               |
| Quinine Salts        | :Meat Extract                           | :Recommended                    | : 101               |
| Quinine Salts        | :Milk                                   | :Best taste<br>:corrective      | : 101               |
| Quinine Salts        | :Milk                                   | :Effective taste<br>:corrective | : 102               |
| Quinine Salts        | :Sodium Biphosphate                     | :Effective taste<br>:corrective | : 102               |
| Quinine Salts        | :Sodium Biphosphate                     | :Recommended                    | : 20                |
| Quinine Sul-<br>fate | :Acid Carbonic &<br>:Orange Syrup       | :Recommended                    | : 16                |
| Quinine Sul-<br>fate | :Acid Tannic & Orange<br>:Syrup         | :Bitterless                     | : 98                |
| Quinine Sul-<br>fate | :Acid Tannic                            | :Tasteless                      | : 18,<br>25         |

Table II (Continued)

| Distasteful Drug | Vehicle or Taste Corrective                                                    | Comment                                          | Bibliography Number |
|------------------|--------------------------------------------------------------------------------|--------------------------------------------------|---------------------|
| Quinine Sul-fate | :Acid Tartaric &<br>:Orange Syrup                                              | :Acid Tartaric<br>:superior to<br>:Acid Sulfuric | : 2                 |
| Quinine Sul-fate | :Anise                                                                         | :Scarcely bitter                                 | : 1                 |
| Quinine Sul-fate | :Cardamom Compound<br>:Tincture, Acid<br>:Hydrobromic, Anise<br>:Water & Syrup | :Recommended                                     | : 67                |
| Quinine Sul-fate | :Coffee                                                                        | :Bitterness<br>:decreased                        | : 84                |
| Quinine Sul-fate | :Coffee & Chloroform<br>:Syrup or Molasses                                     | :Feebly bitter                                   | : 6                 |
| Quinine Sul-fate | :Glycyrrhiza, Coffee<br>:& Acid Tartaric                                       | :Bitterness<br>:masked                           | : 82                |
| Quinine Sul-fate | :Glycyrrhizin,<br>:Ammoniated                                                  | :Taste covered                                   | : 86                |
| Quinine Sul-fate | :Magnesium Carbonate                                                           | :Taste concealed                                 | : 37                |
| Quinine Sul-fate | :Milk                                                                          | :Almost<br>:bitterless                           | : 20                |
| Quinine Sul-fate | :Milk                                                                          | :Taste disguised                                 | : 24                |
| Quinine Sul-fate | :Olive Oil & Milk                                                              | :Taste disguised                                 | : 28                |
| Quinine Sul-fate | :Orange Peel                                                                   | :Scarcely bitter                                 | : 1                 |
| Quinine Sul-fate | :Saccharin & Sodium<br>:Bicarbonate                                            | :Good taste<br>:corrective                       | : 12                |
| Quinine Sul-fate | :Saccharin, Acid<br>:Sulfuric &<br>:Peppermint Spirit                          | :Bitterless                                      | : 15,<br>77         |
| Quinine Sul-fate | :Sugar                                                                         | :Bitterness<br>:predominates                     | : 1                 |

Table II (Continued)

| Distasteful Drug           | Vehicle or Taste Corrective | Comment                     | Bibliography Number |
|----------------------------|-----------------------------|-----------------------------|---------------------|
| Quinine Sulfate            | Valerian                    | Scarcely bitter             | 1                   |
| Quinine Tannate            |                             | Least bitter salt           | 107                 |
| Quinine Tannate, Tasteless |                             | Mixture of 4 true tannates  | 26                  |
| Quinine Tartrate           | Water                       | 1-10,000 dilution is bitter | 17                  |
| Salicylates                | Cinnamon Syrup              | Excellent vehicle           | 81                  |
| Salicylates                | Cinnamon Syrup              | Very good disguise          | 92                  |
| Salty Drugs                | Acacia Syrup                | Good vehicle                | 81                  |
| Salty Drugs                | Cherry Syrup                | Unsatisfactory              | 92                  |
| Salty Drugs                | Cinnamon Syrup              | Good disguise               | 92                  |
| Salty Drugs                | Cinnamon Syrup              | Excellent vehicle           | 81                  |
| Salty Drugs                | Citric Acid Syrup           | Recommended                 | 81                  |
| Salty Drugs                | Citric Acid Syrup           | Good disguise               | 92                  |
| Salty Drugs                | Eriodictyon Aromatic Syrup  | Unsatisfactory              | 92                  |
| Salty Drugs                | Glycyrrhiza Syrup           | Poor disguise               | 92                  |
| Salty Drugs                | Glycyrrhiza Syrup           | Superior to Cherry Syrup    | 46                  |
| Salty Drugs                | Orange Syrup                | Good disguise               | 92                  |
| Salty Drugs                | Sarsaparilla Compound Syrup | Good disguise               | 92                  |
| Salty Drugs                | Sarsaparilla Compound Syrup | Recommended                 | 81                  |

Table II (Continued)

| Distasteful<br>Drug        | Vehicle or<br>Taste Corrective                         | Comment                                                            | Bibli-<br>ography<br>Number |
|----------------------------|--------------------------------------------------------|--------------------------------------------------------------------|-----------------------------|
| Salty Drugs                | Wild Cherry Syrup                                      | Good disguise<br>but inferior to<br>Sarsaparilla<br>Compound Syrup | 92                          |
| Salty Drugs,<br>Moderately | Cherry Syrup                                           | Recommended                                                        | 81                          |
| Senna                      | Saccharinated Solu-<br>tion of Tolu & Red<br>Fat Sugar | Coating<br>Conceals taste                                          | 42                          |
| Sodium<br>Biphosphate      | Grape Syrup                                            | Recommended                                                        | 91,<br>92                   |
| Sodium<br>Biphosphate      | Pineapple Syrup                                        | Good disguise                                                      | 91                          |
| Sodium<br>Biphosphate      | Pineapple Syrup                                        | Recommended                                                        | 92                          |
| Sodium Bromide             | Cinnamon Syrup                                         | Best of 5<br>vehicles tested                                       | 108                         |
| Sodium Citrate             | Cherry Syrup                                           | Good vehicle                                                       | 54                          |
| Sodium Citrate             | Citric Acid Syrup                                      | Good vehicle                                                       | 54                          |
| Sodium Citrate             | Cranberry Syrup                                        | Poor vehicle                                                       | 54                          |
| Sodium Citrate             | Orange Syrup                                           | Fair vehicle                                                       | 54                          |
| Sodium Citrate             | Pineapple Syrup                                        | Good vehicle                                                       | 48                          |
| Sodium Citrate             | Raspberry Syrup                                        | Good vehicle                                                       | 54                          |
| Sodium Citrate             | Strawberry Syrup                                       | Good vehicle                                                       | 57                          |
| Sodium Citrate             | Syrup (Simple)                                         | Poor vehicle                                                       | 54                          |
| Sodium<br>Salicylate       | Cinnamon Syrups                                        | Syrup made from<br>oil superior to<br>that made from<br>crude drug | 54                          |
| Sodium<br>Salicylate       | Lemon Spirit                                           | Recommended                                                        | 31                          |

Table II (Continued)

| Distasteful Drug                             | Vehicle or Taste Corrective  | Comment                                       | Bibliography Number |
|----------------------------------------------|------------------------------|-----------------------------------------------|---------------------|
| Sodium Salicylate & Potassium Bicarbonate    | Cinnamon Syrup               | Recommended                                   | 44, 45              |
| Sour Drugs                                   | Eriodictyon Aromatic Syrup   | Unsatisfactory                                | 92                  |
| Sour Drugs - see also "Acids"                |                              |                                               |                     |
| Strychnine                                   | Eriodictyon Aromatic Syrup   | Recommended                                   | 92                  |
| Strychnine                                   | Eriodictyon Extract          | Superior to salts or Sucrose                  | 104                 |
| Strychnine Alkaloid & Salts                  | Dulcin, Saccharin or Sucrose | Masking effects compared                      | 105                 |
| Strychnine Alkaloid, Sulfate & Hydrochloride | Sucrose Solution             | Superior to Water or Sodium Chloride Solution | 103                 |
| Strychnine Salts                             | Eriodictyon Aromatic Syrup   | Bitterness concealed                          | 81                  |
| Strychnine Sulfate                           | Eriodictyon Aromatic Syrup   | Recommended                                   | 44, 45              |
| Strychnine Tartrate                          | Water                        | 1-48,000 dilution is bitter                   | 17                  |
| Sweet Drugs                                  | Eriodictyon Aromatic Syrup   | Unsatisfactory                                | 92                  |
| Terpin Hydrate                               | Iso-Alcoholic Elixir         | Recommended                                   | 44                  |
| Urea                                         | Acacia Aromatic Syrup        | Colloidalilty has disguising value            | 55                  |

Table II (Continued)

| Distasteful<br>Drug | Vehicle or<br>Taste Corrective                              | Comment                                                     | Bibli-<br>ography<br>Number |
|---------------------|-------------------------------------------------------------|-------------------------------------------------------------|-----------------------------|
| Urea                | :Acacia Syrup                                               | :Recommended                                                | : 44,<br>45,<br>81,<br>92   |
| Urea                | :Althea Syrup                                               | :Recommended                                                | : 92                        |
| Urea                | :Cherry Syrup                                               | :Recommended                                                | : 46,<br>81                 |
| Urea                | :Sodium Biphosphate,<br>:Acid Citric &<br>:Carbonated Water | :Most palatable:<br>:of several<br>:combinations<br>:tested | : 41                        |

EXPERIMENTAL WORK. - METHODS OF COMPARISON OF TASTE-  
DISGUIISING EFFICACY

A careful search of available pharmaceutical literature reveals that very little effort has been made to determine the relative value of the various vehicles used in pharmacy as agents to disguise distasteful drugs. Many vehicles have been recommended for unsavory drugs but in the majority of cases, there has been no obvious scientific basis for these recommendations. It was decided, therefore, to attempt to devise a suitable method whereby the relative worth of these agents can be evaluated. Since the prime purpose of a vehicle is to lessen or completely overcome the disagreeableness of the medicament, it is rational to assume that the threshold of taste of a sapid substance varies directly with the disguising power of the vehicle employed, i. e., the higher the masking power of the vehicle, the higher the threshold value of the sapid substance in that vehicle. If, then, threshold values are determined for a substance in a number of vehicles, that vehicle in which the substance exhibits the highest liminal concentration is the most efficacious of the agents tested.

Various techniques have been employed by different investigators in the determination of taste limens. Komuro<sup>15</sup> sprinkled the tongue with from 200 to 500 cc. of a solution at a definite temperature and, as a control, repeated this procedure using tap water at the same temperature. Kionka and Strätz<sup>17</sup> administered to their subjects from 6 to 10 cc. of solution which was washed back and forth in the mouth. These last named



experimenters started with hyper-threshold concentrations and gradually decreased the strength of the solutions until the liminal strengths were reached, the solutions being maintained at body temperature and administered by means of a graduated pipette with a dropping attachment. Salmon and Blakeslee<sup>21</sup> found that 0.6 cc. was an adequate quantity to administer for a single test and began their determinations with solutions of sub-liminal concentrations, each successive solution being twice the strength of that which preceded. Ward, Munch and their associates (103, 104, 105) have determined strychnine thresholds, employing the technique developed by Munch for the biological assay of capsicum. This method<sup>25</sup> consists of comparing the pungency of an alcoholic extract of capsicum with that of a standard solution of piperine. Salt thresholds have been determined by Richter and MacLean<sup>26</sup> using dilute solutions of sodium chloride. After experimenting with several procedures, they conclude that the method which follows is the most satisfactory. Each subject started with a solution of hypo-threshold strength and tasted successively stronger solutions until the threshold of saltiness was reached. Each concentration tasted was compared with distilled water and the subjects were instructed to taste each solution as often as necessary in order to reach a decision. The solutions employed in this work did not increase in strength in any definite mathematical ratio, as did those employed by Salmon and Blakeslee.

Throughout the experiments which follow, care was taken to maintain as nearly uniform conditions as was practicable.

To avoid the possibility that the small amount of salts present in city water might interfere with threshold determinations, only freshly distilled water was used in the preparation of solutions and for rinsing purposes between tests.

The chemicals employed were of U. S. P. or N. F. quality and were purchased from reputable manufacturers. Some of the pharmaceutical preparations were made in the laboratory according to U. S. P. or N. F. directions and others, for reason of convenience, were purchased from one of the large pharmaceutical manufacturers.

The distilled water and all solutions were stored in glass-stoppered bottles at room temperature which varied from 25° to 28° C. While Komuro<sup>15</sup> has shown that threshold values obtained at 10° C. are much higher than those at 20° C., he also found that the threshold values were not markedly lower at 40° C. than at 20° C. Salmon and Blakeslee<sup>21</sup> made threshold determinations on a number of persons at about 8° C., at room temperature and at about 55° C. and observed no variation in the results at these appreciably different temperatures. In view of the above findings, it was not deemed necessary to store the solutions in an incubator at body temperature as did Kionka and Strätz.<sup>17</sup> Although it is true that the solutions having a temperature of about 26° C. will cause a feeble sensation of coolness in the mouth, this temperature sensation should not interfere with the tasting of solutions since the control solutions used were also at the same temperature.

Glass-stoppered bottles were adopted for the storage of solutions after it was found that some of the more alert

tasters could detect what they described as a "mustiness" in the distilled water and in some of the very weak aqueous solutions which had been kept in bottles with cork stoppers. No such difficulty was encountered after the employment of glass stoppers.

In a further effort to maintain uniform conditions, all subjects participating in the tests were requested not to eat within two hours prior to a threshold determination and the tobacco smokers were asked not to smoke within one-half hour before a test.

#### Method I

A hyper-threshold stock solution of potassium iodide was prepared, using distilled water as the solvent and from this solution, a series of dilutions was made to a point known to be of hypo-threshold strength. The concentration of the chemical in adjacent dilutions in a series differed by approximately 20 per cent, i. e., dilution No. 1 was 80 per cent as strong as the stock solution, dilution No. 2 was 80 per cent as strong as dilution No. 1, and so on down the series.

All bottles in which solutions were stored were labeled in cipher. This was done to prevent the taster from knowing the composition of the solutions. Advance knowledge of the solutions' ingredients or strength is very apt to influence subconsciously the taster in his\* decisions regarding the tastes of solutions. Kionka and Strätz<sup>17</sup> state that

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\*Masculine pronouns used throughout this work refer to both male and female subjects.

contradictory results have been obtained in the determination of taste limens due to the rôle of self-deception.

In carrying out the determinations, the subject first rinsed his mouth several times with distilled water to remove adhering food particles and saliva; the former might introduce a conflicting sensation of taste while the latter would dilute the test solution. After ejection of the rinse water, 5 cc. of the dilution being tested was placed in the mouth and agitated so that it came in contact with all parts of his tongue and oral cavity. This agitation was essential since, as previously discussed, the various parts of the tongue's surface do not respond equally to the several qualities of taste. Meanwhile, the subject determined whether or not the solution possessed taste. After a decision was made, the solution was ejected and the mouth was again rinsed sufficiently to remove all of the sapid solution before testing the next solution. It was observed that the subjects experienced difficulty in recognizing solutions properly at near-threshold concentrations. This obstacle was overcome, to some extent, by administration of a 5 cc. sample of distilled water as a control immediately after ejection of the solution, thereby permitting the subjects to draw a comparison between solution and control. Rinsing between the tasting of the solution and of the control was regarded as unnecessary because the small quantity of solution which may have remained in the mouth was immediately diluted to a high degree by the relatively large volume of control, thereby reducing the concentration of chemical present to a point far below the threshold concentration.

Experience proved the necessity for giving the same quantity (5 cc.) of control as of solution. If a 5 cc. portion of solution was followed with a greater, indefinite quantity (15 to 25 cc.) of control at the same temperature, the control seemed cooler because it was capable of absorbing more heat from the mouth. This temperature sensation could easily have been mistaken for a difference in taste at or near the threshold. Therefore, to eliminate the possibility of error from this source, like quantities of solutions and controls were administered.

At the beginning of a single determination, several dilutions covering a wide range of strengths were given to the subject to obtain a rough approximation of the vicinity of the threshold. The weakest solution distinguished from the control in these preliminary tests served as the real starting point in the determination. This was followed by a series of dilutions successively decreasing in concentration until the point was reached where the subject no longer could differentiate between solution and control. This, of course, was beyond the end-point or limen. The next stronger solution, i. e., the weakest solution having taste, therefore, contained the apparent threshold concentration of chemical. This was checked by readministering the solution of believed threshold concentration several times along with both weaker and stronger solutions. During the check, no set order with respect to strength was followed in the administration of the solutions. This was done to prevent the entrance of the psychological factor, i. e., the factor of self-deception which has already been cited.

The concentration of the weakest solution which provoked a sensation of taste in at least three of four tests was regarded as liminal.

The technique described above was tested on 6 persons, using the solutions of potassium iodide, and the threshold values so obtained are listed in Table III.

Table III. - Taste Thresholds for Potassium Iodide  
in Distilled Water

| Subject<br>Number | : | Normality of<br>Threshold<br>Concentration |
|-------------------|---|--------------------------------------------|
| 1                 | : | 0.0025                                     |
| 2                 | : | 0.0041                                     |
| 34                | : | 0.0041                                     |
| 44                | : | 0.0016                                     |
| 55                | : | 0.010                                      |
| 56                | : | 0.0052                                     |

The values given above possess no real significance other than to show that it is possible to make threshold determinations by the procedure followed and to verify the previously established observation that there is a wide variation in individual thresholds.

Having found the technique employed in the previous experiment suitable for an aqueous solution, it was decided to investigate its applicability to the case of a substance dissolved in a vehicle having taste. Certain vehicles possess a flavor or taste which is easily and quickly removed from the mouth by a single rinsing with water while in others, the taste or flavor

persists after numerous rinsings. If the method employed for the aqueous solution of potassium iodide is fitted for a vehicle of the latter type, there should be no question regarding its suitability for the former. Accordingly, syrup of glycyrrhiza was selected because it possesses, perhaps, as lasting a flavor as any of the more common disguising agents.

In the ordinary determination of taste thresholds of aqueous solutions, the subject simply has to decide whether the solution in question has taste or is tasteless. However, with vehicles other than water, the problem is not so simple. It is necessary for the taster to determine whether the chemical solution has a taste exactly like or different from that of the plain vehicle used as the control.

Solutions of potassium iodide in the syrup were prepared ranging in concentration from 1 N. to 0.01 N. These solutions were given to the 6 individuals who served as tasters of the aqueous solutions, and the procedure followed for administration of the solutions was identical with that already described.

The results obtained were quite disappointing. The glycyrrhiza flavor so persisted that no reasonable number of washings with distilled water would entirely remove it from the mouth. In addition, the intensity of its taste seemed to increase, i. e., the taste successively grew stronger as more samples were tasted. This cumulative effect also was reflected in the ability of the subjects to perceive the taste of the dissolved chemical. As the taste of the vehicle became more intense, a proportionately greater concentration of potassium iodide was required before its taste could be detected. Because of this difficulty, a modification of technique was necessary.

Since the results obtained by any method developed for comparing the efficacy of different flavoring agents in disguising taste would be purely relative, it was reasoned that the use of flavoring vehicles diluted with distilled water would accomplish the same purpose as the undiluted vehicles, provided all were diluted to the same degree. It follows that the higher the dilution, the lower the intensity of the flavor with consequent greater ease of removal from the mouth. With this in mind, 10 per cent by volume of syrup of glycyrrhiza in distilled water was arbitrarily selected for these trials. A series of sodium bromide solutions was made using the diluted syrup as the solvent, and the diluted syrup alone served as the control. Sodium bromide replaced potassium iodide in these trials because of the rapid deterioration of solutions of the latter. Since diluted syrups are prone to fermentation, the syrup of glycyrrhiza was diluted just prior to the time of its use.

Employing the procedure already described, these solutions were administered to 3 subjects and their taste limens for sodium bromide in the diluted syrup were determined. These are presented in Table IV. The obstacle encountered when full-strength syrup of glycyrrhiza was employed had apparently been overcome, since the subjects reported that the taste of the diluted syrup did not persist and that it was rather easily removed by rinsing.



Table IV. - Taste Thresholds for Sodium Bromide  
in 10 Per Cent Syrup of Glycyrrhiza

| Subject<br>Number | : | Normality of<br>Threshold<br>Concentration |
|-------------------|---|--------------------------------------------|
| 2                 | : | 0.008                                      |
| 34                | : | 0.03                                       |
| 44                | : | 0.08                                       |

While threshold determinations can be made by the method just discussed, the method is impractical because of the rather large number of solutions which had to be tasted with the resultant consumption of a considerable amount of time in order to make a single determination. Another criticism of this method is that the subjects frequently had difficulty in properly recognizing the strengths of adjacent solutions in a series. Furthermore, other investigators<sup>21</sup> claim that, due to the high variability of thresholds of a single subject at different times, extreme refinement in technique is unnecessary. It seems, then, that a more practical method would be one employing a fairly large number of subjects in order to overcome individual variations and one in which fewer solutions having greater differences between the concentrations of adjacent dilutions are used. This last named change should not only simplify proper identification but should also effect a great saving of time in making the individual determinations.

## Method II

Because the small differences in concentration between successive solutions previously employed made it very difficult for the subjects to distinguish accurately one from another, the solutions used in these experiments differed in strength, in ascending order, by 100 per cent. In other words, the second solution in a series was double the strength of the first, the third was twice the strength of the second and so on up to a concentration well above the threshold for any of the individuals tasting the solutions.

Thirty-two adults, 16 men and 16 women, served as subjects for these tests. One-half of those in each sex group were tobacco smokers while the remainder did not smoke. The individuals were chosen on this basis in an effort to determine whether or not smoking influences the threshold of taste. It was desirable to have a minimum of 30 subjects for these tests since it has been shown<sup>27</sup> that the accuracy of results obtained in any animal experimental work increases with the number of animals used. This is particularly true when small groups (numbering under 30) of animals are used. When more than 30 animals are employed, the reliability of results is not increased sufficiently to warrant the time and expense of the additional determinations.

Ammonium chloride served as the distasteful drug in these experiments by reason of its disagreeably salty taste, its wide usage as a medicinal agent and because it was desired to compare the results of this work with those of Wright (108) who determined the ammonium chloride disguising value of a

number of flavoring agents by an entirely different method.

A few preliminary tests were conducted to establish the needed range of concentrations and it was found that all persons tested could easily perceive a sensation of saltiness with a 0.64 N. aqueous solution of ammonium chloride and that all subjects declared a 0.00125 N. solution to be tasteless. Accordingly, a series of ten concentration was prepared including the above named strengths as the strongest and weakest respectively. A sufficient number of 5 cc. portions of each concentration were measured into test tubes and the tubes were placed in racks which were numbered from 1 (the weakest) to 10 (the strongest). Another rack contained 5 cc. portions of distilled water, which were used as controls.

Each subject was instructed to rinse his mouth several times with distilled water and then taste the solutions in ascending numerical order, following each solution with a control, until the salt threshold was reached. If a question arose on the part of a subject regarding the taste of one of the solutions, he was instructed to sample another portion of the same solution and if there was still doubt, to taste the solution next higher in concentration and to record this as his threshold if the taste was definite. However, practically no difficulty was encountered in observing the end-point. The values obtained by this procedure are given in Table V.

It will be observed that the mean threshold for all of the non-smokers (0.032 N.) is not significantly different from that for all of the smokers (0.046 N.). There is also no difference between the means for the male (0.032 N.) and female

Table V. - Salt Thresholds for Ammonium Chloride  
in Distilled Water

| Subject Number :                     | Normality of Threshold Concentration : | Subject Number :                 | Normality of Threshold Concentration : |
|--------------------------------------|----------------------------------------|----------------------------------|----------------------------------------|
| Male Non-Smokers                     |                                        | Male Smokers                     |                                        |
| 1 :                                  | 0.01                                   | 28 :                             | 0.01                                   |
| 2 :                                  | 0.08                                   | 30 :                             | 0.02                                   |
| 4 :                                  | 0.005                                  | 32 :                             | 0.02                                   |
| 6 :                                  | 0.01                                   | 34 :                             | 0.01                                   |
| 8 :                                  | 0.04                                   | 35 :                             | 0.04                                   |
| 11 :                                 | 0.02                                   | 36 :                             | 0.01                                   |
| 13 :                                 | 0.01                                   | 38 :                             | 0.04                                   |
| 14 :                                 | 0.08                                   | 44 :                             | 0.005                                  |
| Mean±Std.Dev.*                       | 0.032 ± 0.032                          | Mean±Std.Dev.*                   | 0.019 ± 0.014                          |
| Female Non-Smokers                   |                                        | Female Smokers                   |                                        |
| 18 :                                 | 0.04                                   | 47 :                             | 0.04                                   |
| 19 :                                 | 0.02                                   | 48 :                             | 0.04                                   |
| 20 :                                 | 0.04                                   | 49 :                             | 0.04                                   |
| 21 :                                 | 0.04                                   | 50 :                             | 0.005                                  |
| 22 :                                 | 0.04                                   | 51 :                             | 0.08                                   |
| 23 :                                 | 0.02                                   | 52 :                             | 0.04                                   |
| 24 :                                 | 0.04                                   | 53 :                             | 0.32                                   |
| 25 :                                 | 0.02                                   | 54 :                             | 0.01                                   |
| Mean±Std.Dev.*                       | 0.033 ± 0.010                          | Mean±Std.Dev.*                   | 0.072 ± 0.103                          |
| Mean for All Non-Smokers ± Std.Dev.* | 0.032 ± 0.023                          | Mean for All Smokers ± Std.Dev.* | 0.046 ± 0.076                          |
| Mean for All 4 Groups ± Std. Dev.*   |                                        | 0.039 ± 0.056                    |                                        |

\*The standard deviations were computed from the formula  $\sqrt{\frac{\sum d^2}{n-1}}$  in which "d" represents the deviation of any determination from the mean regardless of whether it is plus or minus, " $\sum d^2$ " represents the sum of these deviations squared and "n" the number of determinations in the series.

(0.033 N.) non-smokers. There is, however, apparently a difference between the means for male (0.019 N.) and female (0.072 N.) smokers. This can be accounted for by the fact that female subject 53 possessed a much higher taste threshold than the others in this group. For some reason, this subject frequently gave inconsistent responses throughout all of the experiments. When the mean values are recalculated excluding the threshold for subject 53, the mean for the remaining 7 female smokers becomes 0.036 N. and the mean for the group of 31 males and females is then 0.030 N. From these values, it can be concluded that the effect of tobacco smoking on salt taste is apparently negligible. Further experimentation, however, is necessary to substantiate this.

In this method of threshold determination, the subjects reported, in many cases, that the point at which the threshold was reached was so well defined that they found the need for controls unnecessary. The amount of time consumed was only about one-fourth that required for the procedure employed at first. An average of only 5.3 solutions per person was tasted in this experiment.

The principal objection to this method is the fact that the values are necessarily higher than they would have been by the first procedure in which smaller differences in strength existed between contiguous solutions. For example, let it be assumed that the salt threshold concentration for a certain individual is 0.024 N. By either method, a 0.020 N. solution would be tasteless. Employing Method I, the next stronger solution would be 0.025 N. (using a factor of 1.25) and this

figure would be recorded as the threshold, whereas in the second method, the next stronger solution would be 0.040 N. (using a factor of 2) and this figure would have to represent the threshold value. While greater accuracy might be desirable, this drawback is not a serious one since the ultimate goal is to obtain comparative data on a number of flavoring agents and even if all results are correspondingly higher than the true values, this goal will have been reached.

After determining the limens with the series of aqueous solutions, essentially the same procedure was repeated using a number of flavoring vehicles of the United States Pharmacopoeia and National Formulary, each of which had been diluted with distilled water so that the solutions, when ready for use, contained 10 per cent by volume of the flavoring agent. The procedure differed only in that the subject rinsed his mouth with distilled water after comparing a solution with the control and before tasting the next solution. The individual limens thus obtained are given in Appendix I. The mean threshold values and their respective standard deviations and standard errors are presented in Table VI, in which the vehicles are listed in the order of decreasing mean thresholds.

The standard errors were obtained by dividing the standard deviations by the square root of "n".

From an inspection of the mean values, it appears that since the mean ammonium chloride threshold is highest in syrup of citric acid, this syrup should be the best of those tried for concealing the taste of the salt. However, the differences

Table VI. - Ammonium Chloride Disguising Efficacy  
of 7 Diluted Vehicles\*

| Vehicle                           | : Number:<br>: of<br>: Persons:<br>: Tested: | : Mean<br>: Normality<br>: of Threshold:<br>: Concentration: | :<br>: Standard:<br>: Deviation: | :<br>: Standard:<br>: Error |
|-----------------------------------|----------------------------------------------|--------------------------------------------------------------|----------------------------------|-----------------------------|
| Syrup of Citric<br>Acid           | : 32                                         | : 0.042                                                      | : 0.029                          | : 0.005                     |
| Aromatic Syrup of<br>Eriodictyon  | : 32                                         | : 0.039                                                      | : 0.018                          | : 0.003                     |
| Syrup of Wild<br>Cherry           | : 32                                         | : 0.036                                                      | : 0.018                          | : 0.003                     |
| Syrup of Cherry                   | : 32                                         | : 0.035                                                      | : 0.018                          | : 0.003                     |
| Syrup of Cinnamon                 | : 32                                         | : 0.031                                                      | : 0.015                          | : 0.003                     |
| Compound Syrup of<br>Sarsaparilla | : 32                                         | : 0.031                                                      | : 0.016                          | : 0.003                     |
| Syrup (Simple)                    | : 32                                         | : 0.030                                                      | : 0.010                          | : 0.002                     |

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\*Each solution contained 10 per cent by volume of the respective vehicle; the remainder of the solvent was distilled water.

in the means may not be entirely due to differences in the disguising power of the vehicles but may be caused, in part, by inherent variations in the subjects. In order to determine whether there is an actual difference between two vehicles or if this difference is due only to the inherent variations in the subjects, calculations employing the formula  $\frac{m_1 - m_2}{\sqrt{e_1^2 + e_2^2}}$  and the values given in Table VI were made. The terms " $m_1$ ," and " $m_2$ " represent the two means and " $e_1$ ," and " $e_2$ " are their respective standard errors. The values obtained are tabulated in Table VII. The larger the value, the smaller the chance that the observed difference is due to variations in sensitivity of the subjects. For example, the value 0.67449 in Appendix II of Burn's book<sup>28</sup> indicates that the observed difference with the number of subjects involved would be caused by individual variations 50 per cent of the time and is therefore not significant. The value 1.95996 indicates that the chance of error due to individual variations is only 5 per cent or would occur only once in 20 trials, and 2.57582 indicates that the chance of error is 1 per cent or would occur only once in 100 times. Most workers agree that if the value calculated from the formula is 1.96 or greater, then the two results may be regarded as differing significantly.

It can be observed that the difference in disguising power between any of the vehicles to the right of the heavy vertical line in Table VII is not significant. Of the six comparisons enclosed in heavy lines, only the difference in disguising power between simple syrup and aromatic syrup of



Table VII. - Significance of Differences between the Mean  
Ammonium Chloride Threshold Values for the Vehicles  
Given in Table VI

(Vehicles arranged in order of decreasing mean thresholds. Values of 1.96 or greater indicate significant difference.)

|                           |                                    |                           |                      |                        |                                     |
|---------------------------|------------------------------------|---------------------------|----------------------|------------------------|-------------------------------------|
| :Syrup of<br>:Citric Acid |                                    |                           |                      |                        |                                     |
| : 0.50                    | :Aromatic Syrup<br>:of Eriodictyon |                           |                      |                        |                                     |
| : 1.01                    | : 0.67                             | :Syrup of<br>:Wild Cherry |                      |                        |                                     |
| : 1.17                    | : 0.89                             | : 0.23                    | :Syrup of<br>:Cherry |                        |                                     |
| 1.93                      | 1.93                               | 1.23                      | 0.99                 | :Syrup of<br>:Cinnamon |                                     |
| 1.88                      | 1.85                               | 1.17                      | 0.94                 | 0                      | :Compound Syrup<br>:of Sarsaparilla |
| 1.90                      | 2.44                               | 1.66                      | 1.39                 | 0.32                   | 0.30 :Syrup<br>:(Simple)            |

eriodictyon is really significant. The other five only approximate the limiting value of 1.96 for significant difference.

This may not be a true picture of the disguising potentialities of these vehicles because of the large increases in concentration of ammonium chloride in successive solutions in a series. The individuals again remarked in all but a few cases that the threshold concentrations were quite sharply defined. This gives rise to the belief that greater accuracy may be attained by decreasing the ratio (1 : 2) of salt concentrations in successive solutions. Therefore, in the next method, the ratio was reduced to 1 : 1.5.

If the syrups used possess any disguising power whatsoever, and it can be shown that they do (Table VIII), then the mean threshold values for the salt in the syrups should be higher in all cases than in plain distilled water. However, this was not true. The average value for the aqueous solution was higher than that for five of the syrups. Even if the unusually high and presumably unreliable figure for subject 53 in distilled water is disregarded, the mean still equals that for simple syrup. The only conclusion to be drawn from this observation is that as the subjects gain experience in tasting, their acuteness of perception apparently increases for a time with a consequent lowering of thresholds.

## Method III

A. Comparison of Efficacy of 19 Official Vehicles in  
Disguising the Saltiness of Ammonium Chloride

The procedure which follows was designed in an effort to overcome the shortcomings of the technique employed in Method II.

The 32 persons who served as tasters in the previous work again participated and ammonium chloride still served as the source of salt taste. In addition to the 7 syrups already used, 12 other popular official vehicles were employed. While a few of these vehicles may possess feeble therapeutic virtues, they are nearly always used for the purpose of presenting other drugs in a palatable liquid form. The solutions containing ammonium chloride as well as the respective controls were again made to contain 10 per cent by volume of the vehicle.

Ten concentrations of ammonium chloride solutions ranging from 0.0044 N. up to 0.17 N. were used. They were made so that a ratio of 1 : 1.5 existed between the strengths of adjacent solutions. This ratio was decided on after past experience had shown that a ratio of 1 : 1.25 was too small for accurate recognition of strengths and that the ratio 1 : 2 was apparently too large to obtain reasonable accuracy in results. The strength and corresponding number of each solution used were as follows:

| Normality | Number |
|-----------|--------|
| 0.0044    | 1      |
| 0.0067    | 2      |
| 0.010     | 3      |
| 0.015     | 4      |
| 0.022     | 5      |
| 0.033     | 6      |
| 0.050     | 7      |
| 0.075     | 8      |
| 0.11      | 9      |
| 0.17      | 10     |

The solutions employed were not of the exact normality indicated, with the exception of No. 10 which was made first. No. 9 was made by diluting a quantity of No. 10 with one-half of its volume of the proper diluent (distilled water or diluted vehicle), No. 8 was made from No. 9 in the same way and so on down to No. 1. The figures given in the normality column represent the strengths to the nearest two significant figures. Portions of 5 cc. of each strength of aqueous solution, each strength of vehicle solution and the diluted vehicle or control were placed in test tubes and the tubes, in turn, were placed in properly numbered racks. Experience showed that measured quantities of distilled water to serve as controls in the determination of the limens in aqueous solution were not necessary. If a subject felt the need for comparing one of the aqueous solutions with pure water, he was instructed to use some of the distilled water supplied for the

purpose of rinsing.

On each working day, the limen for a subject was determined first in distilled water solution and then in the vehicle solution prepared for that day. The subject rinsed his mouth with distilled water and then tasted the aqueous solutions in numerical order, rinsing between each solution tasted, until he reached the first solution which possessed a salty taste. Beginning one number below the number at which the threshold was reached in aqueous solution, the subject then tasted the vehicle solutions in numerical order, following each with a control and rinsing before proceeding with the next solution. This was continued until the vehicle solution gave a sensation of saltiness when compared with the control.

The motive for the daily determination of thresholds in aqueous solutions prior to administration of the vehicle solutions was twofold. In the first place, the results would readily reveal whether or not the threshold values gradually become lower as the subjects gain experience in tasting and secondly, by daily standardization of the subjects, it would be possible to compare not only the mean threshold values, as was done in the previous work, but the differences between the means for aqueous and vehicle solutions. A comparison of these differences should give a more accurate picture of the disguising value of the vehicles. Even if the subjects develop a keener sense of taste or if only the normal fluctuations in taste acuity occur, these differences should remain the same; e. g., if a person's threshold in aqueous solution appeared at

concentration No. 4 and in a certain vehicle at No. 6 and upon repeating the test after an interval of several weeks, the numbers were 2 and 4 respectively, the difference in either case is 2.

Since the object of this method is to establish the relative differences between the thresholds in the aqueous solutions and in the vehicle solutions, the concentrations at which the thresholds are reached simply provide the data for arriving at these differences and bear no other significance. Because of this and since the normalities represented by any two consecutive numbers in a series of solutions are proportionate to those for any other pair of consecutive numbers, the differences are expressed by numerals rather than by actual concentrations in terms of normality in Table VIII. These differences will hereafter be referred to as "disguising potentials." That the 19 vehicles employed actually possess the property of disguising the salty taste of ammonium chloride in comparison with an aqueous solution of the salt can be seen from the sixth column in Table VIII. Every value in this column is greater than 1.96 which means that the threshold for the vehicle in every case is significantly greater than that for distilled water, i. e., each vehicle has a definite disguising power in comparison with distilled water. In Table VIII, the vehicles are listed in the order of decreasing mean disguising potentials. The individual thresholds from which the mean disguising potentials were computed are given in Appendix II.

Table VIII. - Ammonium Chloride Disguising Efficacy of 19 Diluted Vehicles\*

| Vehicle                         | : Number<br>: of<br>: Subjects<br>: Tested | : Mean Threshold:<br>: for Water and<br>: Standard Error:<br>: $m_2 \pm \epsilon_2$ | : Mean Threshold:<br>: for Vehicle and<br>: Standard Error:<br>: $m_1 \pm \epsilon_1$ | : Mean Disguising:<br>: Potential and<br>: Standard Error:<br>: $D \pm \epsilon$ | : Significance of<br>: Difference** |
|---------------------------------|--------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------|
| Syrup of Glycyrrhiza            | : 32                                       | : 3.56 $\pm$ 0.22                                                                   | : 5.72 $\pm$ 0.29                                                                     | : 2.16 $\pm$ 0.24                                                                | : 5.97                              |
| Syrup of Raspberry              | : 32                                       | : 3.91 $\pm$ 0.21                                                                   | : 5.72 $\pm$ 0.23                                                                     | : 1.81 $\pm$ 0.20                                                                | : 5.78                              |
| Syrup of Orange Flowers         | : 32                                       | : 3.81 $\pm$ 0.21                                                                   | : 5.53 $\pm$ 0.26                                                                     | : 1.72 $\pm$ 0.14                                                                | : 5.20                              |
| Syrup of Citric Acid            | : 31                                       | : 4.10 $\pm$ 0.27                                                                   | : 5.81 $\pm$ 0.22                                                                     | : 1.71 $\pm$ 0.24                                                                | : 4.94                              |
| Syrup of Tolu Balsam            | : 32                                       | : 3.87 $\pm$ 0.24                                                                   | : 5.56 $\pm$ 0.27                                                                     | : 1.69 $\pm$ 0.17                                                                | : 4.76                              |
| Syrup of Acacia                 | : 32                                       | : 3.84 $\pm$ 0.24                                                                   | : 5.44 $\pm$ 0.25                                                                     | : 1.60 $\pm$ 0.13                                                                | : 4.60                              |
| Syrup of Orange                 | : 32                                       | : 3.72 $\pm$ 0.20                                                                   | : 5.31 $\pm$ 0.24                                                                     | : 1.59 $\pm$ 0.17                                                                | : 5.13                              |
| Aromatic Syrup of Eriodictyon   | : 31                                       | : 3.84 $\pm$ 0.19                                                                   | : 5.39 $\pm$ 0.20                                                                     | : 1.55 $\pm$ 0.15                                                                | : 5.60                              |
| Syrup of Cherry                 | : 32                                       | : 4.06 $\pm$ 0.23                                                                   | : 5.59 $\pm$ 0.22                                                                     | : 1.53 $\pm$ 0.17                                                                | : 4.78                              |
| Syrup of Cocoa, N.F.V           | : 32                                       | : 4.00 $\pm$ 0.23                                                                   | : 5.50 $\pm$ 0.26                                                                     | : 1.50 $\pm$ 0.16                                                                | : 4.35                              |
| Syrup of Prepared Cacao, N.F.VI | : 32                                       | : 3.97 $\pm$ 0.21                                                                   | : 5.44 $\pm$ 0.27                                                                     | : 1.47 $\pm$ 0.16                                                                | : 4.29                              |
| Syrup of Thyme                  | : 30                                       | : 3.73 $\pm$ 0.18                                                                   | : 5.16 $\pm$ 0.25                                                                     | : 1.43 $\pm$ 0.18                                                                | : 4.60                              |
| Syrup of Wild Cherry            | : 32                                       | : 3.78 $\pm$ 0.23                                                                   | : 5.19 $\pm$ 0.22                                                                     | : 1.41 $\pm$ 0.11                                                                | : 4.39                              |
| Syrup of Cinnamon               | : 32                                       | : 4.03 $\pm$ 0.25                                                                   | : 5.41 $\pm$ 0.25                                                                     | : 1.38 $\pm$ 0.17                                                                | : 3.87                              |
| Syrup of Althea                 | : 32                                       | : 3.81 $\pm$ 0.23                                                                   | : 5.09 $\pm$ 0.24                                                                     | : 1.28 $\pm$ 0.16                                                                | : 3.89                              |
| Elixir of Glycyrrhiza           | : 32                                       | : 3.75 $\pm$ 0.21                                                                   | : 5.03 $\pm$ 0.26                                                                     | : 1.28 $\pm$ 0.19                                                                | : 3.80                              |
| Compound Syrup of Sarsaparilla  | : 32                                       | : 4.03 $\pm$ 0.18                                                                   | : 5.13 $\pm$ 0.20                                                                     | : 1.10 $\pm$ 0.13                                                                | : 4.01                              |
| Aromatic Elixir                 | : 32                                       | : 3.78 $\pm$ 0.21                                                                   | : 4.81 $\pm$ 0.24                                                                     | : 1.03 $\pm$ 0.11                                                                | : 3.21                              |
| Syrup (Simple)                  | : 32                                       | : 4.15 $\pm$ 0.26                                                                   | : 5.15 $\pm$ 0.23                                                                     | : 1.00 $\pm$ 0.17                                                                | : 2.92                              |

\*Each vehicle solution contained 10 per cent by volume of the respective vehicle; the remainder of the solvent was distilled water.

\*\*Calculated from  $\frac{m_1 - m_2}{\sqrt{\epsilon_1^2 + \epsilon_2^2}}$  the significance of difference between the thresholds for distilled water and for each of the vehicles is given in this column. Since each value is greater than 1.96, there is a significant difference between the aqueous and vehicular thresholds

The formula  $\frac{m_1 - m_2}{\sqrt{e_1^2 + e_2^2}}$  was applied to the mean disguising potentials and their standard errors appearing in Table VIII and the values so derived are presented in Table IX.

Judging from the relative ease with which the threshold determinations were made, it appears that the ratio (1 : 1.5) of concentrations used is quite satisfactory. The subjects recognized the threshold points as easily as when the ratio of concentrations was 1 : 2, without the uncertainty and confusion which accompanied the determinations made when the ratio was 1 : 1.25.

A comparison of the 21 values in Table VII with the corresponding values in Table IX shows that 14 of those in the latter table are higher than the corresponding values in the former. Further comparison shows that when the latter procedure was employed, the results differed significantly (values higher than 1.96) in 7 instances, whereas by the former procedure, a significant difference actually occurred only once. Both of these facts are evidence that the results obtained by Method III are superior to those of Method II.

Comparison of the 7 syrups in Table VI, arranged in the order of decreasing mean threshold concentrations, with the same 7 vehicles in Table VIII, listed in the order of decreasing mean disguising potentials, shows that 5 of them appear in the same order in both listings. The syrups of wild cherry and cherry appear in third and fourth places respectively in the former arrangement while they are in fourth and third places in the latter. In this respect, the results of Methods II and III seem to agree very well.



Table IX. - Significance of Differences between the Mean Ammonium Chloride Disguising Potentials for the Vehicles Given in Table VIII

(Vehicles arranged in order of decreasing mean disguising potentials. Values of 1.96 or greater indicate significant difference.)

|                         |                       |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|-------------------------|-----------------------|----------------------------|-------------------------|-------------------------|--------------------|--------------------|----------------------------------|--------------------|--------------------------|------------------------------------|-------------------|-------------------------|----------------------|--------------------|--------------------------|-----------------------------------|--------------------|-------------------|--|
| Syrup of<br>Glycyrrhiza |                       |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
| 1.12                    |                       |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|                         | Syrup of<br>Raspberry |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
| 1.61                    | 0.37                  |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|                         |                       | Syrup of<br>Orange Flowers |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
| 1.34                    | 0.32                  | 0.04                       |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|                         |                       |                            | Syrup of<br>Citric Acid |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
| 1.61                    | 0.45                  | 0.14                       | 0.07                    |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|                         |                       |                            |                         | Syrup of<br>Tolu Balsam |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
| 2.05                    | 0.87                  | 0.63                       | 0.40                    | 0.41                    |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|                         |                       |                            |                         |                         | Syrup of<br>Acacia |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
| 1.96                    | 0.84                  | 0.60                       | 0.41                    | 0.42                    | 0.05               |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|                         |                       |                            |                         |                         |                    | Syrup of<br>Orange |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
| 2.16                    | 1.02                  | 0.83                       | 0.57                    | 0.61                    | 0.25               | 0.18               |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|                         |                       |                            |                         |                         |                    |                    | Aromatic Syrup<br>of Eriodictyon |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
| 2.17                    | 1.06                  | 0.88                       | 0.62                    | 0.67                    | 0.33               | 0.25               | 0.09                             |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|                         |                       |                            |                         |                         |                    |                    |                                  | Syrup of<br>Cherry |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
| 2.32                    | 1.21                  | 1.07                       | 0.74                    | 0.82                    | 0.49               | 0.40               | 0.23                             | 0.13               |                          |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|                         |                       |                            |                         |                         |                    |                    |                                  |                    | Syrup of<br>Cocoa, N.F.V |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
| 2.40                    | 1.31                  | 1.18                       | 0.84                    | 0.94                    | 0.62               | 0.52               | 0.36                             | 0.26               | 0.13                     |                                    |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|                         |                       |                            |                         |                         |                    |                    |                                  |                    |                          | Syrup of Prepared<br>Cacao, N.F.VI |                   |                         |                      |                    |                          |                                   |                    |                   |  |
| 2.46                    | 1.41                  | 1.30                       | 0.95                    | 1.06                    | 0.77               | 0.66               | 0.51                             | 0.41               | 0.30                     | 0.17                               |                   |                         |                      |                    |                          |                                   |                    |                   |  |
|                         |                       |                            |                         |                         |                    |                    |                                  |                    |                          |                                    | Syrup of<br>Thyme |                         |                      |                    |                          |                                   |                    |                   |  |
| 2.87                    | 1.74                  | 1.78                       | 1.15                    | 1.39                    | 1.10               | 0.91               | 0.75                             | 0.60               | 0.48                     | 0.31                               | 0.10              |                         |                      |                    |                          |                                   |                    |                   |  |
|                         |                       |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   | Syrup of<br>Wild Cherry |                      |                    |                          |                                   |                    |                   |  |
| 2.59                    | 1.64                  | 1.58                       | 1.14                    | 1.30                    | 1.03               | 0.89               | 0.75                             | 0.64               | 0.53                     | 0.39                               | 0.21              | 0.15                    |                      |                    |                          |                                   |                    |                   |  |
|                         |                       |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         | Syrup of<br>Cinnamon |                    |                          |                                   |                    |                   |  |
| 3.09                    | 2.07                  | 2.12                       | 1.51                    | 1.77                    | 1.55               | 1.35               | 1.23                             | 1.09               | 1.00                     | 0.84                               | 0.63              | 0.68                    | 0.44                 |                    |                          |                                   |                    |                   |  |
|                         |                       |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      | Syrup of<br>Althea |                          |                                   |                    |                   |  |
| 2.91                    | 1.93                  | 1.91                       | 1.42                    | 1.63                    | 1.40               | 1.24               | 1.12                             | 1.00               | 0.91                     | 0.77                               | 0.58              | 0.61                    | 0.40                 | 0                  |                          |                                   |                    |                   |  |
|                         |                       |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    | Elixir of<br>Glycyrrhiza |                                   |                    |                   |  |
| 3.91                    | 2.95                  | 3.30                       | 2.26                    | 2.76                    | 2.69               | 2.31               | 2.25                             | 2.03               | 1.98                     | 1.79                               | 1.50              | 1.83                    | 1.33                 | 0.89               | 0.79                     |                                   |                    |                   |  |
|                         |                       |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          | Compound Syrup<br>of Sarsaparilla |                    |                   |  |
| 4.28                    | 3.35                  | 3.88                       | 2.59                    | 3.22                    | 3.24               | 2.77               | 2.72                             | 2.46               | 2.44                     | 2.22                               | 1.90              | 2.42                    | 1.74                 | 1.29               | 1.15                     | 0.41                              |                    |                   |  |
|                         |                       |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   | Aromatic<br>Elixir |                   |  |
| 3.94                    | 3.03                  | 3.26                       | 2.41                    | 2.84                    | 2.74               | 2.45               | 2.38                             | 2.20               | 2.15                     | 1.98                               | 1.73              | 2.00                    | 1.58                 | 1.20               | 1.10                     | 0.46                              | 0.14               |                   |  |
|                         |                       |                            |                         |                         |                    |                    |                                  |                    |                          |                                    |                   |                         |                      |                    |                          |                                   |                    | Syrup<br>(Simple) |  |

An examination of the values given in Table IX leads to the following observations. Neither of two vehicles lying adjacent in the table is superior to the other as a disguising agent for ammonium chloride. Syrup of glycyrrhiza is not significantly better as a masking agent than the syrups of raspberry, orange flowers, citric acid and tolu balsam. Syrup of glycyrrhiza is, however, a definitely better disguising agent than any of the vehicles falling below syrup of tolu balsam. The values derived from the comparison of the results for the six vehicles appearing at the bottom of the table reveal that none of these preparations differ significantly from each other in disguising properties. The vehicles from syrup of glycyrrhiza down to syrup of tolu balsam inclusive are the best of the vehicles tested for disguising the taste of ammonium chloride; those from simple syrup up to and including syrup of cinnamon are the poorest; and those lying between syrup of tolu balsam and syrup of cinnamon are mediocre in disguising properties. Any pair of vehicles, the comparative values for which are not enclosed by heavy lines in the table, are not significantly different in their disguising potentialities for ammonium chloride. Any two vehicles, the values for which are enclosed by the heavy lines, are different in their disguising efficacy. The practical value of this lies in the fact that the physician can choose from the vehicles possessing the greatest masking properties. The upper five are the best but are indistinguishable from each other. In the event that one of these may not be palatable

to a particular patient for whom a physician is prescribing, he may choose one of the other four vehicles.

An examination of the mean numerical values representing the ammonium chloride thresholds in aqueous solution was made in an attempt to answer the question regarding the effect of tasting experience on threshold values. It was observed that the values dropped steadily from 4.15 to 3.78 during the first 6 working days. During the remaining 13 days, the values fluctuated irregularly between extremes of 4.00 and 3.56. The former observation is good evidence that the subjects become keener tasters as they gain experience and both of the above observations show the need for the daily standardization of the subjects with aqueous solutions prior to the vehicle solution determinations. Now that it is apparent that thresholds are somewhat higher when the subjects are inexperienced and lower later on, the question arises: how does this affect the disguising potentials? The answer will be found in the next series of experiments in which quinine hydrochloride replaced ammonium chloride and in which the first two determinations were repeated after all others had been made.

Several years ago, Wright (108) compared 13 commonly used official flavoring agents from the standpoints of relative palatability as vehicles and relative efficacy in disguising the salty taste of ammonium chloride and the bitter taste of quinine bisulfate. He made 8 per cent solutions of ammonium chloride in the vehicles and tested these preparations on about six hundred persons. The preparations were given to the

individuals in groups of four flavors at one time and the results were recorded on the basis of 3 points for first choice, 2 for second, 1 for third and no credit for fourth choice. These points were then expressed as a percentage of a perfect first choice. In order to facilitate a comparison between the results obtained by the threshold method and by the method of Wright, the two sets of results appear in Table X. The vehicles are given in the order of decreasing mean disguising potentials. The numerals in the columns captioned "Rank" are given to enable the reader to determine at a glance the relative merit of the vehicles as determined by either method.

It is obvious that there is no agreement in the two methods between the results for the syrups of glycyrrhiza, raspberry, cinnamon and compound sarsaparilla. For syrup of prepared cacao, N. F. VI, there is only fair agreement; the threshold method places it in eighth place while Wright's method places it in eleventh. The results for the remaining 8 vehicles agree rather closely. The greatest discrepancy occurs in the results for syrup of glycyrrhiza and this might be explained as follows: Wright's subjects voted syrup of glycyrrhiza the least palatable of the 13 vehicles, the poorest vehicle for the administration of ammonium chloride and also the poorest vehicle in which to administer quinine. This seems to be indicative of general dislike of the glycyrrhiza flavor rather than of poor disguising qualities. Furthermore, many of the persons on whom the threshold determinations were made expressed their dislike of the flavor of glycyrrhiza even though

Table X. - Ammonium Chloride Disguising Efficacy of  
13 Vehicles Determined by Method III and by Wright's Method

| Vehicle                         | :Threshold Method: |               | :Method of |        |
|---------------------------------|--------------------|---------------|------------|--------|
|                                 | :Rank:             | Mean          | :Rank:     | Score  |
|                                 | : :                | : Disguising: | : :        | : Per  |
|                                 | : :                | : Potential : | : :        | : Cent |
| Syrup of Glycyrrhiza            | : 1 :              | 2.16          | : 13 :     | 11     |
| Syrup of Raspberry              | : 2 :              | 1.81          | : 9 :      | 40     |
| Syrup of Citric Acid            | : 3 :              | 1.71          | : 5 :      | 50     |
| Syrup of Orange                 | : 4 :              | 1.59          | : 2 :      | 61     |
| Aromatic Syrup of Eriodictyon   | : 5 :              | 1.55          | : 4 :      | 54     |
| Syrup of Cherry                 | : 6 :              | 1.53          | : 6 :      | 47     |
| Syrup of Cocoa, N.F.V           | : 7 :              | 1.50          | : 7 :      | 42     |
| Syrup of Prepared Cacao, N.F.VI | : 8 :              | 1.47          | : 11 :     | 34     |
| Syrup of Wild Cherry            | : 9 :              | 1.41          | : 8 :      | 41     |
| Syrup of Cinnamon               | : 10 :             | 1.38          | : 1 :      | 64     |
| Elixir of Glycyrrhiza           | : 11 :             | 1.28          | : 10 :     | 35     |
| Compound Syrup of Sarsaparilla  | : 12 :             | 1.10          | : 3 :      | 58     |
| Aromatic Elixir                 | : 13 :             | 1.03          | : 12 :     | 23     |

they found it to be one of the best disguises for ammonium chloride. It is believed, therefore, that the threshold method gives an accurate estimate of actual disguising properties without regard for palatability whereas the other method does not. On the other hand, Wright's method is not to be condemned because the selection of a palatable vehicle is just as important as disguising the taste of the medicament.

#### B. Comparison of Efficacy of 19 Official Vehicles in Disguising the Bitterness of Quinine

The procedure used for the evaluation of the relative salt-disguising properties of 19 official syrups and elixirs was repeated, using quinine hydrochloride in place of ammonium chloride. Naturally, bitterness rather than saltiness was the end-point sought in these determinations.

This work was carried out at a time when it was known in advance that the attendance of a number of the subjects would be rather irregular. For this reason, a group of 37 persons was chosen to serve as tasters in order to have a minimum of 30 for any one determination. Of these 37 individuals, 15 had served previously.

The strengths of the solutions of quinine hydrochloride used ranged from 0.0000029 N. up to 0.00056 N. and the concentrations of consecutively numbered solutions varied as the ratio 1 : 1.5. All of the strengths employed and the numbers used to designate these strengths were as follows:

| Normality | Number |
|-----------|--------|
| 0.0000029 | 1      |
| 0.0000044 | 2      |
| 0.0000067 | 3      |
| 0.000010  | 4      |
| 0.000015  | 5      |
| 0.000022  | 6      |
| 0.000033  | 7      |
| 0.000050  | 8      |
| 0.000075  | 9      |
| 0.00011   | 10     |
| 0.00017   | 11     |
| 0.00025   | 12     |
| 0.00038   | 13     |
| 0.00056   | 14     |

The results of these determinations are presented in Table XI in the order of decreasing mean disguising potentials. The individual thresholds are given numerically in Appendix III.

In order to determine the significance of the differences between the mean disguising potentials given in Table XI, the formula  $\frac{m_1 - m_2}{\sqrt{\epsilon_1^2 + \epsilon_2^2}}$  was applied and the values appearing in Table XII were obtained.

It will be observed that simple syrup and syrup of wild cherry each appear twice in Tables XI and XII. Threshold determinations employing these syrups were made on the first and second working days during this series of determinations, and then they were repeated after determinations in all of the

Table XI. - Quinine Hydrochloride Disguising Efficacy of 19 Diluted Vehicles\*

| Vehicle                         | : Number<br>: of<br>: Subjects<br>: Tested | : Mean Threshold:<br>: for Water and<br>: Standard Error:<br>: $m_2 \pm \epsilon_2$ | : Mean Threshold:<br>: for Vehicle and<br>: Standard Error:<br>: $m_1 \pm \epsilon_1$ | : Mean Disguising:<br>: Potential and<br>: Standard Error:<br>: $D \pm \epsilon$ | : Significance of<br>: Difference** |
|---------------------------------|--------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------|
| Syrup of Prepared Cacao, N.F.VI | : 30                                       | : 3.50 $\pm$ 0.31                                                                   | : 8.17 $\pm$ 0.40                                                                     | : 4.67 $\pm$ 0.26                                                                | : 9.18                              |
| Syrup of Glycyrrhiza            | : 32                                       | : 3.47 $\pm$ 0.27                                                                   | : 7.88 $\pm$ 0.59                                                                     | : 4.41 $\pm$ 0.49                                                                | : 6.80                              |
| Syrup of Cocoa, N.F.V           | : 30                                       | : 3.87 $\pm$ 0.26                                                                   | : 8.27 $\pm$ 0.40                                                                     | : 4.40 $\pm$ 0.29                                                                | : 9.24                              |
| Aromatic Syrup of Eriodictyon   | : 32                                       | : 3.84 $\pm$ 0.27                                                                   | : 7.78 $\pm$ 0.50                                                                     | : 3.94 $\pm$ 0.38                                                                | : 6.94                              |
| Syrup of Thyme                  | : 30                                       | : 3.67 $\pm$ 0.23                                                                   | : 7.40 $\pm$ 0.27                                                                     | : 3.73 $\pm$ 0.25                                                                | : 10.60                             |
| Elixir of Glycyrrhiza           | : 30                                       | : 3.73 $\pm$ 0.25                                                                   | : 6.93 $\pm$ 0.42                                                                     | : 3.20 $\pm$ 0.34                                                                | : 6.52                              |
| Syrup of Tolu Balsam            | : 30                                       | : 3.47 $\pm$ 0.27                                                                   | : 6.50 $\pm$ 0.31                                                                     | : 3.03 $\pm$ 0.21                                                                | : 7.37                              |
| Compound Syrup of Sarsaparilla  | : 30                                       | : 3.53 $\pm$ 0.28                                                                   | : 6.53 $\pm$ 0.38                                                                     | : 3.00 $\pm$ 0.23                                                                | : 6.34                              |
| Syrup of Raspberry              | : 33                                       | : 3.61 $\pm$ 0.24                                                                   | : 6.12 $\pm$ 0.32                                                                     | : 2.51 $\pm$ 0.27                                                                | : 6.20                              |
| Syrup of Cherry                 | : 33                                       | : 3.61 $\pm$ 0.29                                                                   | : 6.09 $\pm$ 0.40                                                                     | : 2.48 $\pm$ 0.27                                                                | : 4.99                              |
| Syrup of Cinnamon               | : 31                                       | : 3.74 $\pm$ 0.21                                                                   | : 6.13 $\pm$ 0.33                                                                     | : 2.39 $\pm$ 0.23                                                                | : 6.08                              |
| Syrup of Citric Acid            | : 30                                       | : 3.80 $\pm$ 0.25                                                                   | : 6.13 $\pm$ 0.36                                                                     | : 2.33 $\pm$ 0.27                                                                | : 5.33                              |
| Syrup of Althea                 | : 31                                       | : 3.55 $\pm$ 0.27                                                                   | : 5.77 $\pm$ 0.34                                                                     | : 2.22 $\pm$ 0.19                                                                | : 5.12                              |
| Syrup of Wild Cherry            | : 30                                       | : 3.63 $\pm$ 0.23                                                                   | : 5.80 $\pm$ 0.41                                                                     | : 2.17 $\pm$ 0.33                                                                | : 4.59                              |
| Syrup (Simple)                  | : 31                                       | : 3.48 $\pm$ 0.25                                                                   | : 5.64 $\pm$ 0.31                                                                     | : 2.16 $\pm$ 0.19                                                                | : 5.44                              |
| Syrup of Acacia                 | : 33                                       | : 3.58 $\pm$ 0.23                                                                   | : 5.70 $\pm$ 0.30                                                                     | : 2.12 $\pm$ 0.22                                                                | : 5.61                              |
| Syrup of Wild Cherry            | : 36                                       | : 3.44 $\pm$ 0.25                                                                   | : 5.47 $\pm$ 0.41                                                                     | : 2.03 $\pm$ 0.29                                                                | : 4.19                              |
| Syrup of Orange Flowers         | : 31                                       | : 3.45 $\pm$ 0.27                                                                   | : 5.48 $\pm$ 0.31                                                                     | : 2.03 $\pm$ 0.18                                                                | : 4.94                              |
| Syrup (Simple)                  | : 31                                       | : 3.97 $\pm$ 0.26                                                                   | : 5.87 $\pm$ 0.40                                                                     | : 1.90 $\pm$ 0.23                                                                | : 3.97                              |
| Syrup of Orange                 | : 31                                       | : 3.45 $\pm$ 0.27                                                                   | : 5.19 $\pm$ 0.40                                                                     | : 1.74 $\pm$ 0.26                                                                | : 3.59                              |
| Aromatic Elixir                 | : 32                                       | : 3.38 $\pm$ 0.25                                                                   | : 4.97 $\pm$ 0.32                                                                     | : 1.59 $\pm$ 0.17                                                                | : 3.88                              |

\*Each vehicle solution contained 10 per cent by volume of the respective vehicle; the remainder of the solvent was distilled water.

\*\*Calculated from  $\frac{m_1 - m_2}{\sqrt{\epsilon_1^2 + \epsilon_2^2}}$  the significance of difference between the thresholds for distilled water and for each of the vehicles is given in this column. Since each value is greater than 1.96, there is a significant difference between the aqueous and vehicular thresholds.



Table XII. - Significance of Differences between the Mean Quinine Hydrochloride Disguising Potentials for the Vehicles Given in Table XI

Vehicles arranged in order of decreasing mean disguising potentials. Values of 1.96 or greater indicate significant difference.)

|      |                                 |                      |                               |                |                       |                      |                                |                    |                 |                   |                      |                 |                      |                |                 |                      |                         |                |                 |                 |
|------|---------------------------------|----------------------|-------------------------------|----------------|-----------------------|----------------------|--------------------------------|--------------------|-----------------|-------------------|----------------------|-----------------|----------------------|----------------|-----------------|----------------------|-------------------------|----------------|-----------------|-----------------|
| 0.47 | Syrup of Prepared Cacao, N.F.VI |                      |                               |                |                       |                      |                                |                    |                 |                   |                      |                 |                      |                |                 |                      |                         |                |                 |                 |
| 0.70 | 0.02                            | Syrup of Glycyrrhiza |                               |                |                       |                      |                                |                    |                 |                   |                      |                 |                      |                |                 |                      |                         |                |                 |                 |
| 1.58 | 0.75                            | 0.96                 | Aromatic Syrup of Eriodictyon |                |                       |                      |                                |                    |                 |                   |                      |                 |                      |                |                 |                      |                         |                |                 |                 |
| 2.59 | 1.23                            | 1.75                 | 0.46                          | Syrup of Thyme |                       |                      |                                |                    |                 |                   |                      |                 |                      |                |                 |                      |                         |                |                 |                 |
| 3.40 | 2.01                            | 2.68                 | 1.44                          | 1.24           | Elixir of Glycyrrhiza |                      |                                |                    |                 |                   |                      |                 |                      |                |                 |                      |                         |                |                 |                 |
| 4.96 | 2.58                            | 3.89                 | 2.09                          | 2.15           | 0.42                  | Syrup of Tolu Balsam |                                |                    |                 |                   |                      |                 |                      |                |                 |                      |                         |                |                 |                 |
| 4.81 | 2.59                            | 3.81                 | 2.10                          | 2.14           | 0.48                  | 0.10                 | Compound Syrup of Sarsaparilla |                    |                 |                   |                      |                 |                      |                |                 |                      |                         |                |                 |                 |
| 5.82 | 3.39                            | 4.85                 | 3.07                          | 3.32           | 1.59                  | 1.55                 | 1.40                           | Syrup of Raspberry |                 |                   |                      |                 |                      |                |                 |                      |                         |                |                 |                 |
| 5.82 | 3.43                            | 4.87                 | 3.11                          | 3.36           | 1.64                  | 1.61                 | 1.46                           | 0.08               | Syrup of Cherry |                   |                      |                 |                      |                |                 |                      |                         |                |                 |                 |
| 6.57 | 3.71                            | 5.48                 | 3.47                          | 3.92           | 1.96                  | 2.07                 | 1.88                           | 0.34               | 0.25            | Syrup of Cinnamon |                      |                 |                      |                |                 |                      |                         |                |                 |                 |
| 6.27 | 3.70                            | 5.28                 | 3.44                          | 3.79           | 2.00                  | 2.07                 | 1.90                           | 0.48               | 0.39            | 0.17              | Syrup of Citric Acid |                 |                      |                |                 |                      |                         |                |                 |                 |
| 7.63 | 4.14                            | 6.36                 | 4.02                          | 4.78           | 2.50                  | 2.89                 | 2.62                           | 0.89               | 0.79            | 0.57              | 0.34                 | Syrup of Althea |                      |                |                 |                      |                         |                |                 |                 |
| 5.92 | 3.77                            | 5.09                 | 3.49                          | 3.73           | 2.16                  | 2.19                 | 2.05                           | 0.80               | 0.72            | 0.55              | 0.38                 | 0.13            | Syrup of Wild Cherry |                |                 |                      |                         |                |                 |                 |
| 7.87 | 4.27                            | 6.57                 | 4.18                          | 5.00           | 2.66                  | 3.13                 | 2.84                           | 1.08               | 0.97            | 0.78              | 0.52                 | 0.23            | 0.03                 | Syrup (Simple) |                 |                      |                         |                |                 |                 |
| 7.54 | 4.25                            | 6.37                 | 4.14                          | 4.84           | 2.66                  | 3.04                 | 2.79                           | 1.14               | 1.04            | 0.85              | 0.61                 | 0.35            | 0.13                 | 0.14           | Syrup of Acacia |                      |                         |                |                 |                 |
| 6.80 | 4.16                            | 5.84                 | 3.98                          | 4.43           | 2.61                  | 2.83                 | 2.63                           | 1.22               | 1.14            | 0.98              | 0.76                 | 0.55            | 0.32                 | 0.38           | 0.25            | Syrup of Wild Cherry |                         |                |                 |                 |
| 8.41 | 4.54                            | 7.05                 | 4.53                          | 5.52           | 3.03                  | 3.69                 | 3.35                           | 1.51               | 1.39            | 1.24              | 0.94                 | 0.73            | 0.37                 | 0.51           | 0.33            | 0                    | Syrup of Orange Flowers |                |                 |                 |
| 7.94 | 4.60                            | 6.78                 | 4.54                          | 5.32           | 3.13                  | 3.63                 | 3.35                           | 1.73               | 1.62            | 1.49              | 1.21                 | 1.06            | 0.67                 | 0.87           | 0.69            | 0.35                 | 0.45                    | Syrup (Simple) |                 |                 |
| 8.01 | 4.79                            | 6.91                 | 4.76                          | 5.51           | 3.40                  | 3.91                 | 3.65                           | 2.08               | 1.97            | 1.88              | 1.59                 | 1.50            | 1.02                 | 1.32           | 1.13            | 0.75                 | 0.93                    | 0.46           | Syrup of Orange |                 |
| 9.87 | 5.39                            | 8.41                 | 5.60                          | 6.99           | 4.19                  | 5.35                 | 4.91                           | 2.91               | 2.76            | 2.78              | 2.32                 | 2.46            | 1.55                 | 2.24           | 1.91            | 1.31                 | 1.78                    | 1.07           | 0.48            | Aromatic Elixir |

other vehicles had been made. The amount of time intervening between the two determinations in either of the two syrups was 41 days. This repetition was to determine the effect, if any, of experience in tasting on disguising potentials. Prior to this work, none of the subjects had had any experience in making bitter threshold determinations. It was found that the two disguising potentials for simple syrup appearing in Table XI differ by approximately 12 per cent and that those for syrup of wild cherry differ by about 6 per cent. These differences are not significant, as can be seen by inspection of the values appearing in Table XII. From this, it is concluded that satisfactory results can be obtained by Method III whether or not the subjects have had previous experience in the determination of taste thresholds.

A study of Table XII discloses that N. F. VI syrup of prepared cacao, syrup of glycyrrhiza, N. F. V syrup of cocoa and aromatic syrup of eriodictyon are the best of the 19 vehicles for masking the bitter taste of quinine hydrochloride. Other conclusions drawn from this table would be analogous to those in the discussion (pages 69 and 70) of Table IX.

Wright (108) dissolved 0.1 per cent of quinine bisulfate in the 13 vehicles used by him and carried out tests analogous to those in which he used ammonium chloride. Table XIII compares the results obtained by Wright's method with those of the threshold method in which quinine hydrochloride was used.

The most discrepant results in Table XIII are those for syrup of glycyrrhiza. This was also true when ammonium

Table XIII. - Quinine\* Disguising Efficacy of 13  
Vehicles Determined by Method III and by Wright's Method

| Vehicle                         | :Threshold Method: |                | :Method of |        |
|---------------------------------|--------------------|----------------|------------|--------|
|                                 | :Rank:             | Mean           | :Rank:     | Score  |
|                                 | :                  | : Disguising:  | :          | : Per  |
|                                 | :                  | : Potential :  | :          | : Cent |
| Syrup of Prepared Cacao, N.F.VI | : 1 :              | 4.67           | : 4 :      | 67     |
| Syrup of Glycyrrhiza            | : 2 :              | 4.41           | : 13 :     | 12     |
| Syrup of Cocoa, N.F.V           | : 3 :              | 4.40           | : 1 :      | 81     |
| Aromatic Syrup of Eriodictyon   | : 4 :              | 3.94           | : 3 :      | 73     |
| Elixir of Glycyrrhiza           | : 5 :              | 3.20           | : 9 :      | 27     |
| Compound Syrup of Sarsaparilla  | : 6 :              | 3.00           | : 7 :      | 39     |
| Syrup of Raspberry              | : 7 :              | 2.51           | : 2 :      | 77     |
| Syrup of Cherry                 | : 8 :              | 2.48           | : 5 :      | 48     |
| Syrup of Cinnamon               | : 9 :              | 2.39           | : 6 :      | 41     |
| Syrup of Citric Acid            | : 10 :             | 2.33           | : 8 :      | 35     |
| Syrup of Wild Cherry            | : 11 :             | 2.17<br>2.03** | : 12 :     | 14     |
| Syrup of Orange                 | : 12 :             | 1.74           | : 11 :     | 21     |
| Aromatic Elixir                 | : 13 :             | 1.59           | : 10 :     | 27     |

\*Wright used quinine bisulfate while quinine hydrochloride was used in the determinations made by the threshold method.

\*\*Two determinations made.

chloride was used and the explanation for this has already been given (pages 71 and 73). On the whole, however, the agreement in results is a little better this time than in the experiments in which ammonium chloride was employed.

Now that the relative value of various pharmaceutical vehicles as masking agents for ammonium chloride and quinine hydrochloride has been determined, another question arises. Will the vehicles which are effective in disguising the tastes of these substances be effective to the same degree in disguising the salty and bitter tastes of other substances? If there are four different kinds of papillae and four different types of nerves leading from them, each capable of registering only one quality of sensation (evidence in support of this theory - page 8), then it is very likely that the above question should be answered in the affirmative. However, before any definite answer can be given, it will be necessary to experiment with other bitter or salty drugs.

Method III, which was found to be satisfactory for the evaluation of the ammonium chloride and quinine hydrochloride taste-disguising properties of 19 vehicles should be equally satisfactory for similar determinations in any vehicle, using drugs possessing tastes other than salty or bitter.

## CONCLUSIONS

1. A satisfactory method for comparison of the taste-disguising properties of pharmaceutical vehicles has been devised (Method III). This method is dependent upon the threshold of taste and the application of statistical methods for the evaluation of results.

2. The relative worth of 19 vehicles of the United States Pharmacopoeia and National Formulary as agents to disguise the tastes of ammonium chloride and quinine hydrochloride has been established. Of these vehicles, the syrups of glycyrrhiza, raspberry, orange flowers, citric acid and tolu balsam afford the best disguises for ammonium chloride, whereas N. F. VI syrup of prepared cacao, syrup of glycyrrhiza, N. F. V syrup of cocoa and aromatic syrup of eriodictyon are the best to disguise the taste of quinine hydrochloride.

3. The results obtained by Method III were compared with the work done by Wright (108) and it is concluded that Method III evaluates relative taste-disguising efficacy whereas Wright's method appears to evaluate relative palatability.

4. Method I, which was the first method tried, proved to be impractical because of the large number of solutions which had to be tasted in order to make a single determination and because the subjects often experienced difficulty in the proper recognition of strengths of adjacent solutions in a series. One discovery of value, made while employing this method and made use of in Methods II and III, was the fact that undiluted vehicles could not be used satisfactorily as

solvents for the drugs in making threshold determinations because of difficulty of removal from the mouth. Solutions containing 10 per cent by volume of the vehicle were found to be suitable. Other findings made use of in the subsequent methods were the need for the administration of controls for sake of comparison and the necessity of administering the same volume of control as of solution.

5. Method II, which overcame the shortcomings of Method I, was found to be inadequate for the reasons which follow. As the subjects gained experience in tasting solutions, their acuity of perception increased for a time, thereby lowering the thresholds. This necessitated standardization of the subjects with aqueous solutions just prior to each determination with vehicle solutions in order to overcome the effect of tasting experience on threshold values (Method III). Furthermore, the results obtained using Method II, in which the ratio of drug concentration in successive solutions was 1 : 2, were not as significant as those obtained by Method III in which the ratio was 1 : 1.5.

6. An experiment was conducted to determine the effect, if any, of tobacco smoking on salt taste thresholds, and it appears, from the results obtained, that the effect is negligible.

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BIBLIOGRAPHY OF LITERATURE ON DISTASTEFUL DRUGS AND  
AGENTS USED FOR DISGUIISING THEM

(Numerals enclosed by parentheses found in the text refer to articles or books listed below.)

(1) Anon., "Sulfate de quinine," Phila. J. Pharm., through J. pharm. chim., 18 (1832), 169.

The bitterness of quinine sulfate is so intense that it predominates in a mixture of 1 part to 166 of sugar. If 1 part of the sulfate is mixed with 10 or 15 parts of anise, orange peel, or valerian in a fine powder, a mixture is obtained which is scarcely bitter.

(2) Anon., "Disulphate of Quinia Rendered Soluble by Tartaric Acid," L'Abeille Medicale, through Am. J. Pharm., 24 (1852), 169.

M. Righini has proposed the substitution of tartaric acid for sulfuric acid to render quinine sulfate soluble in water. It is less austere and disagreeable to the taste. M. Casorati gives the following formula:

|                 |              |
|-----------------|--------------|
| Quinine Sulfate | 6 grains     |
| Tartaric Acid   | 3 grains     |
| Syrup of Orange | 1 fluidounce |

(3) Anon., "How to Take Quinine without Tasting It," Am. J. Pharm., 27 (1855), 21.

Dr. W. H. Edwards suggests that the quinine salt be placed in the middle of a tablespoonful of thick mucilage of slippery elm and swallowed immediately.

(4) Anon., "Verdeckung des Geruches und Geschmackes des Leberthrans," Pharm. Zentralhalle, 11 (1870), 452.

As the title implies, this article is devoted principally to masking the odor and taste of cod liver oil. However, it is stated that chloroform will decrease the bitterness of quinine at least two-thirds. Persons, for whom the sweetness of sugars is very unpleasant, will find the sweetness of chloroform quite agreeable. In the stomach, chloroform behaves very much like acetic ether, spirit of ethyl nitrite and ether which are frequently employed as taste correctives.

(5) Anon., "The After-taste of Quinine," Med. Press and Circular, through Boston Med. and Surg. J., June 8, 1871, through Am. J. Pharm., 43 (1871), 326.

The mastication of some acid fruit, as an apple or a pear, will permanently remove the disagreeable taste of quinine. The first mouthful of the fruit should be well masticated and rolled through the mouth and then ejected.

(6) Anon., "Wenig bittere Chininmixture," Pharm. Zentralhalle, 14 (1873), 28.

The writer found that a mixture of quinine sulfate, 1, cold coffee, 100, and chloroformed syrup, 30-50, possesses but feeble bitterness. If hot coffee is used or the salt is dissolved with the aid of acid, the bitterness reappears. Molasses may be used in place of chloroformed syrup.

The formula for chloroformed syrup is given as follows:

|            |     |
|------------|-----|
| Chloroform | 5   |
| Alcohol    | 30  |
| Syrup      | 450 |

(7) Anon., Am. J. Pharm., 52 (1880), 123.

A preparation for disguising the taste of quinine, made by Mr. Pennypacker, was exhibited at a meeting of the Alumni Association, Philadelphia College of Pharmacy, on Jan. 8, 1880. The preparation consists of equal parts of fluidextract of taraxacum, fluidextract of licorice root and simple elixir.

(8) Anon., "Geschmackscorrigens für Bittersalz," Deut. med. Z., 6, No. 25, through Pharm. Zentralhalle, 21 (1880), 265.

Oil of peppermint is recommended as a taste corrective for magnesium sulfate. The following proportion is suggested:

|                   |              |
|-------------------|--------------|
| Magnesium Sulfate | 20           |
| Water             | 40           |
| Oil of Peppermint | 2 or 3 drops |

(9) Anon., "Disguising the Taste of Epsom Salts," Gaz. des Hôp, June 12, 1880, through Med. and Surg. Reporter, July 17, 1880, through Am. J. Pharm., 52 (1880), 430.

A formula is given consisting of magnesium sulfate, 20 Gm., water, 40 Gm., and essence of mint, 2 or 3 drops. The essence of mint completely masks the disagreeable taste of the sulfate.

(10) Anon., "Iodide and Bromide of Potassium - Administration," New Rem., July 1883, 195, through Proc. A. Ph. A., 32 (1884), 217.

According to Dr. Seguin, potassium iodide and potassium bromide are best exhibited in slightly alkaline natural or artificial carbonated waters. The salts are less irritating and the taste is very much masked.

(11) Anon., Am. J. Pharm., 59 (1887), 159.

Syrup of gooseberries serves as an excellent vehicle for potassium iodide. In the absence of the fresh fruit, or of the preserved juice, the syrup may be made from a jar of Muir's jam to a quart of syrup.

(12) Anon., "Zur Anwendung des Saccharin," Z. f. Therap., through Pharm. Zentralhalle, 28 (1887), 253.

Saccharin serves as a very good taste corrective for quinine. Fahlberg's saccharin-chinin is a mixture of 36 parts of saccharin and 64 parts of quinine. Pollatschek recommends saccharin, 1, sodium bicarbonate, 1.2, distilled water, 100, and sulfate of quinine, 1. The solubility of saccharin is increased by sodium bicarbonate.

(13) Anon., "Chininum tannicum insipidum Rozsnyay," Pharm. Zentralhalle, 29 (1888), 477.

Tasteless quinine tannate is prepared by adding a solution of tannic acid to a solution of quinine bisulfate. The resulting precipitate is washed with water. The preparation is an almost tasteless powder and contains from 30 to 32 per cent of quinine.

(14) Anon., Pharm. Zentralhalle, 34 (1893), 526.

The taste of potassium iodide may be disguised by the addition of an equal quantity of extract of glycyrrhiza.

(15) Anon., "Quinine - A Non-Bitter Solution of," Bull. Pharm., 1893, 107, through Proc. A. Ph. A., 41 (1893), 575.

The following is recommended as a bitterless quinine preparation:

|                                 |                   |
|---------------------------------|-------------------|
| Quinine Sulfate                 | 15 grains         |
| Diluted Sulfuric Acid           | 15 minims         |
| Saturated Solution of Saccharin | 3 fluidrams       |
| Spirit of Peppermint            | 2 1/2 fluidrams   |
| Water                           | 5 1/2 fluidounces |

(16) Anon., "Zur Verdeckung des Chiningeschmacks," Wien. med. Blätter, through Pharm. Zentralhalle, 40 (1899), 229.

The following is recommended (especially for children) for disguising the taste of quinine:

|                          |           |
|--------------------------|-----------|
| Quinine Sulfate          | 4 Gm.     |
| Citric Acid              |           |
| Syrup                    |           |
| Syrup of Orange, of each | 10 Gm.    |
| Distilled Water          | 10-20 Gm. |

Give 10 drops of the above mixture in 50 cc. of water and add 3 Gm. of sodium bicarbonate. The resultant pleasant-tasting solution should be drunk while the carbonic acid is being evolved.

(17) Anon., Pharm. Zentralhalle, 40 (1899), 364.

According to Buchheim and Engel, the bitter taste of quinine tartrate is still perceptible in a dilution of 1 : 10,000. The taste limit for morphine tartrate is a dilution of 1 : 2,000 and for strychnine tartrate, the limit is 1 : 48,000.

(18) Anon., "Tasteless Quinine Tannate - Formula of the Dutch Pharmacopoeia," Pharm. Post, 36 (1903), 583, through Proc. A. Ph. A., 52 (1904), 939.

Seven parts of quinine sulfate are dissolved in 14 parts of alcohol by warming on a water bath. To this is added a similar alcoholic solution containing 24 parts of anhydrous tannin. The mixture is heated in a covered vessel until homogeneous and then poured into 200 parts of water and agitated until the precipitate becomes pulverulent. The precipitate is then collected and dried at a temperature not exceeding 30° C. It should contain at least 9.5 per cent of quinine.

(19) Anon., "Wohlschmeckende Jodkaliummixture," Pharm. Ztg., 81 (1936), 1379.

The administration of potassium iodide in milk accomplishes little in lessening the disagreeable taste of the chemical. As a taste corrective, Syr. Pruni spinosae, the as yet little-used sloe or blackthorn syrup, is recommended. The following formulas are suggested:

|                              |             |
|------------------------------|-------------|
| Solution of Potassium Iodide | 0.5 : 180.0 |
| Sloe Syrup, to make          | 200.0       |
| or                           |             |
| Solution of Potassium Iodide | 5.0 : 150.0 |
| Sloe Syrup, to make          | 200.0       |

(20) Anon., "Chininlösungen, Geschmacksverdeckung,"  
Pharm. Ztg., 82 (1937), 149.

Either extract of glycyrrhiza or ammoniated glycyrrhizin serves as a good taste corrective for quinine salts. Four parts of either the extract or the ammoniated glycyrrhizin should be sufficient to conceal the taste of 1 part of quinine salt. Extract or infusion of coffee is also suited to the purpose. Thirty Gm. of milk mixed with 0.05 Gm. of quinine sulfate produces an almost bitterless mixture. Syrup of eriodictyon or a 20 per cent solution of monosodium phosphate are likewise recommended.

(21) Anon., "Chininlösungen, Geschmacksverdeckung,"  
Pharm. Ztg., 82 (1937), 173.

Aromatic syrup of eriodictyon, N. F., is recommended as a taste corrective for quinine. So also is compound syrup of yerba santa, licorice and chocolate. Falk's formula is as follows:

|                             |            |
|-----------------------------|------------|
| Bitter Chocolate            | 65.50 Gm.  |
| Fluidextract of Licorice    | 65.50 cc.  |
| Fluidextract of Yerba Santa | 30.00 cc.  |
| Honey                       | 150.00 cc. |
| Potassium Carbonate         | 3.60 Gm.   |
| Saccharin                   | 0.96 Gm.   |
| Oil of Sassafras            | 6 drops    |
| Oil of Anise                | 6 drops    |
| Oil of Cinnamon             | 10 drops   |
| Oil of Genthor.             | 15 drops   |
| Distilled Water, to make    | 480.00 cc. |

The bitter after-taste of quinine can be completely eliminated by the addition of 1 cc. of fluidextract of eriodictyon prepared with 95 per cent alcohol to a solution of 0.04 Gm. of quinine hydrochloride in 40 cc. of water. Quinine solutions can also be improved by the addition of extracts of clove, star anise, cardamom, coriander and orange peel or with small quantities of citric acid. H. von Tappeiner recommends cinnamon water, syrup of cinnamon and syrup of orange as correctives for bitter or otherwise disagreeably tasting medicines.

(22) A. S., "Aromatic Syrup of Licorice," Am. J. Pharm., 49 (1877), 578.

A formula is given for aromatic syrup of licorice containing powdered extract of licorice, 4 ounces, Jamaica ginger, 2 ounces, cloves, 1 ounce, cinnamon bark, 2 ounces, sugar, 60 ounces, and water, sufficient to make 4 pints. It is excellent for disguising the taste of quinine sulfate. One ounce of the syrup will completely cover the taste of 20 grains of quinine sulfate and only a slight bitter taste will be developed ten or fifteen minutes after taking. This may be removed by taking a draught of black coffee with sugar. A note by the editor states that the action probably depends upon the tannin contained in the cinnamon and cloves which produces quinine tannate.

(23) Bachem, C., "Über Geschmacksverbesserung und Geschmacksaufhebung von Arzneimitteln," Münch. med. Wochschr., 71 (1924), 1348, through Jahresber. Pharm., 59 (1924), 58.

Monosodium phosphate, disodium phosphate, tincture of yerba santa and raspberry ether are useful as taste correctives for numerous substances. The constituents of the latter are, for the most part, lipoid-soluble and are able, therefore, to paralyze the superficially situated nerves of taste.

(24) Batterburg, "Geschmacks corrigens für Chinin," Med. Neugier., 30, 248, through Pharm. Zentralhalle, 21 (1880), 283.

Milk is recommended as an excellent solvent for the sulfates of quinine and emphasis is placed on its property of disguising the taste of these salts. Five cg. of the salt can scarcely be tasted in 30 Gm. of milk; with 10 cg. of the salt, the bitter taste does not distinctly stand out; even 25 cg. still causes no unpleasant bitter taste. Accordingly, this means of administration is recommended for children.

(25) Bernick, A., "Tasteless Tannate of Quinia," Pharm. Ztg., No. 30, through Am. J. Pharm., 50 (1878), 259.

Tasteless tannate of quinia is obtained by mixing 20 parts of quinine sulfate with 600 parts of distilled water having a temperature of 60 to 70° C. and adding dilute sulfuric acid cautiously so as to leave a few floccules of the quinine undissolved. To this, add a solution of 60 parts of tannin in 600 parts of distilled water. The precipitate which forms is collected and washed.

(26) Biginelli, "Quinine Tannates - True and False Kinds," Gazz. chim. ital., through Pharm. Ztg., 1909, No. 74, 726, through Proc. A. Ph. A., 58 (1910), 366.

A distinction is made between true tannates of quinine which are definite chemical compounds and false tannates which are simply addition products. Tasteless quinine tannate is a mixture of 4 true tannates.

(27) Boehringer, C. F. and Soehne, Brit. Patent 15,392, June 27, 1910, through Chem. Abstr., 5 (1911), 2416.

Tasteless quinine compounds are manufactured by subjecting quinine and diglycolic acid to a process of esterification.

(28) Borde, "Zur Verdeckung des Chiningschmacks," Semana méd., No. 9, through Pharm. Zentralhalle, 44 (1903), 361.

The following method is recommended to mask the taste of quinine: triturate 1 Gm. of quinine sulfate with 8 Gm. of olive oil. Twenty drops of this mixture will contain 0.05 Gm. of the quinine salt. Several drops are given in a tablespoon half filled with cold milk, the oil forming a film on the surface of the milk. The mass is swallowed without any sensation of taste since the quinine is coated with oil. After a few seconds, a faintly bitter taste is noticed, which may easily be removed by subsequent drinking of fluids.

(29) Candidus, P. C., "Compound Elixir Taraxacum - The Best Vehicle for Quinine," Proc. A. Ph. A., 17 (1869), 395.

The following is reputed to mask completely the bitterness of quinine:

|                    |                    |
|--------------------|--------------------|
| Rad. Taraxaci      | 6 ounces <u>or</u> |
| Ext. Tarax. fluid. | 6 fluidounces      |
| Cort. Pruni Virg.  | 4 ounces           |
| Rad. Gentianae     | 1 ounce            |
| Cort. Aurantii     | 2 ounces           |
| Cort. Cinnamomi    | 1 ounce            |
| Sem. Coriandri     | 1 ounce            |
| Sem. Anisi         | 2 drams            |
| Sem. Carvi         | 2 drams            |
| Sem. Card.         | 2 drams            |
| Rad. Glycyrrh.     | 1 ounce            |
| Syrup. Simpl.      | 2 1/2 pints        |

Percolate the mixed vegetable drugs with a menstruum consisting of 1 part of alcohol and 3 parts of water until 6 1/2 pints of percolate have been obtained and then add the syrup.

The quinine should be added to the elixir immediately before taking, although after having been mixed for several days, it is still tasteless.

(30) Chopra, R. N., "Indigenous Drugs of India,"  
The Art Press, Calcutta (1933), page 319.

Edgeworth noticed that when the leaves of *Gymnema sylvestre* were chewed, the power of the tongue to appreciate the taste of sugar and all saccharine substances was abolished. This was confirmed later by Hooper who discovered that the leaf also had the valuable property of completely removing the taste of bitter articles such as quinine. The loss of these sensations lasts only for one or two hours and not for twenty-four hours as was stated by Edgeworth.

(31) Cyx., "Geschmacksverbesserungsmittel," Pharm. Zentralhalle, 37 (1896), 31.

Vinegar is a very good taste corrective for potassium bromide. Spirit of lemon is recommended for sodium salicylate.

(32) de Bessl, Hérard, "Zur Verdeckung des bitteren Chiningeschmackes," Jour. d. practic., 1903, No. 13 through Pharm. Zentralhalle, 44 (1903), 438.

Ammoniated glycyrrhizin is recommended to disguise bitterness in liquid preparations containing quinine salts. Two formulas are given as follows:

|       |                                  |     |     |
|-------|----------------------------------|-----|-----|
| No. 1 | Quinine Hydrochloride or Sulfate | 1   | Gm. |
|       | Ammoniated Glycyrrhizin          | 10  | Gm. |
|       | Distilled Water, to make         | 60  | cc. |
| No. 2 | "Rp. Euchinin"                   | 2   | Gm. |
|       | Ammoniated Glycyrrhizin          | 4   | Gm. |
|       | Alcohol                          | 9.3 | Gm. |
|       | Distilled water, to make         | 60  | Gm. |

(33) Delgado, Frank A. and Kimball, Arthur A.,  
"Prescription Department Sales Analysis in Selected Drug Stores,"  
U. S. Department of Commerce, Bureau of Foreign and Domestic  
Commerce, Domestic Commerce Series No. 61 (1932), 34.

Prescriptions totaling 15,063 and filled in eight stores were analyzed with regard to frequency of occurrence of ingredients. A table includes all ingredients which appeared 25 times or more in the prescriptions. The following, selected from this table, shows the frequency of occurrence of vehicles and some medicinal agents which are frequently employed as vehicles.



| Galenical Preparation                | Times Prescribed |
|--------------------------------------|------------------|
| Compound Elixir of Pepsin            | 388              |
| Peppermint Water                     | 319              |
| Syrup of Wild Cherry                 | 315              |
| Elixir of Lactated Pepsin            | 269              |
| Syrup of Tolu                        | 236              |
| Simple Syrup                         | 209              |
| Compound Elixir of Pepsin and Rennin | 141              |
| Glycerinated Elixir of Gentian       | 133              |
| Syrup of Sarsaparilla                | 128              |
| Camphor Water                        | 86               |
| Syrup of White Pine                  | 83               |
| Aromatic Elixir                      | 81               |
| Syrup of Acacia                      | 76               |
| Syrup of Lemon                       | 62               |
| Chloroform Water                     | 61               |
| Syrup of Raspberry                   | 52               |
| Syrup of Glycyrrhiza                 | 49               |
| Syrup of Orange                      | 37               |
| Compound Tincture of Cardamom        | 26               |

(34) de Savignac, Delioux, Apoth. Ztg., 1872, No. 33, through Proc. A. Ph. A., 21 (1873), 378.

The administration of quinine dissolved in a dilute alcoholic liquid (whisky, etc.), tea or coffee is recommended to disguise the taste of the quinine. When tea or coffee is used, a small quantity of lemon juice should be added to render the tannate formed soluble.

(35) Diner, Jacob, "Magnesium Sulphate - Palatable Mixtures," Jour. A. Ph. A., 7 (1918), 157.

The following 5 prescriptions are offered as palatable means for administering magnesium sulfate:

|                               |         |
|-------------------------------|---------|
| 1. Magnesium Sulfate          | 30 Gm.  |
| Aromatic Sulfuric Acid        | 8 cc.   |
| Water                         | 60 cc.  |
| Glycerin, to make             | 120 cc. |
| 2. Magnesium Sulfate          | 30 Gm.  |
| Fresh Orange Juice            | 30 cc.  |
| Water                         | 60 cc.  |
| Glycerin, to make             | 120 cc. |
| 3. Magnesium Sulfate          | 30 Gm.  |
| Compound Tincture of Cardamom | 10 cc.  |
| Citric Acid                   | 1 Gm.   |
| Water                         | 60 cc.  |
| Glycerin, to make             | 120 cc. |

|                                                                          |          |
|--------------------------------------------------------------------------|----------|
| 4. Magnesium Sulfate                                                     | 30 Gm.   |
| Citric Acid                                                              | 1 Gm.    |
| Compound Syrup of Sarsaparilla                                           | 60 cc.   |
| Water, to make                                                           | 120 cc.  |
| 5. Carlton ( <u>Medical News</u> , Oct. 1904)<br>suggests the following: |          |
| Magnesium Sulfate                                                        | 1000 Gm. |
| Compound Fluidextract of Cardamom                                        | 30 cc.   |
| Vanillin                                                                 | 1.5 Gm.  |
| Garantose                                                                | 16 Gm.   |
| Alcohol                                                                  | 16 cc.   |
| Glycerin                                                                 | 60 cc.   |
| Coffee (roasted and ground)                                              | 60 Gm.   |
| Water, to make                                                           | 2000 cc. |

(36) Dodson, E. R., "Palatable Quinia," Chicago Medical Revue, December, through Am. J. Pharm., 53 (1881), 83.

The unpleasant taste of quinine is greatly improved by administering it with Liebig's liquid extract of beef.

(37) Donovan, "On a New and More Efficient Preparation of Cinchona Bark," Pharm. J., 4 (1844-5), 155.

Directions are given for the preparation of a syrup which contains all of the therapeutically active ingredients of cinchona bark. The writer claims that the preparation is not liable to spoiling, is less disagreeable than any other and may be rendered even agreeable.

Aromatics, such as anise or fennel, are said to mask perfectly the bitterness of preparations of quinine.

M. Pierquin states that 32 grains of magnesium carbonate conceal the taste of 6 grains of quinine sulfate without interfering with its virtues.

(38) Edel, Frank, "On the Manufacture of Household Remedies," West. Drug., 20 (1898), 546.

The following is a formula for "syrup of tasteless quinine" or "tasteless chill tonic":

|                      |                |
|----------------------|----------------|
| Quinidine (Alkaloid) | 256 grains     |
| Sodium Bicarbonate   | 20 grains      |
| Reduced Iron         | 128 grains     |
| Saccharin            | 20 grains      |
| Essence of Orange    | 2 drams        |
| Syrup, to make       | 16 fluidounces |

(39) Egyetemes-Kiserletezo Intezet, Brit. Patent 23,062, Oct. 18, 1907, through Chem. Abstr., 2 (1908), 1072.

A process for the manufacture of purgative lemonades from epsom salt is covered. It consists of mixing  $MgSO_4 \cdot 2H_2O$  with  $Na_2SO_4 \cdot 10H_2O$ , 3-5, for the purpose of counteracting the bitter taste, preferably, however, in the proportion of 7 to 4, respectively.

(40) Engel, "Geschmacksverbesserung des Chinins," Med.-chirurg. Rundschau, 1886, 871, through Pharm. Zentralhalle, 27 (1886), 641.

It has long been known that extract of licorice is useful as a taste corrective for quinine. Engel states, however, that the bitter taste of quinine is completely masked in the following mixture: 1 part of quinine hydrochloride, 1 part of ammonium chlorate and 4 parts of extract of licorice and water when desired.

(41) Eschenbrenner, H., "Über Geschmacksverbesserung von Harnstoff," Pharm. Ztg., 74 (1929), 93.

After discussing several methods of masking the undesirable taste of urea, Eschenbrenner recommends the following as the most efficacious: pure urea, 50 Gm., monosodium phosphate, 10 Gm., citric acid, 1 Gm., and distilled water, 50 cc. This solution may be taken without difficulty in carbonated water.

(42) Fantus, Bernard, "Tolu and Sugar Coating in the Disguising of Medicines," Jour. A. Ph. A., 7 (1918), 248.

Medicinal agents, in a No. 40 powder, are coated with a sweetened alcoholic solution of tolu which can be administered in the form of powders or compressed tablets. Formulas are given for preparing tolu coated calcium salicylate, senna, ipecac and digitalis in tablet form as follows:

|                                                |        |
|------------------------------------------------|--------|
| Sweet Tablets of Calcium Salicylate (0.06 Gm.) |        |
| Calcium Salicylate (granular)                  | 6 Gm.  |
| Saccharinated Solution of Tolu                 | 3 cc.  |
| White Fat Sugar                                | 24 Gm. |

Pour the tolu solution over the calcium salicylate and mix well without pressure. Place the sugar upon a No. 20 sieve and pass the tolu-coated calcium salicylate through the sieve repeatedly to sugar-coat the granules. Compress into 100 tablets weighing 0.3 Gm. each.

The saccharinated solution of tolu consists of 2 parts each of tolu and saccharin in 100 parts of alcohol. The white fat sugar is composed of 2 parts of spirit of peppermint, 20 parts of fat starch and 80 parts of powdered sugar. The fat starch is prepared by mixing 15 parts of a 3 per cent

alcoholic solution of saccharin with 75 parts of starch, permitting the alcohol to evaporate and then incorporating 25 parts of liquid petrolatum.

Sweet Tablets of Senna (0.06 Gm.)

|                                |        |
|--------------------------------|--------|
| Senna, No. 40 Powder           | 6 Gm.  |
| Saccharinated Solution of Tolu | 6 cc.  |
| Red Fat Sugar                  | 24 Gm. |

Prepare a granulation and compress into 100 tablets.

The red fat sugar consists of 6 parts of solution of carmine, 1 part of 10 per cent spirit of cinnamon, 20 parts of fat starch and 80 parts of powdered sugar.

Sweet Tablets of Ipecac (0.03 Gm.)

|                                |        |
|--------------------------------|--------|
| Ipecac, No. 40 Powder          | 3 Gm.  |
| Saccharinated Solution of Tolu | 3 cc.  |
| Cacao Sugar                    | 27 Gm. |

Prepare a granulation and compress into 100 tablets.

The cacao sugar is prepared by mixing 0.5 part of 10 per cent spirit of cinnamon with 10 parts of cacao powder, 10 parts of dextrose and 80 parts of powdered sugar.

Sweet Tablets of Digitalis (0.008 Gm.)

|                                |          |
|--------------------------------|----------|
| Digitalis, No. 40 Powder       | 0.8 Gm.  |
| Saccharinated Solution of Tolu | 1.6 cc.  |
| Cacao Sugar                    | 29.2 Gm. |

Prepare a granulation and compress into 100 tablets.

This coating does not interfere with the activity of digitalis, senna and calcium salicylate but it may lessen somewhat the effect of ipecac upon the stomach.

(43) Fantus, Bernard, "Iso-Alcoholic Elixirs," Jour. A. Ph. A., 9 (1920), 708.

Aromatic elixir falls short of its purpose as a general vehicle by reason of its fixed alcohol content. The pharmacist should adjust the proportion of alcohol in the elixir to make it compatible with the medicament it is to carry. A formula is given for an aromatic elixir containing about 5 per cent alcohol, to which sufficient alcohol should be added to make the vehicle compatible with the medicament. This formula is as follows:

|                           |          |
|---------------------------|----------|
| Compound Spirit of Orange | 10 cc.   |
| Syrup                     | 375 cc.  |
| Purified Talc             | 30 Gm.   |
| Alcohol                   | 50 cc.   |
| Distilled Water, to make  | 1000 cc. |

Also given is a table for adjustment of alcohol strength. Compound elixir of almond is suited for use as an iso-alcoholic elixir without any change in its formula. Aqueous elixir of glycyrrhiza is unsuited because it is precipitated when mixed with considerable quantities of alcohol. Compound elixir of vanillin and compound elixir of cardamom might be modified to reduce their alcohol content to 5 per cent.

(44) Fantus, Bernard, "Advances in Therapeutic Technic,"  
J. Am. Med. Assoc., 105 (1935), 877.

Surgical dressings, hypodermic administration and medication of mucous membranes are discussed. A section on internal medication contains the prescriptions which follow, the vehicles employed representing palatable means for dispensing the respective distasteful drugs.

|                                                    |             |
|----------------------------------------------------|-------------|
| 1. Tincture of Digitalis                           | 15 cc.      |
| Iso-Alcoholic Elixir, to make                      | 60 cc.      |
| 2. Tincture of Belladonna                          | 10 cc.      |
| Iso-Alcoholic Elixir, to make                      | 60 cc.      |
| 3. Fluidextract of Ergot                           | 30 cc.      |
| Iso-Alcoholic Elixir, to make                      | 60 cc.      |
| 4. Fluidextract of Cannabis                        | 15 cc.      |
| Iso-Alcoholic Elixir, to make                      | 60 cc.      |
| 5. Terpin Hydrate                                  | 5 Gm.       |
| Iso-Alcoholic Elixir, to make                      | 60 cc.      |
| 6. Phenobarbital                                   | 1.5 Gm.     |
| Iso-Alcoholic Elixir, to make                      | 60.0 cc.    |
| 7. Potassium Bromide                               | 30 Gm.      |
| Anise Water                                        | 30 cc.      |
| Syrup of Glycyrrhiza, to make                      | 120 cc.     |
| 8. Urea                                            | 15 Gm.      |
| Syrup of Acacia, to make                           | 60 cc.      |
| 9. Diluted Hydrochloric Acid                       | 5 cc.       |
| Raspberry Syrup, to make                           | 60 cc.      |
| 10. Syrup of Hydriodic Acid                        | 10 cc.      |
| Cherry Syrup, to make                              | 60 cc.      |
| 11. Sodium Salicylate                              | 10 Gm.      |
| Potassium Bicarbonate                              | 10 Gm.      |
| Cinnamon Water                                     | 60 cc.      |
| Syrup of Cinnamon (N.F. VI), to make               | 120 cc.     |
| 12. Iron and Ammonium Citrates                     | 10 Gm.      |
| Water                                              | 10 cc.      |
| Syrup of Cinnamon (N.F. VI), to make               | 120 cc.     |
| 13. Quinine Ethylcarbonate                         | 5 Gm.       |
| Aromatic Syrup of Eriodictyon, to make             | 60 cc.      |
| 14. Codeine Phosphate                              | 0.1 Gm.     |
| Aromatic Syrup of Eriodictyon                      | 60.0 cc.    |
| 15. Strychnine Sulfate                             | 0.015 Gm.   |
| Aromatic Syrup of Eriodictyon                      | 120.000 cc. |
| 16. Aminopyrine                                    | 2.5 Gm.     |
| Alkaline Elixir of Eriodictyon<br>(Recipe Book II) | 60.0 cc.    |

(45) Fantus, Bernard, "Some Useful Disguises," Merck Rep., 46 (1937), No. 2, 9.

Prescriptions are given employing syrup of glycyrrhiza as the vehicle for potassium bromide and ammonium chloride; syrup of glycyrrhiza and syrup of acacia for potassium iodide; syrup of cherry for diluted hydrochloric acid, syrup of hydriodic acid and ephedrine sulfate; syrup of cinnamon for iron and ammonium citrates, ethyl carbamate and a mixture of sodium salicylate and potassium bicarbonate; syrup of acacia for urea and calcium chloride; aromatic syrup of eriodictyon for quinine ethylcarbonate, codeine phosphate and strychnine sulfate; iso-elixir for tincture of digitalis, fluidextract of ergot and fluidextract of cannabis; glycerin and soluble saccharin for soluble barbital and soluble phenobarbital; and glycerin, sucrose and tincture of lemon for acetylsalicylic acid.

(46) Fantus, Bernard and Dyniewicz, H. A., "The Vehicle Value of Syrup of Cherry, N. F. VI," Jour. A. Ph. A., 25 (1936), 701.

Syrup of cherry is superior as a vehicle to syrup of wild cherry because of its palatability and fewer incompatibilities. Syrup of cherry is recommended as a vehicle for iron salts, acids (because of buffer action) and acrid substances (urea and ethyl carbamate). Syrup of glycyrrhiza is better for salines and aromatic syrup of eriodictyon is superior for bitter alkaloids although syrup of cherry may be used satisfactorily with moderately bitter alkaloids such as atropine or ephedrine. Alkalinity, even in a slight degree, is the most important incompatibility. The syrup, due to its content of benzoic acid, also possesses the incompatibilities of the benzoates. The incompatibilities of syrup of wild cherry are given.

(47) Fantus, Bernard and Dyniewicz, H. A., "Barbiturate Vehicles," Jour. A. Ph. A., 25 (1936), 993.

Low alcoholic elixir is a palatable vehicle for soluble barbital but glycerin, in the opinion of the writers, is the most palatable vehicle for soluble barbital and soluble phenobarbital. Aromatic syrup of eriodictyon, syrup of cherry and syrup of raspberry are not suitable as vehicles for the soluble barbiturates. High alcoholic elixir is recommended for barbital and phenobarbital.

(48) Fantus, Bernard and Dyniewicz, H. A.,  
"Pineapple Syrup," Jour. A. Ph. A., 26 (1937), 857.

Syrups of peach, apricot and pineapple were prepared. The peach and apricot syrups were found to have very little disguising value but the pineapple syrup proved to be a good vehicle for sodium or potassium citrate. The syrup is prepared by crushing pineapple in a grinder, dissolving 0.1 per cent of benzoic acid in the mixture and allowing it to stand at room temperature until a portion of the filtered juice produces a clear solution with one-half of its volume of alcohol. Press out the juice and filter; add 850 Gm. of sucrose to each 450 cc. of filtered juice. Dissolve the sucrose by heat on a water-bath, cool and remove the scum. Add 20 cc. of alcohol for each 1000 cc. of syrup. It is permissible to use canned pineapple juice.

(49) Fantus, Bernard, Dyniewicz, H. A. and Dyniewicz, J. M.,  
"A Study of Vehicles for Medicines. I. The Eriodictyon Preparations," Jour. A. Ph. A., 22 (1933), 323.

Eriodictyon preparations are used chiefly to disguise bitter remedies. A brief history of the use of eriodictyon is given. Adsorption tests were made by mixing the fluid-extract with varying quantities of quinine, strychnine and methylene blue; eriodictyon resinoid was mixed with methylene blue. In all experiments, the quantity of alkaloid or methylene blue adsorbed and the quantity remaining in solution were determined and the results tabulated. The resin, which is responsible for the masking property of eriodictyon, is specific for bases only and will not disguise an acidic bitter substance such as phenobarbital. Only the bitter taste of basic bodies given in very small doses can be satisfactorily disguised by eriodictyon. Aromatic syrup of eriodictyon is an elegant preparation for which no improvement is suggested. The authors recommend the deletion from the N.F. of the unstable, unsatisfactory aromatic elixir of eriodictyon.

(50) Fantus, Bernard, Dyniewicz, H. A. and Dyniewicz, J. M.,  
"A Study of Vehicles for Medicines. II. Aromatic Elixirs,"  
Jour. A. Ph. A., 22 (1933), 655, 751.

Methods for preparing aromatic elixir suggested by Crockett, Silver and Shiflett are discussed. All of these deal with the sequence of mixing. It is stated that viscosity should be kept low until after clarification, that filtration through absorbent powder must be abandoned, and that precipitation of the oils in globules so fine that they pass through the filter paper should be avoided. The authors suggest a rapid method for preparing the elixir by adding

the compound spirit of orange to a mixture of the alcohol and water, agitating the mixture frequently during 24 hours, filtering through a hard filter and dissolving the sucrose in the filtered liquid. The idea of an iso-alcoholic elixir is presented. Examples of advantages of this preparation over aromatic elixir are given. Formulas for the aqueous and alcoholic elixirs and a table for adjustment of alcoholic strength are given.

(51) Fantus, Bernard, Dyniewicz, H. A. and Dyniewicz, J. M., "A Study of Vehicles for Medicines. III. Elixir of Phenobarbital," Jour. A. Ph. A., 23 (1934), 127.

Elixir of phenobarbital should be of rather high alcoholic strength (approximately 30 per cent) and not diluted before taking because dilution brings out the bitterness. A formula for the elixir is given as follows:

|                           |            |
|---------------------------|------------|
| Phenobarbital             | 3.75 Gm.   |
| Gluside                   | 1.50 Gm.   |
| Compound Spirit of Orange | 7.00 cc.   |
| Alcohol                   | 300.00 cc. |
| Glycerin                  | 200.00 cc. |
| Water                     | 410.00 cc. |
| Sucrose                   | 170.00 Gm. |
| Tincture of Cudbear       | 6.00 cc.   |

Compound, filter, and add a sufficient quantity of the mixed solvents through the filter to produce 1000 cc. of elixir.

(52) Fantus, Bernard, Dyniewicz, H. A. and Dyniewicz, J. M., "A Study of Vehicles for Medicines. IV. Elixir of Amidopyrine," Jour. A. Ph. A., 23 (1934), 128.

Elixir of amidopyrine should be a strongly alcoholic elixir (about 50 per cent). The presence of eriodictyon resin in alkaline solution greatly increases, by adsorption of the amidopyrine, the disguising power of an elixir intended to carry it. The proposed formula is as follows:

|                                 |            |
|---------------------------------|------------|
| Oil of Bitter Almond            | 0.5 cc     |
| Vanillin                        | 1.0 Gm.    |
| Gluside                         | 1.5 Gm.    |
| Amidopyrine                     | 37.5 Gm.   |
| Fluidextract of Eriodictyon     | 30.0 cc.   |
| Solution of Potassium Hydroxide | 27.5 cc.   |
| Alcohol                         | 500.0 cc.  |
| Syrup                           | 350.0 cc.  |
| Orange Flower Water, to make    | 1000.0 cc. |

The above formula, less the amidopyrine and under the title "alkaline elixir of eriodictyon," is suggested as a useful vehicle for alkaloids or other similar agents.



(53) Fantus, Bernard, Dyniewicz, H. A. and Dyniewicz, J. M., "A Study of Vehicles for Medicines. V. Compound Elixir of Chloral and Bromide," Jour. A. Ph. A., 23 (1934), 232.

It is proposed that compound mixture of chloral and potassium bromide be deleted from the N. F. and that a compound elixir of chloral and bromide be introduced. The proposed formula is as follows:

|                                            |            |
|--------------------------------------------|------------|
| Chloral Hydrate                            | 62.5 Gm.   |
| Sodium Bromide                             | 125.0 Gm.  |
| Soluble Gluside                            | 0.5 Gm.    |
| Fluidextract of Cannabis                   | 12.5 cc.   |
| Fluidextract of Hyoscyamus                 | 25.0 cc.   |
| Alkaline Elixir of Eriodictyon,<br>to make | 1000.0 cc. |

(54) Fantus, Bernard, Dyniewicz, H. A. and Dyniewicz, J. M., "Vehicles for Medicines. VI. Syrup of Cinnamon," Jour. A. Ph. A., 23 (1934), 698.

A solution of sodium salicylate in the official syrup of cinnamon was found to have a disagreeable taste. Probable reasons are given. Experiments were conducted making syrups from the oil rather than from the drug (official method) and a formula given for a syrup which disguises sodium salicylate better than the official syrup. The syrup is colored with compound tincture of cudbear which renders unnoticeable any discoloration which the salicylate may undergo. Potassium bicarbonate is added to the salicylate mixture to prevent precipitation of the salicylate in the form of salicylic acid by the acid of the gastric juice. The syrup is also recommended for iron salts, whereas the official syrup could not be used because of "ink" formation. The formula for the improved syrup is as follows:

|                              |            |
|------------------------------|------------|
| Oil of Cassia                | 0.5 cc.    |
| Compound Tincture of Cudbear | 60.0 cc.   |
| Sucrose                      | 850.0 Gm.  |
| Water, to make               | 1000.0 cc. |

(55) Fantus, Bernard, Dyniewicz, H. A. and Dyniewicz, J. M., "A Study of Vehicles for Medicines. VII. Aromatic Syrup of Acacia," Jour. A. Ph. A., 23 (1934), 812.

Colloidalilty has disguising value. The taste of urea was found to be much more disagreeable in simple syrup than in syrup of acacia. The authors then attempted to improve the taste and keeping qualities of syrup of acacia. The improved formula, under the title of "aromatic syrup of acacia", is given as follows:

|                        |          |
|------------------------|----------|
| Acacia, in fine powder | 100 Gm.  |
| Sodium Benzoate        | 1 Gm.    |
| Methyl Salicylate      | 1 cc.    |
| Syrup, to make         | 1000 cc. |

(56) Fantus, Bernard, Dyniewicz, H. A. and Dyniewicz, J. M. "A Study of Vehicles for Medicines. VIII. The Glycyrrhiza Vehicles," Jour. A. Ph. A., 23 (1934), 915.

The Prescription Ingredient Survey by Gathercoal (A. Ph. A., Washington, D. C., 1933) shows the value of glycyrrhiza as a disguising agent. Experiments show that syrup of glycyrrhiza is a better vehicle for halides than simple syrup or fluidextract of glycyrrhiza. Experiments were conducted to determine the mode of action of colloids in lessening taste sensation but no conclusive results were obtained. Nevertheless, colloidalilty has disguising value. It is believed to be a mistake to use elixirs for the disguising of water-soluble, alcohol-insoluble salines because the best solvent is the best vehicle. For the disguising of alkaloids, syrup of glycyrrhiza was found to be inferior to aromatic syrup of eriodictyon. Neither was of any value in disguising aloin. Syrup of glycyrrhiza was best for the alkaline taste but unsuited for masking the acid taste since glycyrrhizin is precipitated by acid. An enormous difference exists in the palatability of equivalent preparations on the market as well as preparations made in the laboratory by identical methods from different samples of drug. Therefore, experiments toward obtaining a uniformly pleasant product were undertaken. A syrup of glycyrrhizin was developed but it is unstable. Improved formulas for fluidextract of glycyrrhiza and pure extract of glycyrrhiza are recommended. Fluidextract of glycyrrhiza offers a palatable means of administering chloral hydrate. An aromatic syrup of glycyrrhiza is recommended which possesses an anise bouquet. This aromatic syrup serves as a splendid vehicle for bromide. The incompatibilities of glycyrrhiza are listed.

(57) Fantus, Bernard, Dyniewicz, H. A. and Dyniewicz, J. M., "A Study of Vehicles for Medicines. IX. Fruit Syrups," Jour. A. Ph. A., 24 (1935), 46.

Possibly the reason for the limited use of fruit syrups is the variable factor of fermentation which is relied upon to destroy pectin. At times, the fermentation advances to the stage of vinegar production. To control the fermentation, the addition of 0.1 per cent of benzoic acid is recommended. It appears that the presence of benzoic acid permits the activity of the pectase but inhibits vinegar and other bacterial fermentation. Methods for the preparation of syrup of raspberry, syrup of strawberry and syrup of cherry are submitted for consideration by the U. S. P. and N. F. committees. These syrups are prepared as follows: express the juice (in the case of cherry syrup, crush the kernels), dissolve 0.1 per cent of benzoic acid in the expressed juice, let stand at room temperature until a small portion of the filtered juice produces a clear solution when mixed with half its volume of alcohol, filter, dissolve sucrose (850 Gm.) in the filtered juice (450 cc.) with the aid of heat from a water bath, cool and

remove the scum. Syrup of raspberry is recommended for antipyrine or diluted hydrochloric acid. Syrup of strawberry serves as a good vehicle for sodium citrate. Syrup of cherry is suggested for codeine phosphate, diluted hydrochloric acid or iron and ammonium citrate. The advantages of syrup of cherry over syrup of wild cherry are given.

(58) Fantus, B. and Sisson, O. U., "Syrup of Ammonium Mandelate," Jour. A. Ph. A., 25 (1936), 1138.

Because of the costliness of the proprietary mandelic acid preparations on the market, the writers offer a formula for a syrup of ammonium mandelate to serve as a basis for discussion, criticism and possible improvement. The formula is as follows:

|                                                |          |
|------------------------------------------------|----------|
| Soluble Saccharin                              | 1 Gm.    |
| Ammonium Chloride                              | 50 Gm.   |
| Ammonium Carbonate, in hard translucent pieces | 80 Gm.   |
| Mandelic Acid                                  | 200 Gm.  |
| Sucrose                                        | 400 Gm.  |
| Benzaldehyde                                   | 0.04 cc. |
| Oil of Fennel                                  | 0.10 cc. |
| Anethol                                        | 1 cc.    |
| Fluidextract of Glycyrrhiza                    | 175 cc.  |
| Water, to make                                 | 1000 cc. |

(59) Fantus, Bernard and Snow, Clyde M., "Elixirs of the United States Pharmacopoeia and National Formulary," Jour. A. Ph. A., 10 (1921), 277.

This article is, to some extent, a repetition of Fantus's paper "Iso-Alcoholic Elixirs," Jour. A. Ph. A., 9 (1920), 708. Elixir of anise, which contains 25 per cent alcohol, may be made into a palatable aqueous elixir by reducing the alcohol content to 5 per cent. The use of elixir of pepsin and compound elixir of pepsin and rennin as vehicles is undesirable. Compound elixir of almond is recommended to replace aromatic elixir to disguise the disagreeable odor of pepsin in the preceding pepsin preparations. Glycerinated elixir of gentian made with aqueous aromatic elixir is more pleasant to the taste and less sour than the N. F. elixir even though both contain the same amount of phosphoric acid. This is evidence of the fact that alcohol increases salty and sour taste sensations. The writers point out that compound elixir of taraxacum could be improved by employing aqueous aromatic elixir instead of the official aromatic elixir. Alcoholic elixir is recommended for elixir of buchu. The terpin hydrate content of elixir of terpin hydrate can be increased by employing alcoholic elixir. Aqueous elixir is recommended

for salines. Aqueous elixir of glycyrrhiza is an excellent vehicle for most salines and is suggested as a vehicle for the official elixir of sodium bromide, elixir of potassium bromide and elixir of sodium salicylate. Compound elixir of almond serves as an excellent vehicle for elixir of potassium acetate. As vehicles for bitter drugs, aqueous elixir of glycyrrhiza and aromatic elixir of eriodictyon are recommended. The writers were unable to improve the disagreeable taste of elixir of iron, quinine and strychnine.

(60) Feist, K., "Geschmackskorrigens für Jodkalium-Mixturen," Apoth. Ztg., 49 (1934), 437.

The taste of potassium iodide can be disguised very satisfactorily by the use of syrups prepared from the fresh fruit of *Prunus spinosa*. The action of these syrups is attributed to their content of tannin which affects the tongue, preventing the potassium iodide from being tasted. Two formulas are given for preparing the syrups as follows:

1. Extract 1000 Gm. of fresh blackthorn berries with 2000 cc. of water by boiling for 30 minutes. Add an equal quantity of sugar and dissolve with the aid of heat. Filter.
2. Fresh Blackthorn Berries 1000 Gm.  
Water 1500 Gm.  
Alcohol 500 Gm.

Powder the stones from about 100 of the berries and macerate the mixed ingredients in a closed container for 7 days. Add an equal quantity of sugar and dissolve it without heat. Filter.

No. 1 is richer in tannin but less aromatic than No. 2.

(61) Fiebert, Julius, "Ueber die Bereitung des Chininum tannicum neutrale (Chininum insipidum)," Zeitschr. d. Oestr. Apoth.-Ver., Nr. 31, through Pharm. Zentralhalle, 23 (1882), 550.

Quinine tannate is prepared by mixing an alcoholic solution of quinine with an aqueous solution of tannic acid. The precipitate which results is washed with distilled water.

(62) Grès, "Zur Darreichung von Chinin," Petit Monit. de la pharm., through Pharm. Zentralhalle, 36 (1895), 532.

One part of quinine salt (either the sulfate, hydrobromide or hydrochloride) mixed with 4 parts of ammoniated glycyrrhizin is recommended to disguise the bitter taste of quinine, especially for children who cannot take pills or capsules.

(63) Harrop, Joseph, "On the Fluid Extract of Licorice Root as an Excipient for Quinine," Am. J. Pharm., 41 (1869), 117.

Harrop criticizes Kemble's article (No. 68, this bibliography) on syrup of chocolate. Harrop employed powdered extract of licorice and found it to be unsatisfactory. He then tried fluidextract of licorice and found that it completely concealed the quinine. It is believed that the glycyrrhizin is partly destroyed in the powdered extract. Fluidextract of licorice is also suggested for masking the taste of aloe.

(64) Henry, M., "Action du sulfate de quinine sur différens vins, et observations sur les moyens d'y reconnaître ce sel," J. pharm. chim., 11 (1825), 337.

Henry observes that the tannin in alcoholic tincture of nutgall unites with quinine to form a tannate of quinine which is not bitter and is soluble in alcohol or acids.

(65) Hoffer, Max, assignor to Hoffmann-LaRoche Inc., U. S. Patent 2,039,415, May 5, 1936, through Pharm. Abstr., 2 (1936), 331.

There is claimed as new the 2,3-dihydroxynaphthalene-*o*-monoacetate of quinine, which crystallizes in needles melting at 195° C., is difficultly soluble in water, rather difficultly soluble in alcohol, and has practically no taste.

(66) Hommell, P. E., "Quinine, Suitable Vehicle for Disguising," Proc. N. J. Pharm. Assoc., 1888, 84, through Proc. A. Ph. A., 36 (1888), 550.

Hommell observes that a vehicle which will completely destroy the bitter taste of quinine without abstracting some of its therapeutic virtues is very hard to obtain. He finds licorice best and gives formulas for an aromatic syrup, an aromatic elixir and an aromatic honey.

(67) Hommell, R. E., "Aromatic Syrup of Quinine," Proc. N. J. Pharm. Assoc., 1912, 96, through Year Book A. Ph. A., 1 (1912), 66.

Hommell criticizes the enormous waste of quinine when administered in pill or tablet form and recommends the following:

|                                                            |               |
|------------------------------------------------------------|---------------|
| Quinine Sulfate                                            | 1 dram        |
| Diluted Hydrobromic Acid, sufficient to dissolve the above |               |
| Compound Tincture of Cardamom                              | 4 fluidrams   |
| Anise Water                                                | 4 fluidrams   |
| Syrup, to make                                             | 4 fluidounces |

Hydrobromic acid tends to overcome the untoward action of the quinine.

(68) Kemble, James, "On Syrup of Chocolate as a Vehicle for Quinine," Am. J. Pharm., 40 (1868), 517.

Kemble found that syrup of chocolate (2 ounces of cake chocolate to the pint) disguised the taste of quinine perfectly. However, it is not entirely satisfactory from the therapeutic standpoint in that no antiperiodic action was noted in one case. Aromatic sulfuric acid was found to develop bitterness in the syrup, so it is suggested that the quinine be given in the chocolate syrup and followed by a small quantity of acid or lemonade.

(69) Keyes, "Ueber Anwendung von Jodkalium in Milch," Wien. med. Blätter, 8, 42, through Pharm. Zentralhalle, 26 (1885), 526.

According to Keyes, milk is the best solvent for potassium iodide, especially if the latter is employed in large doses. Ten grains (0.64 Gm.) of the salt in 150 Gm. of cool milk make a pleasant drink which possesses only a very slight metallic after-taste.

(70) Keyes, E. L., "Milk as a Vehicle for Iodide of Potassium," N. Y. Med. Jour., Cinci. Lancet, May 23, 1885, through Am. J. Pharm., 57 (1885), 556.

The stomach does not rebel when milk is used as a vehicle for potassium iodide. Ten or more grains of potassium iodide in a gill of milk make a palatable drink.

(71) Lemanski, "Zur Darreichung von Chinin," Monit. de la Pharm., 1895, 1777, through Pharm. Zentralhalle, 36 (1895), 532.

Quinine is best given in black, weak alcoholic coffee. Experiments have shown that the medicament is found in the urine after 20 minutes. By application in suppository form (0.1 to 1 Gm. of quinine in 5 Gm. of cacao butter) the characteristic reaction for quinine in the urine is gotten after 15 minutes.

(72) Lewin, L., "Gegen die Verwendung von Sirupen zur Geschmacksverbesserung von Arzneien," Berl. Klin. Wochschr., 1894, 644, through Jahresber. Pharm., 29 (1894), 614.

Lewin disputes the generally accepted fact that the addition of sugar to bad-tasting medicines improves the taste. He recommends the following drugs for this purpose: *Bumelia dulcifica*, *Phrynium Danielli*, *Gymnena silvestre* and *Eriodictyon glutinosum*. Saccharin and dulcin are not means of improving taste but under certain conditions they are potent drugs.

(73) Little, "Syrup of Magnesium Sulfate, Palatable," Therap. Gaz., (3), 19, 319, through Year Book Pharm. Trans., 1904, 309.

Magnesium sulfate dissolved in syrup of raspberry is prescribed thus:

|                    |               |
|--------------------|---------------|
| Magnesium Sulfate  | 4 drams       |
| Syrup of Raspberry | 2 fluidounces |

(74) Lubitz, J. A., Fellers, C. R. and Clague, J. A., "Syrup of Cranberry, A New Pharmaceutical Vehicle," Jour. A. Ph. A., 29 (1940), 323.

After reviewing the literature on the cranberry, two methods for the preparation of cranberry syrup were tried. The method recommended is one in which the cranberry juice is expressed cold, filtered, boiled and sweetened in the proportion of 850 Gm. of sucrose to 450 cc. of filtered juice. Organoleptic tests were carried out in order to compare its palatability with that of five other syrups and also to compare its masking properties of five drugs with those of the other syrups. The palatability preference was as follows: syrup of raspberry, first; syrup of cranberry, second; syrup of orange, third; syrup of cherry, fourth; syrup of citric acid, fifth; and simple syrup, sixth. As a disguise for potassium iodide, raspberry and simple syrups tied for first place; cherry syrup ranked third; orange syrup, fourth; cranberry syrup, fifth; and citric acid syrup, sixth. For chloral hydrate, cranberry and citric acid syrups were tied for first place; orange syrup, third; simple syrup, fourth; cherry syrup, fifth; and raspberry syrup, sixth. For potassium acetate, orange syrup rated first; cranberry and citric acid syrups, tied for second place; raspberry syrup, fourth; cherry syrup, fifth; and simple syrup, sixth. For ammonium chloride, cranberry syrup was first; cherry syrup, second; citric acid syrup, third; orange syrup, fourth; simple syrup, fifth; and raspberry syrup, sixth. For sodium citrate, cherry syrup ranked first; raspberry and citric acid syrups were tied for second; orange syrup, fourth; simple syrup, fifth; and cranberry syrup, sixth. Incompatibilities and storage requirements for the syrup of cranberry are given also.

(75) Lucchini, V., "Some Tasteless Derivatives of Quinine," Ind. chim., 13, pages 113, 139, 148, through Chem. Abstr., 7 (1913), 2832.

A review.

(76) Lucchini, Virginio, "Tasteless Quinine Derivatives," Boll. chim. farm., 53 (1914), 344, through Chem. Abstr., 9 (1915), 3327.

Lucchini has reviewed the most important portion of the literature which relates to tasteless derivatives of quinine, especial reference being made to aristoquinine, insipin, quinaphenin, rheumatin, euquinine and saloquinine.

(77) Lutz, "Potion à la quinine sans amertume," J. méd. Paris, 23 mars 1890, 189, through J. pharm. chim., 21 (1890), 683.

The following is recommended as a non-bitter quinine preparation:

|                                 |          |
|---------------------------------|----------|
| Quinine Sulfate                 | 0.5 Gm.  |
| Diluted Sulfuric Acid           | 0.5 Gm.  |
| Spirit of Peppermint            | 5 drops  |
| Saturated Solution of Saccharin | 10.0 Gm. |
| Distilled Water                 | 90.0 Gm. |

(78) Mason, David J., "Grapefruit, Citrus Grandus, C. Decumana and Related Species as a Pharmaceutical Flavoring Agent and Vehicle," Jour. A. Ph. A., 27 (1938), 42.

Because of the abundant national supply, its low cost and its pleasant taste and aroma, Mason sees in the grapefruit a potentially new pharmaceutical vehicle. This paper, the first of a series, concerns itself with the bibliography, a description of the chemical and physical properties of the grapefruit constituents, and the botanical classification.

(79) Matsumae, Akiyoshi, U. S. Patent, 2,125,577, Aug. 2, 1938, through Pharm. Abstr., 5 (1939), 291.

An auxiliary medical agent to be used for the administration of unpleasant-tasting medicine is prepared by grinding together an alkali carbonate, an acid-reacting substance, a water-soluble adhesive gum, a flavoring substance and a perfume. Upon the addition of water, the mixture yields a pleasant-tasting liquid and a mass of lasting bubbles of carbon dioxide.



(80) Mondolfi, N., "Masking the Bitter Taste of Quinine (in Solution of Quinine Containing Iron and Arsenic)," Boll. chim. farm., 49, 387, through Chem. Zentr., 1 (1911), 506, through Chem. Abstr., 5 (1911), 2899.

The following formula is recommended:

|                         |        |
|-------------------------|--------|
| Quinine Hydrochloride   | 36 Gm. |
| Glycerin                | 60 Gm. |
| Green Ammonium Citrate* | 10 Gm. |
| Sodium Methylarsenate   | 10 Gm. |

The above is added to the taste corrective consisting of the following:

|                   |          |
|-------------------|----------|
| Citric Acid       | 350 Gm.  |
| Tannin            | 50 Gm.   |
| Ammonium Chloride | 120 Gm.  |
| Sodium Saccharate | 16 Gm.   |
| Glycerin          | 1500 Gm. |

The whole is then diluted to 2 liters.

(81) Nacca, Raphael M., "Masking the Unpleasant Taste of Medicines," Drug. Circ., 81 (1937), No. 5, 24.

The salty taste of bromides, chlorides and iodides is best disguised by syrup of glycyrrhiza, N. F. VI. Alcoholic licorice preparations such as the elixirs are not as good as the syrup for salty drugs.

Bitter alkaloids are best disguised by the use of aromatic syrup of eriodictyon. The best form of quinine to use with this syrup is quinine ethyl carbonate. The bitterness of the salts of codeine and strychnine is satisfactorily concealed by this syrup.

Syrup of cinnamon is an excellent vehicle for salicylates, iron salts, ammonium chloride and other saline drugs.

Syrup of raspberry is one of the most effective all-purpose flavoring agents. It is an especially good mask for bitter drugs, antipyrine and acids.

Syrup of cherry is the ideal vehicle for the administration of acids. This syrup ranks only slightly below syrup of raspberry as an all-round flavoring agent. Moderately salty, bitter and acrid drugs such as ephedrine and urea, can be disguised with this vehicle. Syrup of cherry is also a good vehicle for iron salts.

Syrup of acacia is a good vehicle for salty, bitter or acrid drugs. It is claimed to be well suited for disguising the sharp, disagreeable, salty taste of urea.

Syrup of prepared cacao, N. F. VI ranks high as an all-round masking vehicle. It is effective for bitter drugs such as quinine, alkaline mixtures and citrates.

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\*It is believed that "Green Iron and Ammonium Citrates" is intended.

Compound syrup of sarsaparilla is recommended for iodides and other saline drugs.

Syrup of citric acid is suggested for bitter and salty drugs.

Other outstanding vehicles which exhibit effective masking qualities are syrup of orange, aromatic elixir and iso-alcoholic elixir.

(82) Pavese, C., "Sulpho-Tartrate of Quinine Glycyrrhized with Coffee," Gaz. Med. di Torino, through Drug. Circ., 28 (1884), 4.

Pavese recommends the following for masking the bitterness of quinine:

|                              |          |
|------------------------------|----------|
| Quinine Sulfate              | 1 part   |
| Tartaric Acid                | 1 part   |
| Powdered Licorice Root       | 5 parts  |
| Powdered Roasted Coffee      | 25 parts |
| Water, a sufficient quantity |          |

The mixed licorice and coffee are extracted with hot water and the liquid is evaporated to a syrupy consistence. To this are added the quinine sulfate and the tartaric acid and the whole is evaporated to dryness by low heat. A syrup of sulpho-tartrate of quinine with licorice may be prepared by dissolving 50 parts of sugar and 1 part each of quinine sulfate and tartaric acid in the decoction of coffee and licorice. This is then evaporated by low heat to the consistence of a thick syrup.

(83) Produits Roche, Soc. Anon., Belgian Patent 410,695, Sept. 30, 1936, through Pharm. Abstr., 3 (1937), 378.

This patent protects a process for preparing a quinine derivative having but little taste. A quinine salt is dissolved in water together with a soluble salt of 2,3-dioxynaphthalene-o-monoacetic acid, or quinine base is made to react with this acid in a suitable solvent.

(84) Quevenne, M., "Remarques sur les causes de la diminution d'amertume du sulfate de quinine dans le café," J. pharm. chim., 3rd series, 12 (1847), 343.

Coffee decreases the bitterness of quinine sulfate due to tannate formation, the quinine tannate being considerably less soluble than the sulfate.

(85) Redgrove, H. Stanley, "Flavouring Essence Progress in 1937," Food Manuf., 13 (1938), 10.

A subsidiary problem of interest to the flavoring industry is that of disguising the taste of nauseous drugs. The era has passed when the efficacy of a medicine was thought to be in direct proportion to its nastiness; and today, there is a growing demand for medicines which are pleasant to take. There are two methods of approach in disguising the taste of a drug. The taste or flavor of the drug, although repellent in itself, may be blended with other flavors to produce a palatable combination. For example, bitterness is commonly regarded as unpleasant, yet a bitter taste may be blended with certain flavors to produce a decidedly pleasant combination. When this is not possible, a strong flavor may be added to overpower the nauseous taste of the drug. This is less satisfactory since the medicine, in this case, usually leaves an unpleasant after-taste. Wright's work on vehicles for medicines is reviewed (No. 108, this bibliography). A discussion of progress in the food flavor industry is included.

(86) Rittenhouse, Henry N., "Ammoniacal Glycyrrhizin," Proc. A. Ph. A., 24 (1876), 543.

Attention is called to the fact that glycyrrhizin combines with ammonia and gives a very desirable form for its use. It is especially efficacious in covering the taste of quinine sulfate. Ammoniacal glycyrrhizin is 16 times stronger than good licorice root and is said to be 100 times sweeter than sugar.

(87) Roch, "Quinine - Means of Masking the Taste of," Répertoire, (3), 18, 356, through Year Book Pharm. Trans., 1907, 281.

The quinine salt is rolled into boluses with cacao butter and taken in hot milk.

(88) Roloff, W., "Herba Eriodictyonis als Geschmackskorrigens," Pharm. Ztg., 74 (1929), 231.

Three methods of using eriodictyon as a taste corrective are listed, namely, (1) chewing the cut eriodictyon prior to the administration of the substance with a disagreeable taste, (2) painting the tongue with a fluid extract or tincture of the eriodictyon and (3) directly mixing the eriodictyon with the substance to be taken. The second method is recommended as the most efficacious. Also given is a formula for a syrup of eriodictyon as follows:

|                             |    |
|-----------------------------|----|
| Fluidextract of Eriodictyon | 2  |
| Magnesium Oxide             | 1  |
| Distilled Water             | 15 |
| Sucrose                     | 28 |

(89) Rother, R., "Quinium Salts," Am. J. Pharm., 55 (1883), 175 (part abstracted - pages 175-76).

Syrup of yerba santa is growing in popularity as a vehicle for quinine in tasteless form. The principles of eriodictyon are discussed and a formula for the syrup is given as follows: 1 ounce of yerba santa leaves is extracted by percolation with an aqueous menstruum containing 1 fluidram of ammonia water and 2 fluidounces of alcohol to the pint. One pint of percolate is collected and to it is added 28 ounces of sugar, which is dissolved with the aid of a gentle heat.

(90) Sartorius, T., German Patent 281,390, Sept. 24, 1912, through Chem. Abstr., 9 (1915), 1976.

This patent covers the manufacture of tasteless quinine compounds as follows: quinine hydrochloride is pulverized and warmed with pure gelatin, with suitable addition of water, until complete solution of the hydrochloride is effected. After cooling, a hard, stiff mass of quinine gelatin results which can be pulverized to any desired degree of fineness. The particles of suitable size are then immersed for a short time in an alcohol-ether solution of tolu balsam whereby the particles of quinine gelatin become coated with a fine layer of this resin. The preparation is then spread out for drying. The balsam coating restrains the action of the saliva until the product is in the stomach where it dissolves quickly and liberates the quinine.

(91) Schicks, George C., "New Fruit Syrups Offer Promise of Effective Disguise," Drug. Circ., 82 (1938), No. 1, 20.

|                                                |         |
|------------------------------------------------|---------|
| Syrup of Grape (made from Welch's grape juice) |         |
| Grape Juice                                    | 450 cc. |
| Sugar                                          | 850 Gm. |

Add 0.1 per cent of benzoic acid to the grape juice. Dissolve the sugar in this liquid with the aid of heat and remove any scum if present. Methenamine, ammonium chloride, potassium iodide, sodium acid phosphate and potassium citrate are made more agreeable to the taste by use of this syrup.

## Sugarless Syrup - Orange

|                                                |          |
|------------------------------------------------|----------|
| Oil of Orange                                  | 3 cc.    |
| Citric Acid                                    | 10 Gm.   |
| Saccharin Soluble                              | 1 Gm.    |
| Glycerin                                       | 500 cc.  |
| Distilled Water, to make                       | 1000 cc. |
| Color-Certified Dye Naphtha Yellow (4.8 cc. of |          |

a 1/200 solution).

## Sugarless Syrup - Anise

|                          |            |
|--------------------------|------------|
| Oil of Anise             | 1.5 cc.    |
| Oil of Fennel            | 1.5 cc.    |
| Saccharin Soluble        | 1.0 Gm.    |
| Glycerin                 | 500.0 cc.  |
| Solution of Amaranth     | 4.8 cc.    |
| Distilled Water, to make | 1000.0 cc. |

The above sugarless syrups make very good disguises for ammonium carbonate, potassium acetate, potassium citrate and potassium iodide. These syrups seem to make a better disguise for the drugs named than do those containing sugar.

Syrup of pineapple (Fantus) made according to the directions for the N. F. VI syrup of cherry is valuable for disguising sodium acid phosphate, potassium citrate, ammonium chloride and methenamine.

Syrup of cherry N. F. VI is an excellent vehicle, especially for acids. It is preferred of syrup of wild cherry as a vehicle for alkaloids and iron salts.

(92) Schicks, George C., "A Practical Guide to the Use of Pharmaceutical Flavors," Drug. Circ., 83 (1939), No. 10, 27.

The value of syrup of acacia and syrup of althea in disguising disagreeable taste is due to their colloidal properties. These syrups are useful in disguising urea but are not satisfactory as suspending agents. Syrup of althea is satisfactory for disguising mandelic acid and the following formula is suggested:

|                                              |            |
|----------------------------------------------|------------|
| Soluble Saccharin                            | 0.25 Gm.   |
| Ammonium Chloride                            | 12.50 Gm.  |
| Ammonium Carbonate (hard translucent pieces) | 20.00 Gm.  |
| Mandelic Acid                                | 50.00 Gm.  |
| Distilled Water                              | 100.00 cc. |
| Syrup of Althea (N.F.VI), to make            | 250.00 cc. |

Syrup of cinnamon is very efficacious for masking the taste of salicylates, good for salty tastes and fair for bitter tastes.

The salty taste of bromides is well disguised by syrup of raspberry. Waters and elixirs are not satisfactory. Bromides may be disguised in soups. Syrup of raspberry is also efficacious for bitter drugs and tincture of digitalis.

Syrup of orange and syrup of citric acid are valuable in disguising salty tastes.

Aromatic syrup of eriodictyon is effective for bitter drugs such as quinine, strychnine and codeine. Sour, salty or sweet tastes are not well disguised by it.

Syrup of prepared cocoa disguises the bitter taste of alkaloids and the salty taste of ammonium chloride. It is also excellent for suspending insoluble substances.

Syrup of cherry is an effective disguise for acids, moderately bitter alkaloids and castor oil. This syrup does not well disguise salty taste.

Mercuric salts are well disguised by compound syrup of sarsaparilla. This syrup is also good for salty tastes and fair for bitter ones.

Syrup of wild cherry is poor for bitter taste and good for salty substances. However, it is inferior to compound syrup of sarsaparilla in disguising salty taste.

Syrup of licorice is poor for salty tastes and fair for bitter ones.

Syrup of grape (non-official) is recommended for methenamine, ammonium chloride, potassium iodide, sodium acid phosphate and potassium citrate.

Syrup of pineapple (non-official) is suggested for sodium acid phosphate, potassium citrate, ammonium chloride and methenamine.

Elixir of saccharin aromatic (Snow-Fantus) is a more acceptable agent to carry bromides than aromatic elixir. Its formula is as follows:

|                           |           |
|---------------------------|-----------|
| Compound Spirit of Orange | 0.5 cc.   |
| Saccharin                 | 0.2 Gm.   |
| Glycerin                  | 20.0 cc.  |
| Alcohol                   | 25.0 cc.  |
| Water, to make            | 100.0 cc. |

The formula for elixir of saccharin (Recipe Book II) is given without comment.

Sugarless diabetic syrup (non-official) is recommended for ammonium carbonate, potassium acetate, potassium citrate and potassium iodide.

(93) Schneider, "Verdeckung des bitteren Geschmacks des Chinins," Corresp.-Bl. f. Schweizer Aerzte, through Pharm. Zentralhalle, 37 (1896), 291.

The bitterness of quinine can be disguised by placing the powdered quinine on a small quantity of the pulp of a ripe, somewhat sour apple. Over this place another layer of apple pulp. The whole may be swallowed without any trace of quinine taste. Other sour fruits may replace the apple. Another method consists of dissolving the desired dose of quinine in half a liqueur glass of cognac or whisky and adding lemon juice. Swallow, and rinse the mouth with a sweet-sour liqueur (cherry or the like).

(94) Schröder, "Zur Darreichung von Chinin," Pharm. Zentralhalle, 36 (1895), 585.

Purified extract of licorice is recommended as a taste corrective for quinine. Pralines of quinine are suggested for children.

(95) Schwarz, C., "Chininum tannicum," Pharm. Ztg., Nr. 53, through Pharm. Zentralhalle, 26 (1885), 471.

Quinine tannate is prepared by mixing solutions of quinine bisulfate and tannic acid and subsequently washing the precipitate of quinine tannate with water. This preparation contains  $33 \frac{1}{3}$  per cent of quinine.

(96) Snow, Clyde M. and Fantus, Bernard, "Syrup of Potassium Guaiacolsulfonate," Jour. A. Ph. A., 20 (1931), 473.

The following vehicles were tried in an attempt to make a palatable syrup of potassium guaiacolsulfonate: aromatic syrup of eriodictyon, syrup of orange, syrup of tar, syrup of wild cherry, compound syrup of sarsaparilla, compound syrup of asarum and aqueous elixir of glycyrrhiza. Aromatic syrup of eriodictyon produces the most palatable preparation and a formula is submitted for consideration by the N. F. Revision Committee as follows:

|                                        |          |
|----------------------------------------|----------|
| Potassium Guaiacolsulfonate            | 75 Gm.   |
| Water                                  | 100 cc.  |
| Aromatic Syrup of Eriodictyon, to make | 1000 cc. |

(97) Stevens, Luther F., "Condensed Notes Upon Trials for a Quinine Mask," Proc. A. Ph. A., 36 (1888), 89.

Stevens carried out numerous tests using one or more of the following vehicles in varying proportions: compound elixir of taraxacum, syrup, fluidextract of yerba santa, aromatic elixir, cologne spirit, syrup of coffee, elixir of coca (used on the theory that coca would produce its anesthetic effect upon the nerves of taste thereby dulling taste sensation), fluidextract of licorice, wine of coca and glycerin. Aromatic elixir of yerba santa is concluded to be the best mask for quinine.

(98) Thomas, Richard H., "Method of Depriving Quinine of its Bitterness," Am. J. Pharm., 22 (1850), 360.

Tannic acid obliterates the taste of quinine. Thomas suggests the following prescription:

|                 |             |
|-----------------|-------------|
| Quinine Sulfate | 10 grains   |
| Tannic Acid     | 2 grains    |
| Water           | 6 fluidrams |
| Syrup of Orange | 2 fluidrams |

(99) von Hösslin, "Jodkaliumwasser," Zeitschr. f. Mineralw.-Fabr., 2, 211, through Pharm. Zentralhalle, 26 (1885), 607.

According to von Hösslin, potassium iodide can be taken in weak acidulous mineral water more easily than in ordinary water. The author recommends that the salt be given as an artificial carbonic acid-potassium iodide solution. The strength can be selected optionally, usually 1 or 2 Gm. of the salt to the ordinary small mineral water bottle.

(100) W., Pharm. Zentralhalle, 68 (1927), 608.

As a taste corrective, the following mixture, which has various applications, is recommended:

|                              |    |
|------------------------------|----|
| Ol. Menth. Pip.              | 30 |
| Ol. Caryophyll.              | 15 |
| Tr. Sem. Abelmoschi (1 : 10) | 5  |

To 100 Gm. of liquid, add from 5 to 8 drops of the above mixture.

(101) W., Pharm. Zentralhalle, 68 (1927), 700

The best taste corrective for all quinine salts is milk. Drink 2 or 3 spoonfuls of milk with the salt. In addition, coffee, cognac, meat extract and lemon juice are recommended.

(102) W., Pharm. Zentralhalle, 72 (1931), 752.

According to Hager, a mixture of infusion of coffee and chloroform is effective as a taste corrective for quinine salts, e. g., infusion of coffee, 100, and syrup of chloroform, 50. According to Eschenbrenner, milk, 20 per cent of monosodium phosphate or syrup of eriodictyon serves the same purpose. A formula for the syrup follows:

|                    |      |
|--------------------|------|
| Ext. Eriodictyon   | 32   |
| Liq. Kalii Caust.  | 25   |
| Tr. Cardam. Co.    | 65   |
| Ol. Sassafr.       | 0.5  |
| Ol. Citri          | 0.5  |
| Ol. Caryophyll.    | 1    |
| Spir.              | 32   |
| Sacch.             | 800  |
| Aq. Dest., to make | 1000 |



(103) Ward, Justus C. and Munch, James C., "Studies on Strychnine. I. The Relative Sensitivity of Certain Chemical and Physiological Tests," Jour. A. Ph. A., 19 (1930), 954.

Taste limens for strychnine were determined, using the technique developed by Munch for the bio-assay of capsicum. Strychnine in the form of alkaloid, sulfate and hydrochloride was employed. Distilled water, city water, sodium chloride solutions (0.6 and 0.9 per cent) and sucrose solutions (1, 5 and 10 per cent) were employed as solvents. The limen increased with the order of solvents given above. Also given is a table showing the individual variations in strychnine taste limens of five humans. Marked differences in reaction time and place of detection on the tongue were found in different individuals.

(104) Ward, Justus C. and Munch, James C., "Studies on Strychnine. II. The Action of Certain Substances in Masking the Taste of Strychnine," Jour. A. Ph. A., 19 (1930), 1057.

The bitter taste of strychnine may be masked by salts, sucrose and eriodictyon extract. The cation and not the anion is the significant factor in the masking action of salts. No consistent masking effect could be attributed to the anions studied. Taste buds for detecting bitterness are located on the tip as well as on the base and sides of the tongue. No relationship was found between acuity and speed of perception of the bitter taste. The addition of sodium bicarbonate increases bitterness. Eriodictyon extract was the most effective masking agent studied.

(105) Ward, Justus C., Munch, James C., Spencer, H. J. and Garlough, F. E., "Studies on Strychnine. III. The Effectiveness of Sucrose, Saccharin and Dulcin in Masking the Bitterness of Strychnine," Jour. A. Ph. A., 23 (1934), 984.

The taste limens of the sweetening agents and of the strychnine compounds were determined first. The concentrations of the sweetening agents were then increased from 10 to 100 times their thresholds and the limens for the strychnine compounds were determined at each sweetness concentration. Sucrose masks the bitterness of the alkaloid and of the salts to about the same extent; a concentration 100 times its sweetness threshold masks from 14 to 18 times the strychnine threshold. A solution of saccharin 100 times its threshold concentration masks somewhat more than twice the threshold of the alkaloid and from 5 to 7 times the thresholds of the salts. A solution of dulcin 20 times its threshold concentration masks somewhat less than twice the threshold of strychnine alkaloid and somewhat more than 3 times the thresholds of the salts. Increasing concentrations of sweetening agents increase their masking effects.

603. (106) Wilder, Hans, "Quinia," Am. J. Pharm., 53 (1881),

Among all vehicles recommended to mask the taste of quinine, none is better than licorice. Fluidextract or aromatic elixir of licorice is suggested for liquids. For powders, an aromatic powder is recommended as follows:

|                      |           |
|----------------------|-----------|
| Pulv. Aromat.        | 2 drams   |
| Pulv. Ext. Glycyrrh. | 6 drams   |
| Ammon. Carb.         | 15 grains |

Use 4 parts of the above mixture to 1 part of quinine.

(107) Wormley, Theodore G., "On Some of the Tests for Quinine. 4. Test of Taste," Am. J. Pharm., 66 (1894), 572.

Of the ordinary preparations of quinine, the tannate is the least and the free alkaloid the next least bitter; the normal sulfate is less bitter than the bisulfate, hydrobromide or hydrochloride. The taste of the acid sulfate is very distinct in a single drop of a 1-10,000 solution and is still distinct in the same quantity of a 1-20,000 solution but, according to several persons, is not perceived in a drop of a 1-50,000 solution.

(108) Wright, Harold N., "The Comparative Efficiency of the Commonly Used Flavoring Agents," J. Am. Med. Assoc., 108 (1937), 959.

A group of commonly used flavoring agents was tested on approximately 600 individuals to determine their relative palatability as vehicles and also their relative efficacy in disguising bitter (quinine bisulfate), salty (ammonium chloride and sodium bromide) and tincture of digitalis tastes. The preparations were given to the individuals in groups of four flavors at one time. The results were tabulated and scored on the basis of 3 points for first choice, 2 for second choice, 1 for third choice and no credit for fourth choice. The results were then expressed as a percentage of a perfect first choice. The results follow in tabular form.

| Flavoring Agent                   | Preference for Flavor Alone<br>Score, Per Cent |
|-----------------------------------|------------------------------------------------|
| Syrup of Cocoa, N. F. V           | 91                                             |
| Syrup of Prepared Cacao, N. F. VI | 88                                             |
| Syrup of Raspberry, N. F. VI      | 71                                             |
| Syrup of Orange                   | 53                                             |
| Syrup of Cherry, N. F. VI         | 51                                             |
| Compound Syrup of Sarsaparilla    | 48                                             |
| Syrup of Citric Acid              | 46                                             |
| Aromatic Syrup of Eriodictyon     | 35                                             |
| Elixir of Licorice                | 33                                             |
| Syrup of Cinnamon                 | 32                                             |
| Syrup of Wild Cherry              | 29                                             |
| Aromatic Elixir                   | 27                                             |
| Syrup of Licorice                 | 26                                             |

Efficiency in Disguising Bitter Taste  
(Quinine Bisulfate, 0.1 Per Cent)

| Flavoring Agent                   | Score, Per Cent |
|-----------------------------------|-----------------|
| Syrup of Cocoa, N. F. V           | 81              |
| Syrup of Raspberry, N. F. VI      | 77              |
| Aromatic Syrup of Eriodictyon     | 73              |
| Syrup of Prepared Cacao, N. F. VI | 67              |
| Syrup of Cherry, N. F. VI         | 48              |
| Syrup of Cinnamon                 | 41              |
| Compound Syrup of Sarsaparilla    | 39              |
| Syrup of Citric Acid              | 35              |
| Elixir of Licorice                | 27              |
| Aromatic Elixir                   | 27              |
| Syrup of Orange                   | 21              |
| Syrup of Wild Cherry              | 14              |
| Syrup of Licorice                 | 12              |

Efficiency in Disguising Ammonium Chloride,  
8 Per Cent

| Flavoring Agent                   | Score, Per Cent |
|-----------------------------------|-----------------|
| Syrup of Cinnamon                 | 64              |
| Syrup of Orange                   | 61              |
| Compound Syrup of Sarsaparilla    | 58              |
| Aromatic Syrup of Eriodictyon     | 54              |
| Syrup of Citric Acid              | 50              |
| Syrup of Cherry, N. F. VI         | 47              |
| Syrup of Cocoa, N. F. V           | 42              |
| Syrup of Wild Cherry              | 41              |
| Syrup of Raspberry, N. F. VI      | 40              |
| Elixir of Licorice                | 35              |
| Syrup of Prepared Cacao, N. F. VI | 34              |
| Aromatic Elixir                   | 23              |
| Syrup of Licorice                 | 11              |

Efficiency in Disguising Tincture of  
Digitalis, 10 Per Cent

| Flavoring Agent                            | Score, Per Cent |
|--------------------------------------------|-----------------|
| Syrup of Raspberry, N. F. VI               | 83              |
| Syrup of Prepared Cacao, N. F. VI          | 77              |
| Aromatic Syrup of Eriodictyon              | 73              |
| Syrup of Cherry, N. F. VI                  | 60              |
| Syrup of Citric Acid                       | 60              |
| Tincture of Vanillin, 20 per cent in Syrup | 59              |
| Syrup of Orange                            | 57              |
| Syrup of Wild Cherry                       | 54              |
| Aromatic Elixir                            | 32              |
| Iso-Alcoholic Elixir (high)                | 24              |
| Iso-Alcoholic Elixir (50-50)               | 24              |
| Iso-Alcoholic Elixir (low)                 | 14              |
| Tincture of Vanillin, 10 per cent in Syrup | 10              |

As a further test of the efficiency of the four flavoring agents found most effective in disguising the saline taste, a comparison was made of their efficiency in disguising sodium bromide with that of elixir of sodium bromide, N. F., in which aromatic elixir is used as the vehicle.

Comparative Efficiency in Disguising Ammonium Chloride  
and Sodium Bromide

| Flavoring Agent                | 8 Per Cent<br>Ammonium<br>Chloride | 17.5 Per Cent<br>Sodium<br>Bromide |
|--------------------------------|------------------------------------|------------------------------------|
| Syrup of Cinnamon              | 64                                 | 66                                 |
| Syrup of Orange                | 61                                 | 64                                 |
| Compound Syrup of Sarsaparilla | 58                                 | 52                                 |
| Aromatic Syrup of Eriodictyon  | 54                                 | 47                                 |
| Aromatic Elixir                | 23                                 | ..                                 |
| Elixir of Sodium Bromide       | ..                                 | 23                                 |

When equal weight is given to each of the four characteristics which were studied, the following average figures are obtained:

All-Round Efficiency of the Various Flavoring Agents

| Flavoring Agent                   | Score, Per Cent |
|-----------------------------------|-----------------|
| Syrup of Cocoa, N. F. V.          | 71              |
| Syrup of Prepared Cacao, N. F. VI | 67              |
| Syrup of Raspberry, N. F. VI      | 68              |
| Aromatic Syrup of Eriodictyon     | 59              |
| Syrup of Cherry, N. F. VI         | 52              |
| Compound Syrup of Sarsaparilla    | 48              |
| Syrup of Orange                   | 48              |
| Syrup of Citric Acid              | 47              |
| Syrup of Cinnamon                 | 46              |
| Syrup of Wild Cherry              | 35              |
| Elixir of Licorice                | 32              |
| Aromatic Elixir                   | 27              |

(109) Yvon, "Zur Verdeckung des Chiningeschmackes,"  
Presse méd., 1905, 336, through Pharm. Zentralhalle,  
47 (1906), 28.

In Algiers, large quantities of quinine are dispensed in lemon juice to disguise the taste of the quinine. Children who do not like lemon juice take the quinine suspended in a fatty compound mixed with sodium bicarbonate. Ninety Gm. of quinine and 10 Gm. of almond oil produce a pasty mass which, after addition of sodium bicarbonate, gives a faint lemon or peppermint taste. Rapid swallowing leaves no unpleasant after-taste. Rhubarb can also be given in this manner.

(110) Zeelt, H. C., "Bereiding van smakelooze looizure chinine," Pharm. Weekblad, 36 (1900), No. 36.

Zeelt recommends the following method for the preparation of tasteless quinine tannate. Dissolve 100 Gm. of quinine alkaloid in 125 cc. of alcohol, place on a water bath, gradually add 400 Gm. of tannin and stir until a homogeneous mixture is obtained. The whole is then added with constant stirring to 3000 cc. of water. The precipitate is collected, expressed and dried at a low temperature.

Appendix I. - Individual Salt Thresholds for  
Ammonium Chloride in Diluted Vehicles\*

| Sub-ject No.: | Normality of Threshold Concentration |                               |                      |                 |                  |                                |                |      |
|---------------|--------------------------------------|-------------------------------|----------------------|-----------------|------------------|--------------------------------|----------------|------|
|               | Syrup of Citric Acid                 | Aromatic Syrup of Eriodictyon | Syrup of Wild Cherry | Syrup of Cherry | Syrup of Cinamon | Compound Syrup of Sarsaparilla | Syrup (Simple) |      |
| 1             | 0.04                                 | 0.04                          | 0.02                 | 0.04            | 0.04             | 0.04                           | 0.04           | 0.02 |
| 2             | 0.04                                 | 0.04                          | 0.04                 | 0.02            | 0.01             | 0.02                           | 0.02           | 0.04 |
| 4             | 0.04                                 | 0.04                          | 0.01                 | 0.08            | 0.02             | 0.02                           | 0.02           | 0.02 |
| 6             | 0.02                                 | 0.04                          | 0.04                 | 0.02            | 0.02             | 0.04                           | 0.04           | 0.04 |
| 8             | 0.04                                 | 0.08                          | 0.04                 | 0.04            | 0.02             | 0.02                           | 0.02           | 0.04 |
| 11            | 0.04                                 | 0.04                          | 0.04                 | 0.04            | 0.04             | 0.04                           | 0.04           | 0.04 |
| 13            | 0.02                                 | 0.04                          | 0.04                 | 0.04            | 0.04             | 0.04                           | 0.04           | 0.02 |
| 14            | 0.16                                 | 0.08                          | 0.04                 | 0.08            | 0.08             | 0.08                           | 0.08           | 0.04 |
| 18            | 0.04                                 | 0.04                          | 0.04                 | 0.04            | 0.04             | 0.04                           | 0.02           | 0.04 |
| 19            | 0.04                                 | 0.04                          | 0.02                 | 0.04            | 0.02             | 0.02                           | 0.02           | 0.02 |
| 20            | 0.02                                 | 0.04                          | 0.04                 | 0.04            | 0.04             | 0.04                           | 0.02           | 0.04 |
| 21            | 0.02                                 | 0.04                          | 0.04                 | 0.04            | 0.01             | 0.02                           | 0.02           | 0.04 |
| 22            | 0.04                                 | 0.02                          | 0.08                 | 0.08            | 0.02             | 0.04                           | 0.04           | 0.04 |
| 23            | 0.01                                 | 0.02                          | 0.04                 | 0.04            | 0.04             | 0.04                           | 0.02           | 0.04 |
| 24            | 0.08                                 | 0.04                          | 0.02                 | 0.04            | 0.04             | 0.04                           | 0.04           | 0.04 |
| 25            | 0.02                                 | 0.08                          | 0.04                 | 0.04            | 0.04             | 0.04                           | 0.02           | 0.02 |
| 28            | 0.02                                 | 0.02                          | 0.04                 | 0.02            | 0.04             | 0.04                           | 0.01           | 0.02 |
| 30            | 0.04                                 | 0.04                          | 0.02                 | 0.02            | 0.04             | 0.04                           | 0.02           | 0.02 |
| 32            | 0.04                                 | 0.02                          | 0.01                 | 0.04            | 0.04             | 0.04                           | 0.04           | 0.04 |
| 34            | 0.08                                 | 0.04                          | 0.08                 | 0.02            | 0.04             | 0.04                           | 0.02           | 0.02 |
| 35            | 0.08                                 | 0.02                          | 0.08                 | 0.04            | 0.04             | 0.04                           | 0.04           | 0.04 |
| 36            | 0.04                                 | 0.04                          | 0.02                 | 0.02            | 0.01             | 0.02                           | 0.02           | 0.02 |
| 38            | 0.02                                 | 0.04                          | 0.04                 | 0.02            | 0.02             | 0.02                           | 0.02           | 0.02 |
| 44            | 0.02                                 | 0.02                          | 0.04                 | 0.02            | 0.02             | 0.02                           | 0.02           | 0.02 |
| 47            | 0.04                                 | 0.08                          | 0.04                 | 0.04            | 0.04             | 0.04                           | 0.04           | 0.04 |
| 48            | 0.02                                 | 0.02                          | 0.02                 | 0.02            | 0.02             | 0.02                           | 0.02           | 0.02 |
| 49            | 0.08                                 | 0.02                          | 0.04                 | 0.02            | 0.04             | 0.04                           | 0.04           | 0.02 |
| 50            | 0.04                                 | 0.04                          | 0.02                 | 0.02            | 0.04             | 0.04                           | 0.04           | 0.02 |
| 51            | 0.02                                 | 0.02                          | 0.04                 | 0.04            | 0.04             | 0.04                           | 0.02           | 0.02 |
| 52            | 0.04                                 | 0.04                          | 0.02                 | 0.04            | 0.02             | 0.02                           | 0.02           | 0.04 |
| 53            | 0.04                                 | 0.02                          | 0.04                 | 0.01            | 0.01             | 0.08                           | 0.08           | 0.02 |
| 54            | 0.04                                 | 0.04                          | 0.02                 | 0.02            | 0.02             | 0.04                           | 0.04           | 0.04 |

\*Each solution contained 10 per cent by volume of the respective vehicle; the remainder of the solvent was distilled water.

## Appendix II. - Individual Salt Thresholds for

## Ammonium Chloride in Distilled Water and in Diluted Vehicles\*

| Sub-<br>ject<br>No.: | Number of Threshold Concentration |     |                               |     |                                  |     |                               |     |                               |     |                       |     |                       |     |
|----------------------|-----------------------------------|-----|-------------------------------|-----|----------------------------------|-----|-------------------------------|-----|-------------------------------|-----|-----------------------|-----|-----------------------|-----|
|                      | Syrup<br>of<br>Glycyrrhiza        |     | Syrup<br>of<br>Rasp-<br>berry |     | Syrup<br>of<br>Orange<br>Flowers |     | Syrup<br>of<br>Citric<br>Acid |     | Syrup<br>of<br>Tolu<br>Balsam |     | Syrup<br>of<br>Acacia |     | Syrup<br>of<br>Orange |     |
|                      | W.:                               | V.: | W.:                           | V.: | W.:                              | V.: | W.:                           | V.: | W.:                           | V.: | W.:                   | V.: | W.:                   | V.: |
| 1                    | 3                                 | 6   | 5                             | 8   | 4                                | 7   | 5                             | 8   | 4                             | 7   | 4                     | 7   | 4                     | 7   |
| 2                    | 4                                 | 5   | 4                             | 5   | 4                                | 5   | 5                             | 6   | 4                             | 5   | 4                     | 5   | 4                     | 5   |
| 4                    | 3                                 | 5   | 4                             | 7   | 3                                | 5   | 3                             | 6   | 3                             | 5   | 4                     | 5   | 3                     | 4   |
| 6                    | 3                                 | 5   | 3                             | 5   | 2                                | 4   | 3                             | 7   | 2                             | 6   | 2                     | 4   | 3                     | 5   |
| 8                    | 3                                 | 5   | 4                             | 7   | 5                                | 6   | 4                             | 6   | 5                             | 6   | 4                     | 6   | 3                     | 5   |
| 11                   | 3                                 | 6   | 4                             | 7   | 4                                | 6   | 4                             | 7   | 4                             | 7   | 3                     | 5   | 4                     | 5   |
| 13                   | 4                                 | 8   | 4                             | 6   | 4                                | 5   | 4                             | 6   | 4                             | 6   | 4                     | 5   | 4                     | 5   |
| 14                   | 6                                 | 8   | 6                             | 8   | 6                                | 8   |                               |     | 6                             | 8   | 7                     | 9   | 6                     | 9   |
| 18                   | 4                                 | 4   | 3                             | 4   | 3                                | 4   | 5                             | 6   | 4                             | 4   | 4                     | 4   | 4                     | 5   |
| 19                   | 1                                 | 3   | 1                             | 4   | 2                                | 3   | 3                             | 5   | 1                             | 3   | 1                     | 3   | 2                     | 3   |
| 20                   | 4                                 | 5   | 5                             | 5   | 3                                | 5   | 5                             | 5   | 3                             | 4   | 4                     | 4   | 4                     | 4   |
| 21                   | 2                                 | 3   | 2                             | 4   | 2                                | 4   | 2                             | 4   | 3                             | 4   | 2                     | 4   | 1                     | 4   |
| 22                   | 3                                 | 3   | 6                             | 6   | 6                                | 9   | 7                             | 6   | 5                             | 7   | 6                     | 8   | 5                     | 6   |
| 23                   | 4                                 | 6   | 4                             | 5   | 5                                | 5   | 4                             | 6   | 4                             | 6   | 4                     | 5   | 4                     | 5   |
| 24                   | 3                                 | 8   | 5                             | 7   | 6                                | 8   | 6                             | 7   | 6                             | 7   | 6                     | 7   | 6                     | 7   |
| 25                   | 2                                 | 7   | 3                             | 7   | 3                                | 5   | 2                             | 7   | 3                             | 5   | 3                     | 5   | 3                     | 6   |
| 28                   | 3                                 | 4   | 3                             | 6   | 3                                | 5   | 3                             | 5   | 3                             | 5   | 3                     | 6   | 2                     | 5   |
| 30                   | 4                                 | 7   | 4                             | 6   | 4                                | 5   | 4                             | 6   | 5                             | 5   | 4                     | 6   | 5                     | 7   |
| 32                   | 3                                 | 6   | 4                             | 6   | 4                                | 6   | 3                             | 6   | 3                             | 5   | 3                     | 6   | 3                     | 5   |
| 34                   | 4                                 | 7   | 4                             | 7   | 4                                | 6   | 5                             | 6   | 4                             | 7   | 4                     | 6   | 5                     | 6   |
| 35                   | 3                                 | 6   | 3                             | 5   | 3                                | 7   | 3                             | 4   | 4                             | 6   | 3                     | 5   | 4                     | 5   |
| 36                   | 4                                 | 5   | 4                             | 5   | 5                                | 7   | 4                             | 5   | 5                             | 5   | 4                     | 6   | 4                     | 6   |
| 38                   | 4                                 | 6   | 4                             | 6   | 4                                | 6   | 4                             | 5   | 4                             | 5   | 4                     | 5   | 4                     | 5   |
| 44                   | 2                                 | 5   | 3                             | 4   | 2                                | 3   | 3                             | 4   | 2                             | 3   | 2                     | 3   | 2                     | 3   |
| 47                   | 3                                 | 6   | 2                             | 6   | 3                                | 5   | 1                             | 4   | 3                             | 6   | 3                     | 4   | 3                     | 5   |
| 48                   | 6                                 | 8   | 5                             | 6   | 5                                | 7   | 7                             | 8   | 4                             | 6   | 5                     | 7   | 4                     | 6   |
| 49                   | 5                                 | 6   | 5                             | 5   | 4                                | 5   | 3                             | 3   | 4                             | 5   | 4                     | 5   | 4                     | 6   |
| 50                   | 4                                 | 5   | 4                             | 6   | 4                                | 5   | 6                             | 7   | 4                             | 5   | 3                     | 5   | 4                     | 5   |
| 51                   | 2                                 | 3   | 2                             | 2   | 2                                | 3   | 4                             | 5   | 2                             | 3   | 3                     | 4   | 2                     | 3   |
| 52                   | 4                                 | 5   | 4                             | 5   | 4                                | 5   | 5                             | 6   | 4                             | 5   | 4                     | 5   | 4                     | 5   |
| 53                   | 7                                 | 8   | 6                             | 6   | 5                                | 7   | 7                             | 7   | 8                             | 10  | 7                     | 8   | 5                     | 5   |
| 54                   | 4                                 | 9   | 5                             | 7   | 4                                | 6   | 3                             | 7   | 4                             | 7   | 5                     | 7   | 4                     | 8   |

\*Each vehicle solution contained 10 per cent by volume of the respective vehicle; the remainder of the solvent was distilled water.

\*\*"W." and "V." respectively stand for "distilled water solution" and "vehicle solution".

## Appendix II (Continued)

| Sub-<br>ject<br>No.: | Number of Threshold Concentration                  |                        |                                |                                           |                      |                                 |                              |     |     |     |     |     |     |     |
|----------------------|----------------------------------------------------|------------------------|--------------------------------|-------------------------------------------|----------------------|---------------------------------|------------------------------|-----|-----|-----|-----|-----|-----|-----|
|                      | Aro-<br>matic<br>Syrup<br>of<br>Erico-<br>dictyon: | Syrup<br>of<br>Cherry: | Syrup<br>of<br>Cocoa,<br>N.F.V | Syrup<br>of<br>pared<br>Cacao,<br>N.F.VI: | Syrup<br>of<br>Thyme | Syrup<br>of<br>Wild:<br>Cherry: | Syrup<br>of<br>Cin-<br>namon | W.: | V.: | W.: | V.: | W.: | V.: | W.: |
| 1                    | 3                                                  | 6                      | 5                              | 5                                         | 4                    | 7                               | 5                            | 7   | 4   | 6   | 4   | 4   | 3   | 7   |
| 2                    | 5                                                  | 6                      | 5                              | 6                                         | 4                    | 5                               | 4                            | 5   | 4   | 5   | 5   | 6   | 5   | 6   |
| 4                    | 3                                                  | 5                      | 4                              | 6                                         | 3                    | 4                               | 3                            | 5   | 3   | 4   | 4   | 6   | 3   | 5   |
| 6                    | 4                                                  | 6                      | 4                              | 6                                         | 3                    | 5                               | 3                            | 4   |     |     | 3   | 5   | 3   | 6   |
| 8                    | 4                                                  | 5                      | 6                              | 8                                         | 4                    | 6                               | 3                            | 5   | 4   | 4   | 5   | 6   | 5   | 6   |
| 11                   | 3                                                  | 4                      | 4                              | 6                                         | 4                    | 6                               | 4                            | 6   | 4   | 6   | 3   | 4   | 4   | 6   |
| 13                   | 5                                                  | 6                      | 5                              | 7                                         | 4                    | 6                               | 4                            | 6   | 4   | 5   | 5   | 6   | 6   | 7   |
| 14                   | 6                                                  | 8                      | 6                              | 7                                         | 6                    | 8                               | 6                            | 8   | 6   | 8   | 7   | 8   | 8   | 9   |
| 18                   | 4                                                  | 4                      | 4                              | 4                                         | 4                    | 4                               | 4                            | 4   | 4   | 4   | 2   | 3   | 4   | 5   |
| 19                   | 3                                                  | 4                      | 3                              | 5                                         | 2                    | 3                               | 2                            | 3   | 2   | 3   | 2   | 4   | 4   | 5   |
| 20                   | 3                                                  | 5                      | 4                              | 4                                         | 4                    | 4                               | 4                            | 4   | 4   | 3   | 3   | 4   | 3   | 3   |
| 21                   | 1                                                  | 3                      | 3                              | 6                                         | 2                    | 3                               | 2                            | 3   | 2   | 3   | 2   | 3   | 1   | 3   |
| 22                   | 4                                                  | 6                      | 6                              | 6                                         | 4                    | 7                               | 6                            | 8   | 5   | 7   | 5   | 6   | 7   | 7   |
| 23                   | 4                                                  | 6                      | 4                              | 5                                         | 3                    | 5                               | 3                            | 6   | 3   | 5   | 3   | 5   | 4   | 6   |
| 24                   | 4                                                  | 6                      | 4                              | 7                                         | 6                    | 8                               | 6                            | 7   | 4   | 5   | 4   | 6   | 4   | 5   |
| 25                   | 2                                                  | 5                      | 2                              | 5                                         | 4                    | 6                               | 4                            | 7   | 4   | 6   | 2   | 4   | 3   | 6   |
| 28                   | 3                                                  | 5                      | 3                              | 4                                         | 3                    | 5                               | 3                            | 6   | 2   | 6   | 3   | 5   | 2   | 4   |
| 30                   | 4                                                  | 7                      | 3                              | 6                                         | 4                    | 6                               | 4                            | 6   | 4   | 7   | 4   | 6   | 4   | 6   |
| 32                   | 4                                                  | 5                      | 3                              | 5                                         | 4                    | 6                               | 3                            | 5   | 4   | 5   | 3   | 4   | 3   | 3   |
| 34                   | 5                                                  | 7                      | 4                              | 6                                         | 4                    | 6                               | 4                            | 5   | 4   | 6   | 4   | 6   | 4   | 6   |
| 35                   | 5                                                  | 6                      | 3                              | 6                                         | 3                    | 5                               | 3                            | 6   | 4   | 5   | 4   | 5   | 4   | 6   |
| 36                   | 5                                                  | 5                      | 4                              | 5                                         | 5                    | 6                               | 5                            | 6   |     |     | 4   | 5   | 5   | 6   |
| 38                   | 5                                                  | 5                      | 4                              | 6                                         | 4                    | 6                               | 4                            | 5   | 3   | 5   | 4   | 5   | 5   | 6   |
| 44                   | 2                                                  | 3                      | 2                              | 3                                         | 2                    | 3                               | 3                            | 3   | 2   | 3   | 1   | 3   | 3   | 3   |
| 47                   | 4                                                  | 5                      | 2                              | 3                                         | 4                    | 5                               | 4                            | 6   | 4   | 5   | 4   | 5   | 2   | 3   |
| 48                   | 5                                                  | 7                      | 5                              | 7                                         | 6                    | 6                               | 5                            | 6   | 4   | 6   | 6   | 7   | 5   | 6   |
| 49                   | 4                                                  | 6                      | 5                              | 7                                         | 5                    | 5                               | 4                            | 4   | 4   | 5   | 5   | 6   | 4   | 4   |
| 50                   | 4                                                  | 5                      | 4                              | 5                                         | 4                    | 5                               | 4                            | 6   | 3   | 4   | 4   | 5   | 4   | 6   |
| 51                   | 3                                                  | 6                      | 4                              | 5                                         | 2                    | 3                               | 2                            | 2   | 3   | 4   | 3   | 5   | 3   | 4   |
| 52                   | 4                                                  | 5                      | 4                              | 6                                         | 4                    | 6                               | 4                            | 5   | 4   | 5   | 4   | 5   | 4   | 5   |
| 53                   |                                                    |                        | 8                              | 8                                         | 8                    | 8                               | 7                            | 8   | 6   | 8   | 6   | 8   | 6   | 7   |
| 54                   | 4                                                  | 5                      | 3                              | 4                                         | 5                    | 8                               | 5                            | 7   | 4   | 7   | 3   | 6   | 4   | 6   |

## Appendix II (Continued)

| Sub-<br>ject<br>No.: | Number of Threshold Concentration |                             |                        |                         |                        |     |     |     |     |     |
|----------------------|-----------------------------------|-----------------------------|------------------------|-------------------------|------------------------|-----|-----|-----|-----|-----|
|                      | Syrup<br>of<br>Althea             | Elixir<br>of<br>Glycyrrhiza | Com-<br>pound<br>Syrup | Aro-<br>matic<br>Elixir | Syrup<br>(Sim-<br>ple) | W.: | V.: | W.: | V.: | W.: |
| 1                    | 4                                 | 6                           | 4                      | 4                       | 4                      | 6   | 3   | 4   | 4   | 6   |
| 2                    | 4                                 | 4                           | 5                      | 5                       | 6                      | 6   | 4   | 5   | 6   | 6   |
| 4                    | 4                                 | 5                           | 4                      | 5                       | 4                      | 5   | 4   | 4   | 4   | 5   |
| 6                    | 3                                 | 6                           | 4                      | 6                       | 5                      | 6   | 3   | 5   | 3   | 4   |
| 8                    | 4                                 | 5                           | 5                      | 5                       | 5                      | 6   | 4   | 4   | 5   | 6   |
| 11                   | 4                                 | 6                           | 4                      | 4                       | 4                      | 5   | 3   | 5   | 4   | 7   |
| 13                   | 4                                 | 6                           | 5                      | 7                       | 4                      | 7   | 4   | 5   | 4   | 5   |
| 14                   | 6                                 | 7                           | 6                      | 8                       | 6                      | 8   | 6   | 8   | 8   | 8   |
| 18                   | 4                                 | 5                           | 3                      | 3                       | 3                      | 4   | 3   | 3   | 5   | 6   |
| 19                   | 1                                 | 3                           | 1                      | 2                       | 3                      | 4   | 2   | 3   | 3   | 4   |
| 20                   | 2                                 | 3                           | 3                      | 3                       | 4                      | 3   | 4   | 5   | 6   | 5   |
| 21                   | 2                                 | 3                           | 2                      | 3                       | 2                      | 3   | 2   | 3   | 2   | 4   |
| 22                   | 5                                 | 6                           | 4                      | 5                       | 4                      | 5   | 5   | 5   | 7   | 8   |
| 23                   | 4                                 | 4                           | 4                      | 5                       | 4                      | 5   | 4   | 5   | 5   | 6   |
| 24                   | 5                                 | 6                           | 3                      | 4                       | 4                      | 5   | 5   | 7   | 3   | 4   |
| 25                   | 4                                 | 5                           | 3                      | 3                       | 4                      | 5   | 3   | 4   | 3   | 3   |
| 28                   | 3                                 | 5                           | 3                      | 6                       | 3                      | 5   | 3   | 4   | 5   | 6   |
| 30                   | 4                                 | 5                           | 4                      | 6                       | 4                      | 5   | 4   | 5   | 4   | 5   |
| 32                   | 3                                 | 5                           | 3                      | 6                       | 3                      | 5   | 4   | 5   | 3   | 4   |
| 34                   | 4                                 | 6                           | 4                      | 6                       | 5                      | 6   | 5   | 6   | 4   | 6   |
| 35                   | 3                                 | 6                           | 3                      | 4                       | 3                      | 4   | 3   | 4   | 3   | 4   |
| 36                   | 4                                 | 5                           | 4                      | 5                       | 3                      | 4   | 4   | 5   | 5   | 6   |
| 38                   | 4                                 | 6                           | 4                      | 6                       | 4                      | 5   | 4   | 5   | 4   | 5   |
| 44                   | 3                                 | 3                           | 2                      | 4                       | 3                      | 3   | 2   | 4   | 1   | 5   |
| 47                   | 5                                 | 5                           | 3                      | 7                       | 4                      | 6   | 2   | 4   | 2   | 2   |
| 48                   | 5                                 | 6                           | 5                      | 6                       | 5                      | 6   | 6   | 7   | 3   | 5   |
| 49                   | 3                                 | 4                           | 4                      | 4                       | 4                      | 5   | 4   | 5   | 4   | 5   |
| 50                   | 3                                 | 4                           | 4                      | 5                       | 4                      | 5   | 4   | 4   | 5   | 6   |
| 51                   | 2                                 | 2                           | 2                      | 4                       | 3                      | 4   | 2   | 2   | 4   | 5   |
| 52                   | 4                                 | 6                           | 4                      | 5                       | 4                      | 5   | 4   | 5   | 4   | 5   |
| 53                   | 8                                 | 8                           | 7                      | 8                       | 7                      | 7   | 7   | 8   | 6   | 5   |
| 54                   | 4                                 | 7                           | 4                      | 7                       | 4                      | 6   | 4   | 6   | 4   | 4   |



## Appendix III. - Individual Bitter Thresholds for Quinine

Hydrochloride in Distilled Water and in Diluted Vehicles\*

| Sub-ject No.: | Number of Threshold Concentration |     |                       |     |                        |     |                                |     |                 |     |                        |     |                       |     |
|---------------|-----------------------------------|-----|-----------------------|-----|------------------------|-----|--------------------------------|-----|-----------------|-----|------------------------|-----|-----------------------|-----|
|               | Syrup of Prepared Cacao, N.F.VI:  |     | Syrup of Glycyrrhiza: |     | Syrup of Cocoa, N.F.V: |     | Aromatic Syrup of Eriodictyon: |     | Syrup of Thyme: |     | Elixir of Glycyrrhiza: |     | Syrup of Tolu Balsam: |     |
|               | W.:                               | V.: | W.:                   | V.: | W.:                    | V.: | W.:                            | V.: | W.:             | V.: | W.:                    | V.: | W.:                   | V.: |
| 1             | 2                                 | 9   | 2                     | 12  | 5                      | 10  | 2                              | 10  | 3               | 8   | 2                      | 5   | 5                     | 7   |
| 3             | 2                                 | 6   | 4                     | 6   | 4                      | 9   | 4                              | 10  | 3               | 4   | 3                      | 8   | 2                     | 5   |
| 5             | 2                                 | 4   | 3                     | 8   | 3                      | 7   | 4                              | 8   | 3               | 5   | 4                      | 7   | 4                     | 7   |
| 7             | 4                                 | 8   | 3                     | 8   | 4                      | 8   | 3                              | 7   | 2               | 7   | 3                      | 5   | 3                     | 5   |
| 9             | 6                                 | 10  | 5                     | 6   | 7                      | 11  | 5                              | 10  | 5               | 9   | 4                      | 6   | 5                     | 8   |
| 10            | 5                                 | 10  | 6                     | 13  | 5                      | 11  | 5                              | 12  | 5               | 9   | 5                      | 9   | 5                     | 8   |
| 12            | :                                 | :   | :                     | :   | :                      | :   | :                              | :   | :               | :   | :                      | :   | :                     | :   |
| 14            | 6                                 | 11  | 7                     | 11  | 5                      | 9   | 7                              | 11  | 6               | 10  | 7                      | 9   | 7                     | 10  |
| 15            | 2                                 | 6   | 1                     | 3   | 3                      | 5   | 3                              | 5   | 3               | 5   | :                      | :   | 1                     | 5   |
| 16            | 2                                 | 6   | 1                     | 1   | 2                      | 6   | 1                              | 1   | 2               | 6   | 1                      | 3   | 1                     | 5   |
| 17            | :                                 | :   | :                     | :   | :                      | :   | :                              | :   | :               | :   | :                      | :   | :                     | :   |
| 19            | 1                                 | 4   | :                     | :   | 1                      | 2   | 1                              | 4   | :               | :   | :                      | :   | 2                     | 5   |
| 20            | 3                                 | 8   | 3                     | 3   | 3                      | 5   | 3                              | 5   | :               | :   | 3                      | 4   | 1                     | 6   |
| 21            | 2                                 | 8   | 2                     | 6   | :                      | :   | 2                              | 5   | 2               | 7   | 2                      | 8   | 2                     | 6   |
| 22            | 6                                 | 10  | 4                     | 7   | 5                      | 11  | 5                              | 9   | 3               | 8   | 5                      | 10  | 4                     | 9   |
| 24            | 4                                 | 9   | :                     | :   | 4                      | 8   | 5                              | 8   | 4               | 6   | 4                      | 6   | :                     | :   |
| 26            | 4                                 | 10  | 4                     | 12  | :                      | :   | 5                              | 12  | 4               | 5   | 5                      | 10  | 4                     | 6   |
| 27            | :                                 | :   | 4                     | 13  | :                      | :   | :                              | :   | 3               | 9   | :                      | :   | 3                     | 7   |
| 28            | :                                 | :   | 5                     | 8   | 3                      | 9   | 4                              | 8   | 4               | 8   | 4                      | 6   | 3                     | 6   |
| 29            | 7                                 | 12  | 3                     | 7   | 6                      | 10  | :                              | :   | :               | :   | 4                      | 10  | :                     | :   |
| 30            | 5                                 | 8   | 5                     | 8   | 5                      | 9   | 5                              | 10  | 5               | 8   | 5                      | 8   | :                     | :   |
| 31            | 2                                 | 3   | 1                     | 3   | 4                      | 6   | 2                              | 7   | 4               | 6   | 2                      | 3   | 3                     | 4   |
| 33            | 4                                 | 8   | 4                     | 9   | 5                      | 8   | 4                              | 4   | 3               | 7   | 5                      | 8   | 4                     | 6   |
| 37            | 2                                 | 9   | 3                     | 9   | 3                      | 7   | 6                              | 10  | 3               | 6   | 3                      | 8   | 3                     | 7   |
| 38            | :                                 | :   | 4                     | 7   | :                      | :   | 4                              | 7   | 4               | 7   | 4                      | 6   | 5                     | 8   |
| 39            | :                                 | :   | :                     | :   | 3                      | 5   | 4                              | 4   | :               | :   | 4                      | 3   | 2                     | 2   |
| 40            | 2                                 | 8   | 2                     | 9   | 2                      | 9   | 2                              | 8   | 2               | 8   | :                      | :   | :                     | :   |
| 41            | 5                                 | 10  | 5                     | 12  | 4                      | 10  | 5                              | 12  | 5               | 9   | 5                      | 10  | 5                     | 8   |
| 42            | 6                                 | 11  | 6                     | 12  | 6                      | 10  | 7                              | 9   | 6               | 8   | 6                      | 8   | 6                     | 8   |
| 43            | 5                                 | 10  | 4                     | 8   | :                      | :   | 5                              | 10  | 5               | 9   | 5                      | 10  | 5                     | 8   |
| 44            | 2                                 | 8   | 3                     | 11  | 3                      | 8   | 3                              | 4   | :               | :   | 3                      | 8   | 3                     | 6   |
| 45            | 3                                 | 10  | 3                     | 4   | 3                      | 7   | 2                              | 5   | 3               | 8   | 2                      | 6   | 4                     | 9   |
| 46            | :                                 | :   | 5                     | 10  | 6                      | 11  | :                              | :   | 6               | 9   | :                      | :   | :                     | :   |
| 48            | 1                                 | 6   | 1                     | 10  | 2                      | 8   | 4                              | 6   | 2               | 7   | 2                      | 7   | 3                     | 6   |
| 51            | 3                                 | 6   | 3                     | 5   | 4                      | 11  | 4                              | 8   | 3               | 8   | 4                      | 7   | 3                     | 7   |
| 52            | 3                                 | 9   | 3                     | 9   | 3                      | 9   | 4                              | 11  | 3               | 8   | 3                      | 8   | 4                     | 6   |
| 53            | 4                                 | 8   | 2                     | 2   | 3                      | 9   | 3                              | 9   | 4               | 8   | 3                      | 2   | 2                     | 5   |

\*Each vehicle solution contained 10 per cent by volume of the respective vehicle; the remainder of the solvent was distilled water.

\*\*"W." and "V." respectively stand for "distilled water solution" and "vehicle solution".

## Appendix III (Continued)

| Sub-<br>ject<br>No.: | Number of Threshold Concentration                  |                                |                        |                               |                                |                        |                               |     |     |     |     |     |     |     |
|----------------------|----------------------------------------------------|--------------------------------|------------------------|-------------------------------|--------------------------------|------------------------|-------------------------------|-----|-----|-----|-----|-----|-----|-----|
|                      | Com-<br>pound<br>Syrup<br>of<br>Sarsa-<br>parilla: | Syrup<br>of<br>Rasp-<br>berry: | Syrup<br>of<br>Cherry: | Syrup<br>of<br>Cin-<br>namon: | Syrup<br>of<br>Citric<br>Acid: | Syrup<br>of<br>Althea: | Syrup<br>of<br>Wild<br>Cherry | W.: | V.: | W.: | V.: | W.: | V.: | W.: |
| 1                    | 4                                                  | 7                              | 4                      | 6                             | 3                              | 7                      | 4                             | 6   | 3   | 5   | 4   | 6   |     |     |
| 3                    |                                                    |                                | 4                      | 6                             | 3                              | 5                      | 3                             | 4   | 3   | 5   | 2   | 4   | 4   | 5   |
| 5                    | 4                                                  | 6                              | 4                      | 6                             | 2                              | 4                      | 3                             | 5   | 4   | 7   | 3   | 4   | 3   | 5   |
| 7                    | 3                                                  | 4                              | 4                      | 5                             | 4                              | 5                      | 3                             | 4   | 2   | 3   | 3   | 4   | 3   | 6   |
| 9                    | 4                                                  | 8                              | 6                      | 10                            | 5                              | 10                     | 5                             | 6   | 5   | 9   |     |     | 4   | 6   |
| 10                   | 5                                                  | 9                              | 5                      | 7                             | 3                              | 7                      | 5                             | 8   | 6   | 8   | 5   | 7   |     |     |
| 12                   |                                                    |                                |                        |                               |                                |                        |                               |     |     |     |     |     |     |     |
| 14                   | 5                                                  | 9                              | 4                      | 6                             | 6                              | 8                      | 5                             | 9   | 6   | 9   | 6   | 11  | 6   | 10  |
| 15                   |                                                    |                                | 2                      | 4                             |                                |                        | 3                             | 4   | 3   | 3   | 4   | 5   | 3   | 5   |
| 16                   | 1                                                  | 1                              | 2                      | 4                             | 1                              | 3                      | 1                             | 2   |     |     | 1   | 3   | 3   | 2   |
| 17                   |                                                    |                                |                        |                               |                                |                        |                               |     |     |     |     |     |     |     |
| 19                   | 1                                                  | 4                              | 2                      | 3                             | 1                              | 2                      | 2                             | 3   |     |     | 1   | 3   | 1   | 2   |
| 20                   | 1                                                  | 2                              | 3                      | 5                             | 2                              | 4                      | 2                             | 4   | 2   | 5   | 1   | 3   | 2   | 2   |
| 21                   | 1                                                  | 4                              | 3                      | 5                             | 2                              | 5                      | 2                             | 5   | 2   | 6   | 1   | 4   | 2   | 5   |
| 22                   | 2                                                  | 7                              | 5                      | 7                             | 3                              | 7                      | 4                             | 7   | 4   | 7   | 4   | 7   | 5   | 10  |
| 24                   | 5                                                  | 7                              | 5                      | 6                             | 5                              | 7                      | 4                             | 6   | 4   | 5   | 4   | 5   | 4   | 5   |
| 26                   | 4                                                  | 7                              | 4                      | 8                             | 2                              | 8                      | 4                             | 7   | 3   | 8   | 3   | 6   | 5   | 8   |
| 27                   | 4                                                  | 7                              | 2                      | 6                             | 3                              | 6                      | 4                             | 7   | 3   | 6   | 4   | 6   | 3   | 3   |
| 28                   | 4                                                  | 8                              | 5                      | 9                             | 6                              | 8                      | 4                             | 7   | 6   | 8   | 5   | 7   | 4   | 6   |
| 29                   |                                                    |                                | 2                      | 7                             |                                |                        | 2                             | 9   |     |     |     |     | 2   | 6   |
| 30                   | 4                                                  | 7                              | 5                      | 6                             | 5                              | 7                      | 4                             | 6   | 5   | 5   | 4   | 6   | 5   | 8   |
| 31                   | 2                                                  | 3                              | 3                      | 3                             | 4                              | 4                      | 4                             | 4   |     |     |     |     | 3   | 5   |
| 33                   | 6                                                  | 8                              | 5                      | 7                             | 4                              | 6                      | 4                             | 6   | 4   | 7   | 5   | 7   | 4   | 5   |
| 37                   | 2                                                  | 8                              | 4                      | 10                            | 1                              | 5                      | 4                             | 8   | 4   | 8   | 2   | 7   | 4   | 6   |
| 38                   | 4                                                  | 7                              | 5                      | 7                             | 4                              | 7                      | 4                             | 6   | 4   | 5   | 4   | 6   | 4   | 7   |
| 39                   |                                                    |                                |                        |                               | 5                              | 5                      |                               |     |     |     | 4   | 4   |     |     |
| 40                   | 3                                                  | 7                              | 1                      | 4                             | 3                              | 6                      |                               |     | 3   | 6   | 1   | 4   | 2   | 8   |
| 41                   | 5                                                  | 9                              | 5                      | 8                             | 6                              | 9                      | 5                             | 7   | 5   | 8   | 6   | 8   | 5   | 10  |
| 42                   | 6                                                  | 9                              | 5                      | 9                             | 6                              | 10                     | 6                             | 9   | 7   | 7   | 5   | 7   |     |     |
| 43                   | 5                                                  | 7                              | 4                      | 7                             | 5                              | 8                      | 4                             | 7   | 4   | 8   | 5   | 7   | 5   | 8   |
| 44                   | 3                                                  | 6                              | 3                      | 4                             | 3                              | 3                      |                               |     | 3   | 4   |     |     |     |     |
| 45                   |                                                    |                                | 1                      | 7                             | 1                              | 4                      |                               |     | 2   | 6   | 4   | 6   | 4   | 6   |
| 46                   | 6                                                  | 9                              |                        |                               | 7                              | 12                     | 6                             | 9   | 5   | 9   | 6   | 10  | 5   | 7   |
| 48                   | 3                                                  | 6                              | 1                      | 5                             | 2                              | 5                      | 3                             | 5   | 2   | 4   | 3   | 5   | 2   | 7   |
| 51                   | 4                                                  | 8                              | 5                      | 6                             | 5                              | 6                      | 5                             | 8   | 4   | 6   | 3   | 6   | 4   | 3   |
| 52                   | 3                                                  | 6                              | 3                      | 6                             | 4                              | 6                      | 4                             | 6   | 4   | 6   | 3   | 5   | 3   | 4   |
| 53                   | 2                                                  | 6                              | 3                      | 3                             | 3                              | 2                      | 3                             | 6   | 2   | 1   | 4   | 6   | 5   | 4   |

## Appendix III (Continued)

| Sub-<br>ject<br>No.: | Number of Threshold Concentration |     |                       |     |                            |     |                                  |     |                        |     |                       |     |                         |     |
|----------------------|-----------------------------------|-----|-----------------------|-----|----------------------------|-----|----------------------------------|-----|------------------------|-----|-----------------------|-----|-------------------------|-----|
|                      | Syrup<br>(Sim-<br>ple)            |     | Syrup<br>of<br>Acacia |     | Syrup<br>of Wild<br>Cherry |     | Syrup<br>of<br>Orange<br>Flowers |     | Syrup<br>(Sim-<br>ple) |     | Syrup<br>of<br>Orange |     | Aro-<br>matic<br>Elixir |     |
|                      | W.:                               | V.: | W.:                   | V.: | W.:                        | V.: | W.:                              | V.: | W.:                    | V.: | W.:                   | V.: | W.:                     | V.: |
| 1                    | 3                                 | 5   | 4                     | 6   | 4                          | 8   | 3                                | 5   | 5                      | 7   | 3                     | 5   | 4                       | 6   |
| 3                    |                                   |     | 3                     | 4   | 3                          | 5   |                                  |     |                        |     | 3                     | 4   | 2                       | 1   |
| 5                    | 4                                 | 6   | 2                     | 4   | 2                          | 4   | 4                                | 6   | 5                      | 6   | 3                     | 5   | 4                       | 6   |
| 7                    | 2                                 | 7   | 3                     | 4   | 1                          | 4   | 3                                | 4   | 3                      | 4   | 1                     | 2   | 1                       | 2   |
| 9                    |                                   |     | 6                     | 8   | 7                          | 10  | 4                                | 6   | 6                      | 9   |                       |     | 5                       | 7   |
| 10                   |                                   |     | 5                     | 7   | 5                          | 8   | 5                                | 7   |                        |     | 6                     | 9   | 5                       | 6   |
| 12                   |                                   |     |                       |     | 3                          | 4   |                                  |     | 5                      | 7   |                       |     |                         |     |
| 14                   | 6                                 | 8   | 6                     | 7   | 5                          | 7   | 6                                | 8   | 7                      | 8   | 4                     | 8   | 4                       | 6   |
| 15                   | 2                                 | 4   | 2                     | 5   | 3                          | 4   | 3                                | 5   | 3                      | 3   | 2                     | 2   | 4                       | 4   |
| 16                   | 2                                 | 2   | 2                     | 2   | 1                          | 1   | 1                                | 1   | 2                      | 3   | 1                     | 1   | 1                       | 1   |
| 17                   |                                   |     |                       |     | 2                          | 1   |                                  |     | 3                      | 5   |                       |     |                         |     |
| 19                   | 1                                 | 2   | 1                     | 2   | 1                          | 2   | 2                                | 3   | 1                      | 1   |                       |     | 1                       | 2   |
| 20                   | 1                                 | 3   | 3                     | 5   | 4                          | 4   | 2                                | 4   | 3                      | 5   | 4                     | 5   | 4                       | 5   |
| 21                   | 2                                 | 5   | 2                     | 4   | 2                          | 4   | 1                                | 4   | 3                      | 5   | 3                     | 4   | 2                       | 3   |
| 22                   | 4                                 | 7   | 3                     | 8   | 3                          | 7   | 4                                | 7   | 4                      | 7   | 5                     | 7   | 5                       | 7   |
| 24                   | 4                                 | 6   | 5                     | 7   | 3                          | 4   | 5                                | 6   | 4                      | 5   | 5                     | 6   | 4                       | 5   |
| 26                   | 3                                 | 6   | 3                     | 5   | 3                          | 5   | 3                                | 6   | 6                      | 8   | 2                     | 4   | 3                       | 7   |
| 27                   | 5                                 | 6   | 3                     | 7   | 4                          | 7   | 3                                | 5   | 4                      | 6   | 4                     | 6   | 3                       | 5   |
| 28                   | 3                                 | 5   | 5                     | 7   | 3                          | 9   | 6                                | 8   | 2                      | 4   |                       |     | 2                       | 5   |
| 29                   | 2                                 | 7   |                       |     | 5                          | 6   | 2                                | 6   | 6                      | 10  |                       |     |                         |     |
| 30                   | 5                                 | 7   | 5                     | 6   | 5                          | 8   | 4                                | 7   |                        |     | 4                     | 4   | 6                       | 7   |
| 31                   | 3                                 | 4   | 2                     | 2   | 4                          | 4   | 4                                | 4   | 5                      | 7   | 2                     | 2   | 3                       | 4   |
| 33                   | 5                                 | 7   | 5                     | 7   | 3                          | 5   | 4                                | 8   | 4                      | 11  | 5                     | 7   | 5                       | 7   |
| 37                   | 3                                 | 6   | 3                     | 7   | 4                          | 6   | 3                                | 6   | 3                      | 4   | 2                     | 7   | 1                       | 5   |
| 38                   | 4                                 | 6   | 4                     | 6   | 4                          | 7   | 4                                | 6   | 3                      | 5   | 5                     | 5   | 4                       | 6   |
| 39                   | 3                                 | 4   | 4                     | 4   | 3                          | 3   | 1                                | 2   | 3                      | 6   | 2                     | 3   | 3                       | 5   |
| 40                   | 2                                 | 3   | 1                     | 5   | 2                          | 6   | 2                                | 4   | 2                      | 3   | 3                     | 5   | 3                       | 5   |
| 41                   | 6                                 | 8   | 5                     | 8   | 5                          | 10  | 6                                | 7   | 6                      | 8   | 5                     | 8   | 4                       | 7   |
| 42                   | 6                                 | 8   | 5                     | 7   | 4                          | 4   | 6                                | 8   | 6                      | 8   | 5                     | 6   | 6                       | 7   |
| 43                   | 5                                 | 7   | 5                     | 7   |                            |     | 5                                | 7   |                        |     | 5                     | 8   | 4                       | 6   |
| 44                   |                                   |     | 4                     | 6   | 3                          | 4   |                                  |     | 3                      | 4   | 3                     | 4   | 3                       | 3   |
| 45                   | 3                                 | 5   | 3                     | 7   | 2                          | 4   |                                  |     | 4                      | 6   | 2                     | 7   | 3                       | 3   |
| 46                   | 5                                 | 8   |                       |     | 8                          | 11  |                                  |     |                        |     | 6                     | 9   |                         |     |
| 48                   | 3                                 | 5   | 3                     | 6   | 2                          | 8   | 2                                | 5   | 4                      | 7   | 1                     | 4   | 2                       | 5   |
| 51                   | 4                                 | 7   | 3                     | 7   | 4                          | 6   | 3                                | 6   | 5                      | 6   | 5                     | 7   | 5                       | 7   |
| 52                   | 3                                 | 5   | 4                     | 6   | 4                          | 5   | 3                                | 5   |                        |     | 4                     | 6   |                         |     |
| 53                   | 4                                 | 6   | 4                     | 5   | 3                          | 2   | 3                                | 4   | 3                      | 4   | 2                     | 1   | 2                       | 4   |