

HYPOCHLORITE SOLUTIONS.

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(NO. 2.) LABARRAQUE'S ORIGINAL FORMULA AND MODIFICATIONS OF THIS.

Of the many hypochlorites known to the chemical world, the one of chief interest to the pharmacist is sodium hypochlorite, because it has become of greatest importance in pharmacy and medicine. Interest in this hypochlorite has, since the date of its discovery, gradually increased until it reached its height during the past war, as this substance was found to be an antiseptic of great value. Its introduction in the form of the "new antiseptic" served as a stimulus for more extended research on the chemistry and therapeutics of aqueous hypochlorite solutions and to the introduction of new types of chlorine antiseptics. This fact is emphasized in a recent editorial in the *American Journal of Pharmacy*, as follows:

"When Dakin and Carrel consummated the great discovery that gave surgery and the world the now famous 'Dakin's Solution' they little knew that their invention was to inaugurate a germicidal fad that has since formed a profusion of chlorine containing compounds into an already bulging materia medica."

Although much time and energy have been allotted to *Labarraque's Disinfecting Fluid* and to *Dakin's New Antiseptic Solution* the two are similar in composition, differing only in the alkalinity of the finished product and chlorine content, for Dakin's Solution is merely an outgrowth of *Labarraque's Original Bleaching Fluid*. Labarraque's formula as presented to the Academy of Sciences was as follows:

Chlorure d'oxide de sodium.	
Carbonate de soude pur	2 kil. $\frac{1}{2}$
Eau distillee	10 kil.

Melez, et assurez-vous si la liqueur porte douze degrés au pesesel de Baume. Si la liqueur est trop concentrée, ce qui proviendrait du sel qui seroit effleuri, ajoutez-y la quantité d'eau nécessaire pour la porter au degré indiqué. Si au contraire la solution est trop faible, on ajoute du carbonate de soude en quantité suffisante.

Si le carbonate de soude reenoit constamment la même quantité d'eau, on n'aurait besoin que d'en fixer les doses précises; mais ce sel est loin d'être toujours indentique.

La liqueur est mise dans un flacon d'une contenance assez grande pour qu'il reste le quart environ de vide.

On dispose sue en bain de sable un ballon en verre de quatre pintes, á col allongé et a large ouverture, dens lequel on introduit le mélange suivant:

Hydrochlorate de soude	576 gram
Peroxide de manganèse pulverisé	448 gram

(La quantité de peroxide de manganèse serait trop considérable si ce-te substance se trou-vait toujours de première qualité dans le commerce. Dans aucun cas, son excès ne me semble pouvoir être.)

On lute à l'embouchure du ballon un large tube recourbé et un tube en S pour l'introduction de l'acide affaibli. Le premier tube plonge dans un flacon contenant une petite quantité d'eau, et de ce flacon part un large tube recourbé qui plonge dans le flacon contenant la solution saline.

L'appareil convenablement disposé, et les lute bien secs, on verse dans le tube en S l'acide affaible froid, et mélange depuis quelques heures avec l'eau, dans les proportions suivantes:

Acide sulfuriqui concentré	576 gram
Eau	448 gram

On applique le beu sous le bain de sable, et on le dirige d'une manière graduelle, jusqu'a ce que le dégagement du chlore cesse.

L'operation terminee, on délute l'appareil, et on examine la force decolorante du produit. On prend pour cela une partie du chlorure qu'on introduit dans le berthollimetre, et on verse dessus de la solution de sulfate de indigo preparee comme il suit:

Indigo du Bengal purvérisé	1 partie
Acide sulfurique concentre	6 partie

Faite agir á chaud, et étendez ensuit dans neuf cent quatre-vingt-treize parties d'eau distillis.

Le chlorure doit decolorer dix-huit parties de sulfate d'indigo. Il est essential de faire deux ou trois épreuves de decoloration. Aprés la premiere, qu'on fait en tâtonnant, on doit faire la seconde brusquement, en ajoutant, en une seule fois, toute la quantité de solution de sulfate d'indigo que la précédente épreuve aviait exigée, pour arriver à obtenir un vert fonce. En agissant avec promptitude, la decoloration est plus prononcée (ainsi que l'ont observé MM. Gay-Lussac et Velter); ce qui oblige à afirc une troisième épreuve, après avoir ajouté quelques parries de sulfate d'indigo a la seconde, pour arriver à la couleur verte, et en tenant compte de cette addition dans la dernière experience, qui est la plus concluante.

Si la solution de carbonate de soude n'est pas assez saturée de chlore on doit y faire passer un courant de ce gaz, pour la ramener au point fixe.

Je suis entré ici dans des détails superflus, sans doute, pour des pharmaciens instruits; mais, quoique minutieux pour des chimistes execés, ces details m'ont paru indispensables dans la confection d'un medicament qui, jusqu'a ces derniers temps, m'avait pas été employé en medicine. MM. les pharmaciens voudront bien suivre à la lettre le procede qui vient d'être indiqué, afin d'obtenir toujours un produit indentique, et per cela même d'heureux resultats; car ils n'ignorent pas que, dans la préparation de certains medicamens, le mode opératoire en modifie les caractères extérieurs, et même les vertus.

In 1830 Durand offered the following English version of the formula for *Labarraque's Liquid*, published in the *American Journal of Pharmacy*:

Subcarbonate of soda (cryst.)	640 parts
Distilled water	2500 parts

If the solution is not saturated, add enough sodium carbonate to saturate it, but if the solution is supersaturated, dilute as required.

For chlorine gas:

Sodium chloride	147 parts
Manganese peroxide	112 parts

Acid mixture:

Sulphuric acid	147 parts
Water	112 parts

The nature of *Labarraque's Disinfecting Fluid* was carefully investigated by Faraday. He found that "chloride of soda" was the active principle of the compound and that its properties were considerably modified by the presence of carbonate of soda. Without changing the mode of operation prescribed by Labarraque he altered the proportion of ingredients in such manner so as to utilize all of the carbonate present, thereby obtaining a larger quantity of chlorine in the finished product. The formula is as follows:

Subcarbonate of soda	2800 grs.
Water	1.28 pts.
Sea salt	967 grs.
Manganese peroxide	750 grs.
Sulphuric acid	950 grs.
Water	50 grs.

Becoming interested in the action of chlorine on the subcarbonate solution, he saturated the latter with chlorine until carbon dioxide was given off. The

liquid obtained differed entirely in properties as compared with those of *Labarraque's Fluid*, as it "gave on standing chlorate of soda and common salt" while the latter contained "chlorine and pure soda."

At the same time that Faraday was working on his formula Payen prepared the sodium hypochlorite by double decomposition, using the following:

Chloride of lime	1 part
Water	12 parts
Carbonate of soda (cryst.)	2 parts
Water	4 parts

Cohen, in 1833, criticized this formula, saying: "It is impossible that Payen's process can produce *Labarraque's Liquid*, inasmuch as by the double decomposition ensuing, a portion of the carbonic acid is withdrawn from the soda in combination with the lime, and it is impossible to make a solution in this way, without containing a pretty large proportion of muriate and chlorate, independent of the fact that the solution can never be as concentrated as *Labarraque's Solution*." In spite of the adverse criticism, the revision committee for the 1840 U. S. Pharmacopœia introduced *Labarraque's Solution*, adopting the process of Payen, with the slight modification in parts of water used from sixteen to twelve.

For the next sixty years the development of the formula may be traced in the U. S. Pharmacopœia. The 1850 revision retained the formula unchanged. The 1860 and 1870 revision designated the quantities used in terms of ounces and pints in place of pounds and gallons, leaving the ratio unchanged, but, in 1880, there was a complete revision in the ratio of ingredients, *viz.*:

Chlorinated lime	100
Carbonate of soda	80
Water	1000

Up to this time the ratio of chlorinated lime to carbonate of soda was as one is to two. *Labarraque's Solution* was, from the first, known as strongly alkaline fluid. Faraday had attempted to completely neutralize the carbonate by increasing the amount of chlorine gas in the preparation of the solution. In the 1880 revision, a similar attempt was made by decreasing the amount of sodium carbonate and increasing the amount of chlorinated lime. This revision also increased the volume of the finished product and introduced a purity rubric, *viz.*: "there must be at least two per cent. available chlorine."

The 1890 revision again changed the formula. It returned to the use of the same proportions given by Payen, *viz.*:

Chlorinated lime (35% Cl)	75 Gm.
Carbonate of soda	150 Gm.
Water	1000 Gm.

This formula calls for twice as much sodium carbonate as chlorinated lime and also increases the requirement for available chlorine in chlorinated lime and in the finished product. This solution proved very unsatisfactory as it was almost impossible to obtain a chlorinated lime of the required strength, on the market, the strength varying considerably: For example, Arny and Dawson found a range of eleven to thirty-one per cent. of available chlorine in a series of samples they

analyzed. Solutions which they prepared from these contained on the average 1.8% available chlorine.

Hence the formula was again changed by the 1900 revision to:

Chlorinated lime (30% Cl)	90 Gm.
Sodium carbonate (monohyd.)	65 Gm.
Water	1000 Gm.
Purity rubric—avail. chlorine	2.4%

For the first time the quantities prescribed represent the approximate molecular equivalents necessary to form sodium hypochlorite. Originally the only guide controlling the amounts of ingredients used, was the reaction of the finished solution. Thus Labarraque specified, "pass chlorine into the carbonate solution until one part of the chloride will discolor eighteen parts of sulphate of indigo." In the earlier revisions of the U. S. P. the solution was supposed to "rapidly discolorize a solution of indigo." The 1880 revision introduced a purity rubric for the finished product, and the 1900 revision attempted to insure this purity rubric by properly proportioning the reacting ingredients. Theoretically this was an improvement, practically it failed to bring about the desired result. This was mainly due to the fact that little if any chlorinated lime was on the market having the required thirty per cent. available chlorine. The 1900 revision slightly increased the amount of sodium carbonate used, leaving the purity rubric for the chlorinated lime and finished solutions unchanged. No change was introduced by the 1910 revision. The formula was as follows:

Chlorinated lime (30% Cl)	100 Gm.
Sodium carbonate (monohyd.)	70 Gm.
Water	1000 Gm.
Available chlorine	2.5%

In an attempt to prepare a solution having the required chlorine content, Army and Dawson increased the chlorinated lime, as compared with the U. S. P. amount, and collected only 900 cc. of filtrate. This gave a product of required strength.

Because of a demand made for a *Labarraque's Bleaching Fluid* containing five per cent. available chlorine, Elvove, in 1910, revived Graebe's process, which in turn was a modification of Labarraque's original method. Graebe, according to Elvove, found that upon using one part of chlorine to two parts of sodium hydroxide he obtained a product which deteriorated almost entirely in three days, but upon using two and one-half parts of sodium hydroxide the fluid obtained assayed 5.03% chlorine after standing six days; and that if three parts of sodium hydroxide were used the product assayed 5.37% at the end of twenty-three days.

The problem so far had been to obtain a standard solution with a limit in the amount of deterioration and, if possible, a method of preparation which could be used for both strong and weak solutions.

At the beginning of the world war a new field was opened. Before this the problem of sodium hypochlorite in antiseptiology had been given little consideration. *Labarraque's Solution* was objectionable for this purpose because of its strong alkalinity, which caused irritation when applied to wounds. Dilution was unsuccessful since this decreased the germicidal property in much greater proportion relatively than it did the alkalinity.

From the beginning of the war there was an increasing demand for an antiseptic easily prepared, easily applied, harmless, and producing successful sepsis in wounds. Thus the search for the perfect germicide inaugurated by Lister and Pasteur was revitalized. In 1915 Dakin of the Herter Laboratories, N. Y., then working in the Rockefeller Institute at Compeigne, produced the first formula containing materials to neutralize the excess alkali in *Labarraque's Solution*, viz.:

Sodium carbonate	140 Gm.
Water	10 liters
Chlorinated lime	200 Gm.
Boric acid	20-40 Gm. added

until a drop of the solution would not color powdered phenolphthalein when added to it.

Dr. Carrel used this "new antiseptic" in his clinical work. It did not prove as successful as hoped, for it was instable and variable as to chlorine content. This was probably due to the variability of the chlorinated lime which Dakin had neglected to assay before using. Moreover, the boric acid which was to have aided in the antiseptic action as well as to have neutralized the alkali proved almost as irritating as the caustic soda.

Consequently a modification of this formula was offered by Daufresne who was working under Carrel, viz.:

Chloride of lime (25% Cl)	184 Gm.
Sodium carbonate	92 Gm.
Sodium bicarbonate	76 Gm.
Water sufficient to give a solution which assays 0.5% available chlorine.	

This was simply a modified form of *Labarraque's* original formula in which "subcarbonate of soda and carbonate of soda" were used until a "saturated solution" was obtained. Furthermore in 1865 an article in the *Chemical News*, called attention to the use of sodium bicarbonate in place of the carbonate. Daufresne's modification was at once accepted and soon replaced the original Carrel-Dakin Solution. Very careful instructions as to requirement of finished solution and mode of preparation were formulated. It must assay from 0.45% to 0.5% available sodium hypochlorite and must not color powdered phenolphthalein. This solution was found to be quite stable lasting a week with very little loss and even six months without dropping below the 0.45% requirement. As soon as the "new" formula for this antiseptic was published, many articles appeared describing the solution, the technique of its preparation, and the many precautions to be observed.

This new idea having once been grasped by the pharmaceutical world, it took little time to produce results. The entire field of hypochlorites was invaded. Every acid radicle which would form an insoluble calcium salt was tried, as well as modifications of the boric acid and bicarbonate formulas of Dakin and Carrel.

The sulphate was one of the first to be introduced. In 1919 Ebert offered a formula substituting sodium sulphate for sodium carbonate, as follows:

Chlorinated lime	20 parts
Water	100 parts
Sodium sulphate	28 parts
Water	500 parts

The same year Cowley introduced a method for determining the per cent. soluble calcium salts present in a calcium hypochlorite solution, obtained by macerating chlorinated lime water in water. Based upon this, just enough sodium carbonate was added to exactly precipitate these salts. The procedure was as follows:

Take,	
Chlorinated lime	50 Gm.
Water	500 mils
Filter and make up to	500 mils

Boil 20 mils of this solution with 10 mils dilute hydrochloric acid to expel chlorine, add normal sodium carbonate to neutralization, using methyl orange as indicator. Boil to expel carbon dioxide and again titrate, using phenolphthalein as indicator. From the number of mils used in the last titration the soluble calcium salts present in the 20 mils can be computed.

This method seems quite desirable but has been little used.

In 1920 two modifications of Daufresne's formula were published. One by an unsigned writer as follows:

Chlorinated lime	200 Gm.
Sodium carbonate	10 Gm.
Sodium bicarbonate	50 Gm.
Distilled water	10 liters

According to the writer, this produces a 0.5% solution of sodium hypochlorite. No statement was made concerning the alkalinity.

Éwe offered the other, an elaborate formula, in which calcium chloride is used to neutralize the excess sodium carbonate and slaked lime is added for the excess alkali necessary to stabilize the solution. The whole is then filtered. He states that a solution containing 4 or 5 per cent. available chlorine could be obtained by this method. The formula is as follows:

Chlorinated lime (32.5% Cl)	100 Gm.
Water	127 mils
Sodium carbonate (anhyd.)	40 Gm.
Sodium bicarbonate	41 Gm.
Water	379 mils
Calcium chloride	10 Gm.
Dry slaked lime	5 Gm.
To make	240 mils

Thomas, in 1922, revived the old method of passing chlorine into aqueous solutions of alkalis. He used a decinormal solution of sodium hydroxide, and obtained a product containing 1.5% available chlorine with alkalinity about the same as that of the U. S. P. solution of chlorinated soda.

In 1923 Kelly and Krantz suggested the use of sodium phosphate:

Chlorinated lime	20 Gm.
Sodium phosphate	20 Gm.
Water	1000 mils
Produces a 0.5% available chlorine solution.	

According to the authors the alkalinity of this solution was within the limits required by Dakin's specifications, but only a weak hypochlorite concentration could be obtained. A 0.5 per cent. solution, obtained by this process, was found to be as stable as other weak hypochlorite preparations.

Hypochlorite solutions used for disinfecting water supplies, bathing tanks, streets, and in laundries to destroy microorganisms and to remove stains, are made on a large scale by the electrolytic process. A 4 per cent. solution of sodium chloride in water when treated with 10 amperes direct current at 220 volts, can produce twelve gallons of sodium hypochlorite solution of 2 per cent. strength in one hour. (For references see list following No. 3.)

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(To be continued.)

THE UNITED STATES PHARMACOPŒIA FROM THE STANDPOINT OF THE ANALYST.*

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Before the Food and Drugs Act was passed, in 1906, the Pharmacopœia did not so seriously engage the attention of drug analysts as it has since. Previous to that time it is true that those who were engaged in the production of substances described in the Pharmacopœia were in honor bound to insure that such products conformed in purity to the standards prescribed by the U. S. P., but the analyst was not held to the U. S. P. methods of analysis so long as he was confident that the methods of his own selection were as accurate as those of the Pharmacopœia. However, with the coming of the Food and Drugs Act, added responsibilities were placed on the Pharmacopœia. The regulations for the enforcement of the Food and Drugs Act prescribe that the methods of analysis given in the Pharmacopœia or the National Formulary shall be used in the analysis of all drugs for which the United States Pharmacopœia or the National Formulary describes methods. In this the federal officials have no choice unless it can be shown to the satisfaction of the trial courts that a particular method described in the U. S. P. or N. F. is faulty. Many states and municipalities also have adopted the Pharmacopœia as a standard in the enforcement of their drug laws.

For more than 20 years I have been engaged in the analysis of medicines and in preparing standards for them. During this time I have made use of the seventh, eighth and ninth revisions of the Pharmacopœia. In the earlier editions there were fewer substances (other than the vegetable drugs) for which assays were prescribed than obtain to-day. As the work became of greater and greater importance from a legal standpoint, the number of substances standardized by assay has markedly increased until in the issue now official there are no less than 277 substances for which a quantitative assay is provided. In a few cases an assay is provided for more than one constituent in a preparation. Examples are: Compound solution of iodine which assays the free iodine and the potassium iodide; the same is true for tincture of iodine compound; also for oil of bitter almond which determines the hydrocyanic acid and the benzaldehyde. In the enumeration mentioned the double assay is counted only as one. In addition to the quantitative assay for the chief constituent of many substances, the Pharmacopœia requires the determina-

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