THE ARSENICAL SOLUTIONS.

No. 3.* *Liquor Arseni et Hydrargyri Iodide (Donovan's Solution).*

BY H. A. LANGENHAN.**

History and Original Formula.—The *Solution of Iodohydrargyrate of Arsenic* was first introduced into medical practice by Dr. Donovan of Dublin, in 1839. According to Donovan, the solution was the result of his attempt to administer, in combination, the three common remedies, *viz.*, arsenic, mercury and iodine, that were being used as specifics against "psoriasis, lepra and lupus." Based on the work of Bonsdorff[1] on *iodohydrargyrates* he experimented with mercury di-iodide and arsenic tri-iodide. He found that these two substances would go into solution in water, *i. e.*, the insoluble mercury salt would go into solution in the presence of the soluble arsenic salt, and that the color of the solution of the two salts was different from the color of the solution of arsenic tri-iodide alone. Likewise the red color of the mercury di-iodide disappeared. After examining this solution (see Report in appendix) he concluded that a chemical change took place when the two substances were dissolved in water, resulting in the formation of a new compound, which he designated as an *iodohydrargyrate of arsenic.* Not being satisfied with the purity of the arsenic tri-iodide and the mercury di-iodide found on the market, Donovan resorted to the use of the three elements, iodine, arsenic, and mercury for preparing this compound in solution.

Apparently the method of preparation as suggested by Donovan presented some difficulties and, as a result, Soubeiran[2] in 1841, proposed a modified formula in which he substituted the two iodides in place of the elements.

The Dublin Pharmacopœia of 1851 was the first to adopt this solution to which it applied the title *Arsenici et Hydrargyri Hydriodatis Liquor.* The formula as offered by Donovan was used. The first edition of the British Pharmacopœia (1864) did not contain this liquor but the revision of 1885 adopted it under the title *Liquor Arsenii et Hydrargyri Iodidi* and at the same time adopted the modified formula of Soubeiran. Each following revision of the British Pharmacopœia retained this liquor. Of the revisions of the U. S. Pharmacopœia that of 1850 was the first to contain this liquor, to which it applied the title *Liquor Arsenici et Hydrargyri Iodidi.* This revision adopted the formula suggested by Soubeiran in preference to the more tedious one of Donovan. As its admission into the U. S. P. precedes that into the B. P. it seems probable that the adoption of Soubeiran's formula into England was influenced by the choice of the American revision committee. All succeeding revisions of the United States Pharmacopœia have retained this solution. Other Pharmacopœias than the U. S. P. and B. P. apparently have not introduced it.

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* For No. 1 in "Proc. Wis. Acad. Science Letters and Arts" V. XX. No. 2, JOUR. A. PH. A., Vol. 14, p. 408.

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[1] Kopp, "Geschichte der Chemie," Vol. 3, p. 83; also Federking, "Grundzuege der Geschichte der Pharmacie" (1879), p. 219; Buchner, "Repertorium fuer die Pharmacie," Vol. 30, p. 260 and Vol. 40, p. 288.

[2] *Jour. de Pharm. et de Chim.*, 27, p. 344 (1841).

Comments on the Pharmacopœial Text.

Introductory Statement.—Donovan's Solution was first introduced into medical practice in 1839. Naturally a new preparation of this kind would not be adopted by the pharmacopœial revision committee before its usefulness in medicine had been established. Hence the committee of 1840 did not consider this solution but left it for the next decennial revision committee. The committee of 1850 adopted the solution, which has been retained in all of the following revisions of the U. S. P. Hence there are seven texts to be considered. As with the two arsenical solutions already reviewed, the detailed comments on the text, whether based on the literature of the text or on laboratory experiments or observations, are recorded with those parts of the text to which they have reference. The following are the text subjects commented upon:

1. Title and synonyms.
2. Definition.
3. Preservation.
4. Arsenic tri-iodide as an ingredient.
5. Mercury di-iodide as an ingredient.
6. Ratio of ingredients.
7. Water.
8. Amount of water to effect solution.
9. Solution of arsenic triiodide and mercury diiodide.
10. Volume of finished product.
11. Appearance of finished product.
12. Qualitative tests.
13. Assay.
14. Dose.

1. *Title and Synonyms.*—Donovan in 1839 prepared his original solution from the elements, arsenic, iodine and mercury. To the aqueous solution he applied the title *Liquor hydriodatis arsenici et hydrargyri.* The Dublin Pharmacopœia of 1851 introduced this solution under the title *Arsenici et Hydrargyri Hydriodatis Liquor.* (English, *solution of hydriodate of arsenic and mercury.*)

With the consolidation of the London, Dublin and Edinburg Pharmacopœias, Donovan's Solution was omitted from the British Pharmacopœia of 1864. The next revision, however, that of 1885, contained this solution under the title *Liquor Arsenii et Hydrargyri Iodidi.* The same title was used in the revision in 1898 and also in the last revision, that of 1914.

The U. S. P. of 1850, the first edition to contain this solution, applied the title *Liquor Arsenici et Hydrargyri Iodidi.* This title was also used by the revisions of 1860 and 1870. In 1880 the U. S. P. title was changed to *Liquor Arsenii et Hydrargyri Iodidi,* and to *Liquor Arseni et Hydrargyri Iodidi* in 1890. This title was adopted by the following decennial revision and the present one, that of 1910.

Definition.—As with Fowler's solution, a definition appears for the first time in the revision of 1900. This was modified in the 1910 revision. "An aqueous solution, which should contain not less than 1 per cent of Arsenous Iodide and 1 per cent of Mercuric Iodide," was the 1900 requirement. The modification introduced into the 1910 definition permitted a slight variation in the per cent of each ingredient, *viz.*, "not less than 0.95 per cent nor more than 1.05 per cent."

3. *Preservation.*—The last revision of the U. S. P. (1910) directs that the solution be kept in well-filled amber-colored bottles and that it should not be dispensed if darker than a pale yellow color. What the nature of the composition is if the solution becomes darker in color is not clearly understood. According to an unsigned article[1] in the *American Journal of Pharmacy* the red color appearing in this

[1] *Am. Jour. Pharm.*, 31, p. 409.

solution is due to free iodine contained in the arsenic tri-iodide used. Boiling the solution, the writer states, expels the iodine, though not without some loss of the volatile "arsenical salt." L. A. Brown[1] suggests the addition of a small globule of mercury to the solution and shaking until the red color disappears. The red color he states is due to free iodine, although he does not suggest any cause for this. The presence of free iodine appears doubtful, for it could not be shaken out with chloroform, neither did it give the iodine test with starch. J. Rosin[2] reports that oxidation of arsenous arsenic takes place in this solution. At the end of one year and eleven months he found that it had lost over one-half of its arsenic tri-iodide content, although the total arsenic content remained the same. Whether the appearance of the red color and the oxidation are related is not apparent, from the literature on the subject.

4. *Arsenic Tri-iodide as an Ingredient.*—Donovan,[3] in his original formula, used the elements, arsenic and iodine, for the formation of the arsenic tri-iodide in solution. This procedure was adopted by the Dublin Pharmacopœia of 1851.

In 1841, Soubeiran[4] having computed the amount of arsenic tri-iodide formed according to Donovan's original formula, obtained from a French translation of Donovan's report, suggested the use of this compound in preparing the solution. In 1847 Procter[5] made practically the same suggestion based on the same considerations but gave no credit to Soubeiran. As both the U. S. P. and B. P. used arsenic tri-iodide for preparing the solution and not the two elements, it seems proper to say that the suggestion of Soubeiran was adopted, although the U. S. Dispensatory of 1873, p. 1241, gives Procter credit for the formula adopted by the U. S. P. of 1850.

The revisions of the U. S. P. of 1850, 1860, 1870 and 1880 directed the use of "Iodide of Arsenic;" that of 1890 prescribed "Arsenic Iodide," and the revisions of 1900 and 1910 direct that "Arsenous Iodide" should be taken.

No purity rubric for arsenic tri-iodide was given in the revisions of the U. S. P. of 1860, 1870, 1880 and 1890. Hence some variation in the strength of the solutions may have existed due to the difference in quality of the commercial arsenic tri-iodide. The first three revisions mentioned gave a method for preparing the arsenic tri-iodide, and described its physical properties, as to color, solubility in water and volatility. The revisions of 1880 and 1890 omitted the method of preparation but added several qualitative tests. The revisions of 1900 stated that arsenic tri-iodide "should contain not less than 82.7 per cent of iodide and 16.3 per cent of metallic arsenic." The 1910 revision specifies that arsenic tri-iodide shall contain "not less than 99 per cent AsI_3."

That the products obtained by the various methods prescribed and the composition of the commercial product varied is evidenced by the numerous reports on the composition of arsenic tri-iodide. The following references represent only a few of these. H. F. Fish, *Am. Jour. Pharm.*, 13, p. 97; Plisson, *Annal. d. chim. et d. Physique*, 39, p. 265; Richter, *Apoth. Ztg.*, 26, p. 729; Lyons, "Rep. of

[1] *Ky. Ag. Exp. Sta., Bull.* No. 150, p. 154.

[2] JOUR. A. PH. A., 6, p. 951.

[3] See Donovan's Report in Appendix.

[4] *Jour. de Pharm. et de Chim.*, 27, p. 744 (1841).

[5] *Am. Jour. Pharm.*, 19, p. 93 (1849).

the U. S. P. Rev. Com. 1900," *Cir.*, 300, p. 1282; Cowley & Carford, *Pharm. Jour.*, 21, p. 131 and p. 217; Coblentz, *Am. Jour. Pharm.*, 78, p. 387.

5. *Mercury Di-iodide as an Ingredient.*—Pure mercury and iodine were used in Donovan's original formula and in the formula of the Dublin Pharmacopœia of 1851 for the formation of mercury di-iodide. Soubeiran having computed the amount of mercury di-iodide formed according to Donovan's formula, suggested the use of this salt in place of the two elements. (Compare with arsenic tri-iodide No. 4.) Hence we find that the U. S. P. of 1850 prescribed the salt in place of the two elements.

"Red iodide of mercury" was called for in the revisions of the U. S. P. of 1860 to 1880 inclusive, and "Red mercuric iodide" in the revisions of 1890 to 1910 inclusive.

It was not until 1900 that a purity rubric was adopted for mercury di-iodide. Previous to this, each revision contained directions for preparing the compound. As the methods differed, undoubtedly the composition of the products varied. The revision of 1850 prepared the mercury di-iodide by triturating definite quantities of mercury and iodine in the presence of alcohol, until the color of the iodine had disappeared. The product obtained from this method undoubtedly varied with each manipulator. The remaining revisions, *viz.*, those of 1860 to 1890 inclusive, prepared this salt by mixing aqueous solutions of potassium iodide and mercury dichloride, and collecting the precipitated mercury di-iodide. This was washed and dried. This process undoubtedly gave a more satisfactory product than that of 1850.

6. *Ratio of ingredients.*—Based on the computed iodides, Donovan's original formula contained 36.8 grains of arsenic tri-iodide to 34.7 grains of mercury di-iodide in eight ounces of solution. The formula of the Dublin Pharmacopœia of 1851 contained the equivalent of 36.5 grains of arsenic tri-iodide to 36.25 grains of mercury di-iodide in eight fluid ounces and six fluid drachms of solution.

The British Pharmacopœia of 1885 prescribed 45 grains of each iodide in 10 fluid ounces of solution. In 1898 the change was made to 87.5 grains of each iodide to one pint (Imperial) of solution. The revision of 1914 placed the solution on an approximately 1 p. c. basis, prescribing 10 grams of each iodide to 1000 milliliters of solution.

The 1850, 1860 and 1870 revisions of the U. S. P. directed the use of 35 grains of each iodide to one pint of solution. That of 1880 prescribed one part of each iodide in 100 parts of solution; that of 1890, 10 grams of each iodide in 1000 grams of solution. This formula was also adopted by the 1910 revision.

Consequently in all of the formulas employed the ratio of iodides was 1 to 1, except in the case of Donovan's original formula, which approximates this ratio so closely that its author must have intended it.

7. *Water.*—In his original formula Donovan prescribed *distilled water* and this only has been prescribed in all of the pharmacopœial formulas.

8. *The amount of Water used to effect solution.*—Donovan in his original formula used eight ounces of distilled water to effect the solution of the two iodides; as did the Dublin Pharmacopœia of 1851. The British Pharmacopœia of 1885 used one and one-half ounces of water to 45 grains of each iodide. That of 1898 increased the quantity to "three to four ounces" to dissolve 87.5 grains of each io-

dide, and the revision of 1914 directs the use of 250 milliliters of water to effect the solution of 10 grams of each iodide.

The 1850, 1860 and 1870 revisions of the U. S. P. each called for one-half ounce of distilled water in which to dissolve 35 grains of each of the two iodides. In the 1880 revision 15 parts of water were used for 1 part of each iodide and the remaining three revisions, *viz.*, those of 1890, 1900 and 1910 each prescribed 150 cc. of distilled water to effect the solution of 10 grams of each iodide.

9. *Solution of Arsenic triiodide and Mercury di-iodide.*—Donovan claimed that when the three elements, *viz.*, arsenic mercury and iodine, or their respective iodides, were dissolved in water, a chemical union took place. This new compound he designated as an *iodohydrargyrate of arsenic.* He based his conclusions on the observations that the solution was nearly colorless, having neither the color of an aqueous solution of arsenic tri-iodide nor that of mercury di-iodide, and that the solution could be distilled without decomposition. He also concluded that this combination was similar to those of the double halides reported by Bonsdorff.

Bonsdorff's work was on the halides of the metals. In 1820[1] he reported that certain metallic halides acted as "acid like bodies" and others acted as "base like bodies." These when brought together in solution would combine to form "double salts." For example, he stated that mercury dichloride acted as an acid and that potassium chloride acted as a base. The two would combine to form a double salt. This is an application to the double halides of the electro-salt. This is an application to the double halides of the electro-chemical theory of Berzelius as applied to double salts illustrated by such examples as the double sulphate in alum.

From the long list of double salts of both arsenic and mercury enumerated by Abegg,[2] the following have been selected to show that the so-called double salt of arsenic tri-iodide and mercury di-iodide is by no means an isolated case.

Of the double salts of arsenic halide but two examples are given in vol. 3, part 3 and 2 respectively:

p. 536 $2AsF_5.2KF.H_2O$
p. 641 $AsI_3.3PbI_3.12H_2O$

Of the double halides of mercury the examples are more numerous: vol. 2, part, 2:

p.642	$H_2HgCl_4.7H_2O$	Na_2HgCl_4	NH_4HgI_3	
	$2HgCl_2.HCl.6H_2O$	NH_4HgCl_3	$Hg_2(Hg_2I_6)$ =	$HgI_2.2HgI_2$
	$4HgCl_2.2HCl.9H_2O$	$(NH_4)_2.HgCl_4.H_2O$	Ag_2HgI_4	
	$3HgCl_2.HCl.5H_2O$	$2NH_4Cl.3HgCl_2.4H_2O$	Cu_2HgI_4	
	$KHgCl_3.H_2O$	$2NH_4Cl.9HgCl_2$	p. 629 K_2HgBr_4	
	$K_2HgCl_5.2H_2O$	p. 647 $KHgI_3$	p. 630 K_2HgCl_4	
	$NaHgCl_3.1^1/_2H_2O$	K_2HgI_4		

[1] Kopp, "Geschichte der Chemie," vol. 3, p. 83; see also Frederking, "Grundzeuge der Geschichte der Pharmacie," (1879), p. 219; and Buchner, "Repertorium fuer die Pharmacie," vol. 30, p. 260, and vol. 40, p. 288.

[2] "Handbuch der Anorganischen Chemie," Abegg.

(*To be continued*)