THE PHARMACOPŒIAL STANDARD FOR DESICCATED THYROID GLANDS.

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During the past few years a great many experiments have been made in this laboratory upon the relation between the physiological activity of thyroid and its iodine content. These experiments and practically all that have been described in the literature demonstrate this parallelism; it may therefore be concluded that at present the most satisfactory way to standardize thyroid is by means of the determination of the originally combined iodine which it contains. From the standpoint of the Pharmacopoeia the question resolves itself simply into the selection of the most satisfactory method for the iodine estimation and the adoption of the most reasonable percentage content of iodine as the standard.

Of the methods which may be used for the determination of the iodine there are only two which need to be considered, viz., the older Baumann method which consists of fusion with caustic alkali, liberating the iodine by suitable means from the aqueous solution of the fused residue, extracting it with an immiscible solvent, and estimating its quantity colorimetrically, and the recently proposed Hunter method, which differs from the above in substituting alkali carbonates for the fusion, conversion of the iodine to the iodic state, and estimating its amount by a volumetric procedure. Of these two methods the latter has been found by us to possess advantages both in reliability of the results, and convenience of execution. Furthermore, from the point of view of the Pharmacopoeia it possesses the advantage over the Baumann method that no analytical procedures, volumetric solutions, or reagents, new to the present edition of the Pharmacopoeia, are required.

In his original paper* Dr. Hunter gives very clear and explicit descriptions of all the details of the process, and there is consequently little opportunity for uncertainty in regard to any part of the method. It is the rule, however, in pharmacopoeial descriptions of analytical processes, that only the essential features be included, consequently it appears desirable that a concise description of the Hunter method, in what may be called pharmacopoeial language, be given. Such an outline would be as follows:

Determination of Iodine. (Hunter Method). One gram of desiccated thyroid gland is mixed in a nickel crucible of about 125 Cc. capacity, with 15 grams of a mixture composed of 138 parts by weight of anhydrous K_2CO_3, 106 parts anhydrous Na_2CO_3 and 75 parts KNO_3, and an additional 5 grams of this fusion mixture spread evenly over the surface. The crucible is then heated over a free Bunsen flame until no further carbonization is observed, it is cooled and the friable residue dissolved in about 150 Cc. of distilled H_2O. To this solution contained in an Erlenmeyer flask of about 500 Cc. capacity, is added approximately 50 Cc., or its equivalent, of fresh liquor sodae chlorinatae U. S. P. (containing 2.4 wt. per cent Cl). The mixture is then treated with enough phosphoric acid (1 volume of the 85 per cent syrup and 1 volume of H_2O), to produce a marked yellow tint

* Hunter: Jour. Biol. Chem., 2, 321-349, 1910.

of free chlorine, and an additional 10 Cc. of the phosphoric acid is then added and the contents of the flask boiled for about one-half hour or until the volume has been reduced to about 150 Cc. The liquid is cooled, 10 Cc. of 1 per cent aqueous KI solution is added and the liberated iodine titrated with N/200 sodium thiosulphate, adding starch paste as the indicator just before the end of the reaction.

The N/200 thiosulphate may be made by diluting 25 Cc. of exactly N/10 thiosulphate to 500 Cc., it changes strength rapidly and should be prepared fresh at each time determinations are made. One Cc. of N/200 thiosulphate corresponds to 0.0001058 Gm. iodine derived from the sample of thyroid used.

This method has been tested in this laboratory in comparison with the Baumann method, upon quite a large number of samples of commercial desiccated thyroid glands. The agreements in duplicate determination by the Hunter method were found to be considerably more uniform than those by the Baumann method, and the results in practically every case were from 10 to 15 per cent higher. Since there is a reasonable source of loss at one step of the Baumann method, viz., the acidification of the aqueous solution of the fusion residue, and this particular cause of loss has been obviated by Hunter in his method, there can be little doubt that the higher results are the nearer correct.

Of the commercial samples which we have so far examined, some were purchased on the market during 1907, and the others recently received direct from two American firms which prepare thyroid glands for medicinal use. For these latter we herewith acknowledge our indebtedness to Armour & Co., and Parke, Davis & Co. The samples received direct are portions of the several lots prepared at the particular dates shown in the table.

PERCENTAGE OF IODINE IN COMMERCIAL DESICCATED THYROID U. S. P. AS DETERMINED BY THE HUNTER METHOD.

Lab. No.	Source		Per ct. I.
99	P. D. & Co.	(1907)	0.185
99 (a)	"	"	0.185
100	"	"	0.188
101	"	"	0.153
102	"	"	0.162
103	"	"	0.219
105	"	"	0.138
106	"	"	0.218
106 (b)	"	"	0.212
116	"	"	0.118
117	"	"	0.117
118	"	"	0.158
Average, 0.171.			
358	"	(1911)	0.206
359	"	"	0.206
360	"	"	0.154
361	"	"	0.214
Average, 0.195.			

Lab. No.	Source		Per ct. I.
104	Armour & Co.	(1907)	0.138
107	"	"	0.145
108	"	"	0.138
109	"	"	0.141
109 (a)	"	"	0.142
119	"	"	0.135
120	"	"	0.129
121	"	"	0.140
Average, 0.138.			
345	"	Dec. 16, '09	0.279
346	"	Jan. 23, '10	0.095
347	"	Feb. 15, '10	0.212
348	"	April, '10	0.162
349	"	May, '10	0.146
350	"	June, '10	0.271
351	"	July, '10	0.202
352	"	Aug., '10	0.231
353	"	Sept., '10	0.215
354	"	Oct., '10	0.144
355	"	Nov., '10	0.252
356	"	Jan. 16, '11	0.219
Average, 0.202.			
357	Thyroid Proteid (Armour)		0.607

From the above results it is found that the average of the twelve P. D. & Co. samples received in 1907 is 0.171 per cent I., while that for the Armour samples is 0.138 per cent. On the other hand the average per cents for the recent samples are respectively 0.195 and 0.202, thus showing that in both cases products with higher iodine contents are being prepared. On the whole these results show a very commendable degree of regularity in the percentage of iodine in thyroid at present on the market. With very few exceptions none of these samples might be expected to produce a noticeable variation in physiological effect. There can be no doubt, however, that the interests of both the producer and consumer would be safeguarded by the establishment of a reasonable pharmacopoeial standard of iodine content. Judging from the results upon the samples supplied by the manufacturers themselves, such a limit could be fixed at approximately 0.2 per cent I without causing an undue hardship. This per cent has already been adopted by an English firm. Of course sufficient latitude, of say 0.03 per cent above or below this figure, should be permitted, thus making the extreme limits 0.17 to 0.23 per cent iodine.

The remaining pharmacopoeial description which is necessary is that limiting the source of the raw material to certain animals and prescribing a reasonable limit of moisture and ash, which from our experiments might be placed at not exceeding 6 per cent for the former and 5 per cent for the latter, and finally the prohibition of all iodine in inorganic or any other form of combination than that peculiar to the thyroid.

In regard to the ash content it should be mentioned that in general those samples with the higher percentage of iodine contain the lower percentage of ash, and vice versa. Thus for instance, of 12 samples containing more than 0.2 per cent iodine the variation in the ash content was from only 3 to 4 per cent, while 6 samples containing approximately 0.15 per cent iodine contained more than 4 per cent ash, and one sample with only 0.095 per cent iodine contained more than 5 per cent of ash.

It has recently been suggested by certain investigators that the iodine of thyroid may not all be present in an equally physiologically active form, and consequently that it was possible by certain manipulative processes to remove the less active forms and retain the more active portion in a product which is therefore supposed to contain iodine in a super active condition as compared with that of the untreated material. A number of experiments which we have recently made with one of these products, designated as thyroid proteid, have failed to confirm this hypothesis. These recent experiments indicate even more conclusively than our previous work, the constant behavior of the thyroid-iodine substance and the close relation between the iodine content and the physiological activity of both the desiccated thyroids and the new thyroid proteid.