country and that it also be incorporated in the forthcoming United States Pharmacopœia.

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DISCUSSION.

Clement B. Lowe, of Philadelphia, said that large quantities of crude santonin were being imported into this country, and he wanted to know whether it was possible that this santonica which seemed to yield no santonin had been treated, or could be treated, without altering the physical appearance of the drug. He was aware that this had been done with some drugs, as with opium, for instance, where a part of the morphine content had been abstracted and then the drug fixed up from that.

Prof. Caspari said it was true, that large quantities of crude santonin were imported, but the source was controlled by the Russian government, a close corporation, and he did not believe that the santonica that came in devoid of santonin had been subjected to treatment in the old country. Dr. H. H. Rusby had told him that the spurious article was a different species. Tons of this spurious species were being used all over the country, especially for stock-powders, which were absolutely worthless.

Hermann Engelhardt, of Baltimore, made the comment that out of ten samples of santonica he had examined, he had found nine with no trace of santonin whatever. He expressed the opinion that all of the tests given were uncertain.

Chairman Eldred said that, while it did not bear upon the determination of santonin, he was reminded to say that the representative of a drug importer had told him a few months before that he had considered the handling of santonin, and had gone to Russia to investigate the conditions of the market there, and he had found it just as Mr. Caspari has stated, that it was a very close corporation. An interesting fact was, that some of the growers were paid for their drug, which was then set fire to and burned in the fields, in order to keep from overloading the market with santonin.

DETECTION AND ESTIMATION OF MINUTE QUANTITIES OF FORMALDEHYDE IN PRESENCE OF HEXAMETHYLENAMINE AND OF METHYL ALCOHOL IN PRESENCE OF ETHYL ALCOHOL.

H. A. B. DUNNING, BALTIMORE.

Sometime during the year 1912, Dr. Curtis F. Burnam, member of the staff of Johns Hopkins Hospital, sought my advice as to the most satisfactory method of detecting traces of formaldehyde in urine.

After a careful investigation, I recommended, as most delicate and satisfactory, three tests herein named and described.

Only one of these tests, Rimini's, was of particular value in his work on account of the presence of hexamethylenamine in the material tested. Hehner's milk test, while most delicate, was not suitable on account of being conducted in acid solution, resulting in decomposition of hexamethylenamine with the production of formaldehyde.

While Rimini's test has been found to be most satisfactory in differentiation of formaldehyde in presence of hexamethylenamine, experience teaches that certain precautions should be observed to obtain best results.

The specimens to be examined and all test solutions should be warm, not hot,

and an excess of nitroprusside solution should be avoided. In weak specimens the nitroprusside solution should be diluted five to ten times. In urine, formaldehyde may be detected readily by this test in strength of 1-100,000; in weaker strengths than this, much depends upon the care and experience of the operator.

The test is usually conducted as follows: About 2 cc. of urine specimen, contained in five inch tube, is warmed and two drops of one-half percent fresh solution of phenylhydrazine hydrochloride is added, followed by two drops of one-half percent fresh solution of sodium nitroprusside, the mixture being made strongly alkaline with saturated solution of sodium hydroxide. In strengths 1-20,000 to 1-50,000, deep blue colorization results, changing in a few minutes to green, then yellow, or perhaps, red. In more dilute solutions the blue lasts momentarily only, and is quickly succeeded by green. The blue may be made to last longer and become more distinct by adjustment of the quantities of sodium nitroprusside and phenylhydrazine hydrochloride added, the weaker strengths requiring less nitroprusside and phenylhydrazine. In alkaline solutions phenylhydrazine gives a yellow color, therefore, if there is but a trace of formaldehyde the blue color is masked and converted into green by mixtures of blue and yellow.

The Phloroglucin test, the author of which I have lost record, is quite satisfactory for dilutions of formaldehyde in urine, not exceeding 1-100,000, the red color being masked by yellow of the urine. The author of this test directs that a solution of phloroglucin, 1 gram, alcohol 90 percent, 100 cc. and sodium hydroxide 10 grams, be made fresh. A much better plan is to prepare a solution of phloroglucin in alcohol 1 gram to 100 cc. and add strong solution of sodium hydroxide to specimen at time of testing.

The test is conducted as follows: To 2 cc. of specimen, previously warmed, contained in a five inch test tube, add one drop of alcoholic solution of phloroglucin, then make strongly alkaline with saturated solution of sodium hydroxide, previously warmed. The color produced is red.

These tests have been used with satisfaction in connection with an investigation made by Dr. Burnam and his associates. It seems to me desirable, in connection with this paper, to call attention to the character of Dr. Burnam's work and the importance of the conclusion arrived at.

Dr. Burnam has learned that small doses, as little as five grains per day, of hexamethylenamine may produce formaldehyde in the urine of strength exceeding 1-30,000, this being highly destructive to the mucosa of the bladder, while in other patients or, perhaps, at different times, one hundred grains per day will produce only traces of formaldehyde, or perhaps, none at all. The point of interest is that it is dangerous to give large doses of hexamethylenamine until the patient has first been treated with small doses.

Subsequent to the publication of Dr. Burnam's paper, much interest was evinced by the medical fraternity in the discovery of a test for the quantitative estimation of formaldehyde in the urine that would differentiate hexamethylenamine and yet would be practicable in the hands of the physician.

I offer the following test to fill this requirement: From an assayed specimen of commercial formaldehyde solution, accurate dilutions are prepared of strengths 1-50,000, 1-100,000, 1-200,000, 1-300,000, as standard solutions for

colorimetric comparison. More standard solutions may be prepared if necessary. The test will estimate quantitatively up to 1-500,000 in the urine and 1-30,000,000 in clear water. Dextrose, acetone, acetaldehyde do not interfere in solutions weaker than 1-30,000 and then only on heating or long standing.

The test is conducted as follows: To five cc. of the specimen contained in a five inch test tube, add .1 cc. of 15 p. c. solution of sodium hydroxide and mix well. Then add .1 cc. phenylhydrazine base, not hydrochloride, finally add .7 gram of stick sodium hydroxide and agitate for ten minutes. The strength is estimated colorimetrically by comparing with the standard solutions treated in same manner as specimen, and at the same time. It is important to remember that the several reagents must be added to specimen and standard solutions at the same time; i. e., specimen and standard are treated simultaneously.

Colorimetric comparisons must be made within twenty minutes after stick alkali is added. Usually comparisons are made in about ten minutes subsequent to the addition of stick alkali.

If it is desired to keep specimens for some hours previous to estimation, then the .1 cc. of 15 p. c. solution of sodium hydroxide must be added. This precaution prevents decomposition of hexamethylenamine with production of formaldehyde, which will take place in acid urine on standing. After specimen has been made alkaline as directed in method of assay, no attempt should be made to remove precipitate, as such procedure will remove free formaldehyde wholly or in part. In my experience any attempt to remove color of urine, by charcoal, precipitation, reduction, oxidation, etc., results in removal of some or all of free formaldehyde.

This test has been used with much satisfaction in a series of clinical experiments conducted at the Union Protestant Infirmary by Dr. George Walker, associate professor of Surgery, Johns Hopkins Hospital.

In line with the above work is a recent examination of samples of whiskey submitted by Dr. Hiram Woods, Eye Specialist, of this city. Dr. Woods stated that he was at that time treating a patient almost blind, who could offer no explanation of his condition except that he had partaken rather freely of whiskey mislabelled Sherwood Maryland Rye.

Upon investigating a sample of this brand of whiskey it was found to be a mixture of approximately 30 percent methyl alcohol, about 15 percent grain alcohol and 55 percent water. This sample was tested among other tests, including specific gravity of distillates, as follows:

A test tube partially filled with the sample was heated until vapor formed in upper part of tube, into which a copper spiral heated to redness and slightly cooled in air was plunged. The characteristic odor of formaldehyde and the effect on nasal passages was observed, masked to some extent by acetaldehyde and other odors. The formaldehyde odor was much more characteristic when applied to a fraction of distillate partially freed from water by saturating with potassium citrate and distilling the supernatant layer.

The specimen was further tested as follows: 100 cc. was supersaturated with potassium citrate and thoroughly shaken, when two strata of liquid were formed, the upper measured about 44 cc. This latter liquid was removed into a distilling bulb connected with a distillation tube having several bulbs and carrying glass

beads. The liquid was heated on water bath and began to boil at 68°-70° C., the larger portion distilling over under 75° C., rising to 78° then to 85°. The mixed distillate was twice distilled over lime, practically all coming over under 78° C. This distillate was then carefully fractionated, the lower boiling fractions being collected and refractionated until 19 cc. of liquid boiling at 60°-66° C. was obtained. This distillate tested with the copper spiral gave entirely characteristic formaldehyde effects.

Formaldehyde produced in solution by plunging a heated copper spiral into portion of distillate and testing in accordance with Rimini's Test, gave entirely characteristic reaction, as also Hehner's milk test, the phloroglucin test, and Dunning's test.

Methyl salicylate was produced with salicylic acid and sulphuric acid, but only a trace of iodoform could be produced. The quantity of methyl alcohol, 96 percent, was then estimated with a refractometer and by the method suggested by C. Simmonds in his notes on the determination of small quantities of methyl alcohol,* which are here given:

"Small proportions of methyl alcohol have hitherto been somewhat difficult to determine readily and accurately. Fairly good approximate results can be obtained by comparative experiments with the well known method of Riche and Baddy (Compt. rend., *80*, 1076 [1875]), or with Wolff's modification of Trillat's process (Ann. Inst. Pasteur, *1912*, 8), but these methods are lengthy and rather troublesome. The process described by Thorpe and Holmes (J. Chem. Soc., *85*, 1 (1904), gives good results when the quantity of methyl alcohol is not too small. It is not well adapted, however, for use when the proportion of methyl alcohol is less than about 2 percent of the ethyl alcohol, since the necessary subtractive correction (loc. cit., pp. 2, 3) may in such cases be equal to or may exceed the quantity it is desired to estimate. For determining very small portions of methyl alcohol the method is quite inapplicable. In such cases satisfactory determinations can be made by applying the principle of colorimetric comparison by Deniges' process for detection of methyl alcohol (Compt. rend., 150, 332 [1910]).

"The possibility of thus using the process is indicated by Deniges, (loc. cit., p. 833). The object of the present note is to give the procedure which the writer finds most suitable for utilizing the reaction quantitatively in general analytical work, as, for example, in examining spirituous beverages, medical tinctures, flavoring essences, and so forth.

"The alcoholic mixture is best purified, when necessary, either by the method of Thorpe and Holmes (J. Chem. Soc., *83*, 314 [1903]), or by other suitable means. It is then diluted with water or mixed with ethyl alcohol, as the case may require, until it contains 10 percent of total alcohol by volume.

"To 5 cc. of this prepared liquid contained in a wide test tube are added 2.5 cc. of permanganate solution (2.0 grams $KMnO_4$ per 100 cc), and then 0.2 cc. of strong sulphuric acid. When the reaction has proceeded about five minutes, 0.5 cc. of oxalic acid solution is added (0.6 grams crystallized acid per 100 cc.). On shaking the liquid becomes clear and nearly colorless. One cc. of strong sulphuric acid is now run in and well mixed with the solution, which is finally treated with 5 cc. of Schiff's reagent. A violet color is developed in the course of a few minutes unless mere traces of methyl alcohol were present, when twenty or thirty minutes may be required.

"This color is due, of course, to the reaction of the fuchsin solution with formaldehyde, produced by the oxidation of the methyl alcohol. A sufficient quantity of sulphuric acid is present to prevent the development of color with any acetaldehyde formed from the ethyl alcohol during the oxidation.

*Government Laboratory, London. Analyst 27, 16 (1912).

"A preliminary experiment carried out as described serves to detect the presence of methyl alcohol, if it is not already known, and to give some idea of the quantity. According to the indications thus obtained, another part of the prepared liquid is further diluted, if necessary, with ethyl alcohol of 10 percent strength until it contains from 0.001 to 0.004 grams of methyl alcohol in 5 cc; the experiment is repeated side by side with two or more standards for comparison. These contain 0.001, .002, 0.003, etc., gram of methyl alcohol in 5 cc. of 10 percent ethyl alcohol. The colors produced are compared in small Nessler tubes (25 cc.) or in a suitable colorimeter.

"With properly sensitive Schiff's reagent, 0.0003 gram methyl alcohol in the 5 cc. of liquid taken is readily detected. The best depths of color for comparison, however, are given by the formaldehyde produced in the manner described from quantities of 0.001 to 0.004 gram of methyl alcohol.

"It is convenient to keep a standard solution (1 gram per liter) of methyl alcohol in 10 percent ethyl alcohol. This is diluted as required with 10 percent alcohol to form the standards for comparison. This proportion of ethyl alcohol (10 percent) is a suitable strength for general work, as the distillates ordinarily obtained are stronger, and can be diluted down instead of having to be concentrated.

"The process has the advantage of (1) being rapidly executed, (2) requiring only a small quantity of material, and (3) being directly applicable to weak distillates. The degree of accuracy obtainable is shown by the following results of a typical series of experiments:

	Grams methyl alcohol per 100 cc.						
Present	0.005	0.028	0.044	0.072	0.100	0.500	1.000
Found	0.004	0.029	0.046	0.072	0.104	0.492	0.968

"Formaldehyde, of course, must be absent from the unoxidized solution of the alcohols, or else its effect must be determined and allowed for. Glycerol must also be absent."

The method of purification referred to is for the purpose of getting rid of other volatile substances, such as ether, chloroform, benzene, essentials oils, etc. Twenty-five cc. of the sample are diluted in a separatory funnel with water to 100-150 cc., enough salt added to saturate the solution which is then shaken vigorously for five minutes with 50-80 cc. of light petroleum (boiling below 60°), allowed to stand 0.5 hour, the lower layer drawn off and again extracted if necessary, the petroleum extracts washed with 25 cc. of saturated salt solution, the wash waters added to the main bulk of liquid which is then neutralized if necessary and 100 cc. distilled over. Experiment has shown that all of the alcohol is recovered in the first 100 cc. of distillate.

Sensitive fuchsin bisulphite solution is readily made according to the following formula: In 100 cc. of a saturated solution, less than 1 percent of basic fuchsin, dissolve sodium bisulphite 10 grams and when nearly colorless mix with purified animal charcoal and filter; a perfectly clear solution should result.

DISCUSSION.

Otto Raubenheimer, of Brooklyn, said that hexamethylenamine should be taken internally with caution, as he had learned by an experience in his own family, where the hexamethylenamine, instead of being taken three times a day, in five-grain doses was taken every hour. After the patient had taken five doses she was thrown into a great state of excitement, with impairment of vision, and it was necessary to call in a physician. This experience had

proven to him that hexamethylenamine should be taken inwardly with great caution. He thought that one thing might be stated in the paper by way of caution—a fact well known to chemists—that phenylhydrazine and sodium nitroprusside solutions should be freshly made, as they deteriorated very rapidly and that they should furthermore be protected from light.

METHODS OF ANALYSIS FOR CERTAIN PHARMACEUTICAL PREPARATIONS.

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In the course of a year's work in a laboratory devoted to the analysis of drugs and drug preparations, it often becomes necessary to devise new methods, or to modify old ones, for the analysis of certain drug products that do not have any commonly recognized methods.

So far as the author is aware, the following methods have not appeared in print, and my reason for calling your attention to them is the fact that perhaps someone else may have need for such methods.

DETERMINATION OF MORPHINE IN TABLETS.

Take a sufficient number of tablets to equal about four or five grains of morphine, place in a small Erlenmeyer flask of about 50 cc. capacity, add 10 cc. of water and a drop of dilute sulphuric acid and allow to dissolve. If the tablets are not entirely soluble, as determined by a previous test, place the powdered tablets in a 5.5 cm. plain folded filter and extract with distilled water, applied drop by drop, using if possible not more than 10 to 15 cc. of water.

Now add a few drops of cochineal or methyl red and sufficient ammonia to give neutral point, and then add ½ to 1 cc. of 10% ammonia in excess.

Place sample in an ice chest, preferably resting upon a cake of ice and allow to stand over night, when if precipitation has taken place properly, the morphine will appear as a fine crystalline precipitate. Filter into a weighed Gooch crucible, wash well with cold water, dry at 65° C. and weigh.

Place filtrate from above in a separatory funnel and extract five or six times with 30 cc. portions of a mixture of chloroform 3 parts, and alcohol 1 part, being careful to maintain a very slight excess of ammonia. Wash the united chloroform-alcohol solution of morphine twice with 5 cc. portions of water, and then extract the aqueous washings with an equal volume of chloroform.

Filter the chloroform-alcohol solution of morphine through a small filter wetted with chloroform, into a suitable flask and distill off all but about 10 cc. of the liquid, evaporate the remaining portion to dryness on the water bath, take up in neutral alcohol (2 or 3 cc.) add an excess of N/50 sulphuric acid (about 15 cc.), a few drops of methyl-red or cochineal as indicator and titrate excess of acid with N/50 KOH. Each cc. of N/50 acid consumed is equal to 0.006 gm. crystalized morphine.

Add weight of morphine found in filtrate by titration to that obtained by