to determine whether or not it was present. This test is made as directed by Raschig[1] by treating the solution with ammonia and then adding a small amount of benzaldehyde. The reaction between monochloroamine and ammonia is one of the methods for preparing hydrazine, and in this case if hydrazine were present it would react with benzaldehyde to form the very insoluble benzalazine. No evidence of the presence of monochloroamine could be obtained. It was found that when the solution was treated with an excess of chlorine the only oxidizing compound obtained was nitrogen trichloride. This would lead one to think that nitrogen trichloride was formed by the action of chlorine, which in turn was possibly a decomposition product of dichlorôurea.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF PARKE, DAVIS & CO.]

DIGITALIS LEAVES: EFFECT ON ACTIVITY OF TEMPERATURE IN DRYING.

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Since the first attempt to standardize digitalis leaves and the extracts, it has been observed that they vary greatly in activity.

Bennefield,[2] in 1881, using a method almost identical with that suggested in the 9th Rev. U. S. P. for standardizing the digitalis series of heart tonics found a variation of about 500% in the activity of tinctures from digitalis leaves from various parts of Germany.

Bührer,[3] in 1900, found a difference of 400% in the activity of some fluidextracts. Fränkel[4] found variations of 300 to 400% in tincture and infusions. Edmunds,[5] in 1907, tested 17 commercial tinctures and found a variation of 400%.

Many other similar results have been recorded, in some cases the reason being assigned to climate, soil, variety, or the locality from which the leaves were obtained.

Focke[6] observed that wild digitalis is more toxic than the cultivated and the second year's growth than the first. He also observed that the leaves gathered at seeding time are less active than when collected earlier. He was the first to record his observations as to the causes of deterioration and the effect of light and heat in drying the leaves. The former is negligible but he considered that when dried in the air in the ordinary way without special care in preserving the activity is soon largely lost.

[1] *Ber.*, 40, 4586 (1907).

[2] Bennefield, "Ueber Digitalis Tincturen," Inaug. Diss., Göttingen, 1881.

[3] Bührer, Inaug. Diss., Basel, 1900.

[4] Fränkel, *Therap. Gegenw.*, 43, 106 (1902).

[5] Edmunds, *J. Am. Med. Assoc.*, 48, 1744 (1907).

[6] Focke, *Arch. Pharm.*, 245, 646 (1907).

This he considered to be due to the moisture content, which permitted the enzymes and ferments of the leaves to remain in an active state, and to their action in breaking down the sensitive glucosides to less active substances. His remedy is to heat the leaves rapidly to a temperature not to exceed 100°, drying to a moisture content of about $^1/_2\%$ and preserving in dark air-tight jars.

Tordes,[1] in 1867, claimed that digitalis from the vicinity of Strassburg was better than that from other localities because of the careful selection, drying and preserving of the leaves. They used leaves of the second year's growth only, first dried in the shade, then in an oven at a temperature not over 40°. They were then kept in tin or glass containers away from light or moisture.

Sharp and Lancaster,[2] in a series of careful experiments, showed that digitalis leaves, not specially dried but kept dry, retained their activity for 11 years, while the fluid preparations began to deteriorate between the thirteenth and fifteenth months. They also observed that leaves of first-year plants were intensely bitter and probably very active.

Hatcher and Eggleston[3] found that old samples of digitalis leaves and tinctures, neither of them specially preserved, were not much below their original activity. They concluded that fluid preparations containing not less than 50% alcohol do not deteriorate to any considerable degree. This, however, is not in accord with most investigators, although the higher strengths of alcohol are in general much better for preserving the activity.

Houghton and Hamilton,[4] in a series of tests and retests of digitalis extracts, showed that none of them is free from the fault of deterioration, their results pointing to the apparent fact that the higher percentages of alcohol not only more completely extract but also more thoroughly preserve the active principles.

On the supposition that the strong alcohol destroys the active ferments these results are in accord with the results of Perrot and Goris,[5] who published a method by which the enzymes could be destroyed with the subsequent complete preservative of the drug in its original activity. This was accomplished by subjecting the drug to the vapors of boiling alcohol after which it was dried in the air. Such precautions, however, seem unnecessary in view of the results with old samples of digitalis obtained by the different investigators quoted, especially Hatcher, who found high values in 25-year-old leaves, and Sharp and Lancaster, who found 11-year-old drug to have lost little of its activity.

[1] Tordes, *Gaz. Med. Strassburg*, **27**, 191 (1867).

[2] Sharp and Lancaster, *Pharm. J.*, **32**, 102 (1911).

[3] Hatcher and Eggleston, *Am. J. Pharm.*, **85**, 203 (1913).

[4] Houghton and Hamilton, *Ibid.*, **81**, 461 (1909).

[5] Perrot and Goris, Abs. in *La Presse Medicale*, **17**, 776 (1909).

The writer recently had occasion to extract and test a sample which had been in the possession of Northwestern University for 25 years. Its activity was fully 150% of that of the average drug at present obtainable.

Recently the subject of drying digitalis leaves has come up in connection with the samples of this drug grown wild in Oregon and submitted to the Government for the Medical Department of the Army. It was stated that unless the drug was dried in an oven, at 75 to 90°, it was practically worthless.

This statement being so entirely at variance with the opinions commonly held, some experiments were inaugurated to demonstrate its correctness. Unfortunately, there was not available a sufficient amount of the growing digitalis leaves to make the experiments conclusive but the results are apparently of sufficient importance to be published.

From some previous experiments, unpublished, it has been observed that the fresh leaves extracted with 95% alcohol had a higher degree of activity than the average digitalis on the market and apparently the tincture, so prepared, was more active than that prepared from a part of the same lot of leaves dried before extraction.

The following experiments were, therefore, planned and carried out. Fresh leaves were gathered from the flowering and fruiting plants in July, divided into three equal amounts and extracted as follows:

First: Extracted immediately with 95% alcohol for the moistening and then with 70% alcohol to complete exhaustion.

Second: Dried in an oven at temperatures ranging between 75° and 90°, then extracted with 70% alcohol. The drying covered a period of about 5 hours.

Third: Dried in the air and partly in the sun over a period of 4 days, then extracted with 70% alcohol.

The tinctures were made to the same amount on the basis of the weight of the oven-dried lot, which was considerably less than that of the air-dried sample.

Only two lots of drug were available, one being the official variety *digitalis purpurea*, and the other a non-official variety.

The results of assays are as follows, the method of testing being the M. L. D. method originally applied by Houghton.[1] The correctness of the end result was in every case checked by examining the heart of the dead frog to determine whether death occurred with heart in systole—the characteristic position from digitalis poisoning.

These results coincide with those previously obtained in that the fresh drug has greater toxicity than the dried. The experiments also show that the high temperature employed in the oven caused a greater

[1] Houghton, *J. Am. Med. Assoc.*, 31, 959 (1898).

immediate deterioration than the slower drying at the season temperatures.

TABLE I.—DIGITALIS PURPUREA FROM A FLOWER GARDEN IN DETROIT.

Not dried.			Oven dried.			Sun / Air dried.		
Weight.	Dose.	Result.	Weight.	Dose.	Result.	Weight.	Dose.	Result.
22	0.004	Alive	16.5	0.010	Alive	19	0.010	Dead
22	5	Alive	10.5	0.012	Dead	19	0.012	Dead
22.5	6	Alive	16.5	0.015	Dead	19.5	0.015	Dead
22.5	7	Alive	14	0.020	Dead	20.5	0.018	Dead
23	8	Dead	13.5	0.025	Dead	20.5	0.022	Dead
23.5	0.0045	Alive	23	0.008	Dead	24	0.007	Alive
25	55	Alive	24	0.010	Dead	24.5	0.008	Alive
25	65	Alive	24	0.012	Dead	24.5	0.009	Dead
25	75	Dead	24	0.014	Dead	25	0.010	Dead
26	0.0090	Dead	24	0.016	Dead	26	0.011	Dead
27	0.0055	Alive	20	0.006	Alive	22	0.007	Alive
27	65	Alive	20	0.007	Alive	22.5	0.008	Alive
27.5	75	Alive	21	0.008	Alive	23	0.009	Dead
29.5	85	Dead	21	0.009	Alive	24	0.010	Dead
30	0.01	Dead	21	0.010	Dead	26	0.011	Alive
27	0.0070	Alive	24.5	0.008	Alive	25.5	0.008	Dead
29.5	75	Alive	25	0.009	Dead	25.5	0.009	Dead
29.5	75	Alive	25.5	0.010	Alive	26	0.010	Dead
30.5	80	Dead	25.5	0.011	Dead	26	0.011	Dead
33	80	Dead	25.5	0.012	Dead	26	0.012	Dead

Summarizing the above.

0.007 killed none of 3	0.008 killed 1 of 3	0.008 killed 1 of 3
0.0075 killed 1 of 4	0.009 killed 1 of 2	0.009 killed 3 of 3
0.008 killed 3 of 3	0.010 killed 2 of 4	0.010 killed 4 of 4
	0.011 killed 1 of 1	0.011 killed 2 of 3
	0.012 killed 3 of 3	0.012 killed 2 of 2

Activity.....	153	100	133
H. T. U.....	9+	6	8
M. L. D.....	0.008	0.011	0.009
Activity in terms of undried drug.....	100%	72	81

Further experiments are planned to demonstrate whether the oven-dried drug is more stable than the air-dried sample but this point could not be considered, as not sufficient leaves were available to make the experiment conclusive. Such experiments should be continued over a period not less than three years.

In further consideration of the previously mentioned criticism against the Oregon air-dried leaves it should be noted that the method of testing was also called in question. On this point, while there is a wide divergence of opinion as to which of several methods shows the real value of the drug,

there is quite general agreement on the frog as the test animal, and until clinical evidence is brought forward to negative the results it is logical to assume that the death of the frog with heart in systole, or the stoppage of the heart in systole in one hour is a satisfactory measure of the activity of a digitalis preparation. Compared with the guinea-pig method of Reed and Vanderkleed[1] and the Hatcher cat method,[2] both of which are purly toxicity methods, the frog methods have the advantage that deaths from other than digitalis poisoning are eliminated and form no part of the record.

TABLE II.—DIGITALIS LEAVES NON-OFFICIAL FROM A GARDEN ON GROSSE ILE, MICH.

Not dried.			Oven dried.			Sun / Air dried.		
Weight.	Dose.	Result.	Weight.	Dose.	Result.	Weight.	Dose.	Result.
17	0.004	Dead	20	0.004	Dead	23.5	0.002	Alive
18.5	0.005	Dead	27	0.005	Dead	25	0.003	Dead
19.5	0.006	Dead	23.5	0.006	Dead	25	0.004	Dead
27.5	0.007	Dead	23.5	0.007	Dead	25.5	0.005	Dead
18	0.0010	Alive	21	0.0010	Alive	19.5	0.0010	Alive
19	0.0020	Dead	22	0.0020	Alive	20	0.0015	Alive
19	0.0030	Dead	22.5	0.0030	Alive	20.5	0.0020	Alive
19	0.0040	Dead	25	0.0040	Alive	21.5	0.0025	Alive
20	0.0050	Dead	27.5	0.0050	Dead	22.5	0.0030	Alive
18	0.0010	Alive	23	0.0035	Dead	30	0.0025	Alive
19.5	0.0015	Dead	23	0.0040	Dead	28	0.0030	Dead
20.5	0.0020	Dead	23	0.0045	Dead	28	0.0035	Dead
21	0.0025	Dead	23.5	0.0050	Dead	29	0.0040	Dead
21	0.0030	Dead	23.5	0.0060	Dead	30	0.0045	Dead
			22.5	0.0020	Alive			
			23	0.0025	Alive			
			25	0.0030	Alive			
			27	0.0033	Dead			
			27.5	0.0040	Dead			
M. L. D.....		0.0015		0.0035			0.0030	
H. T. U.....		44		19			22	
% activity.....		730		310			370	
Activity compared to undried.....		100%		42			50	

One may conclude, therefore, that oven drying has no advantage over a reasonably rapid air drying of digitalis leaves, and that the drying causes a marked deterioration, no products more highly toxic than those present in the crude drug having been developed during the process of drying.

DETROIT, MICH.

[1] Reed and Vanderkleed, *Am. J. Pharm.*, **80**, 110 (1908).

[2] Hatcher and Brody, *Ibid.*, **82**, 360 (1910).