The variable extent to which these consistency and color changes occur and the extent and rate of reversion are due or at least intimately related to the original character of the individual particles of which the powder is composed.

We wish to re-emphasize the fact that all discussion in this paper relates only to changes in powders which do not undergo chemical changes during heat test and the object has been to direct attention to and explain certain minor changes observable in tests used to control neoarsphenamine.

BIBLIOGRAPHY.

(1) Treasury Dept., U. S. Public Health Service, Miscel. Pub. No. 22.

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DRUG EXTRACTION. I. A STUDY OF VARIOUS MENSTRUA FROM THE STANDPOINT OF SWELLING EFFECTS, PENETRATION AND EXTRACTION.

BY WILLIAM J. HUSA AND LOUIS MAGID.

(*Continued from page 984, October Journal.*)

PENETRATION OF VARIOUS SOLVENTS.

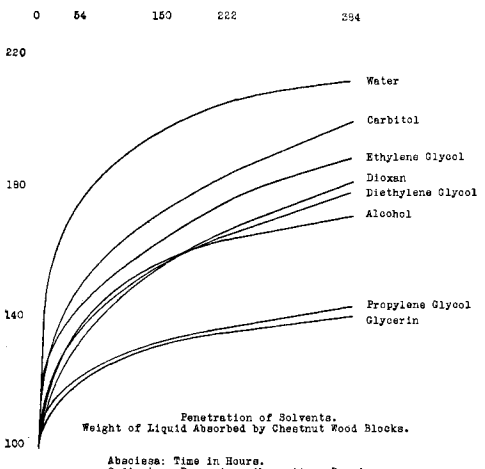
The penetration of liquids through cells is one of the fundamental factors to be considered in drug extraction. Since botanists have been more interested in living tissues, very little has previously been done on the permeability of dried tissues, such as drugs.

Penetration of Various Solvents into Chestnut Wood.—In connection with the tests of swelling on blocks of chestnut wood (see Table X) the rates of penetration of the solvents were determined by weighing the blocks at various intervals, the increase in weight indicating the amount of solvent which entered the block. There is a loss of soluble constituents from the blocks, but this does not introduce a serious error in the case of chestnut wood. For weighing, the blocks were removed from the liquid and the excess liquid on the surface removed by blotting with filter paper. The results are stated on a percentage basis, taking the original weight of the blocks as 100. Each result represents the average of three blocks.

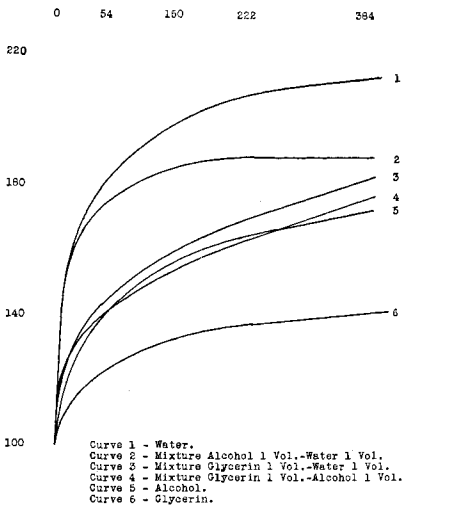
The results in Table XVIII show the rate of penetration and the weight of liquid imbibed in 384 hours by blocks of chestnut wood. The rate of penetration is indicated by the slope of the curves (see graphs) and the time of attainment of equilibrium and from Table XIX. Water shows the most rapid rate of penetration, and a greater weight of water is absorbed. Alcohol also penetrates rapidly, but the weight imbibed is less than the weight of carbitol, ethylene glycol, dioxan and diethylene glycol. Propylene glycol and glycerin show the lowest rate of penetration and are imbibed to a much smaller extent than the other liquids (see Graph 8).

Of the binary mixtures of water, alcohol and glycerin, it is seen that a mixture of equal volumes of alcohol and water shows as fast a rate of penetration as does

water but is imbibed to a lesser extent; mixtures of equal volumes of glycerin and water and glycerin and alcohol show about the same rate of penetration as does alcohol (see Graph 9).



Graph 8.



Graph 9.

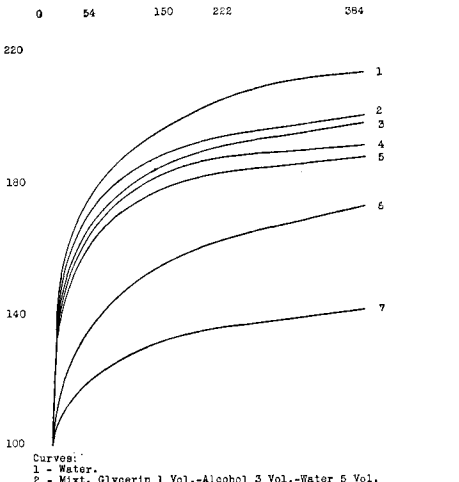
TABLE XVIII.—PENETRATION OF LIQUIDS INTO CHESTNUT WOOD.

Abbreviations: alc. = alcohol, alcoholic; abs. = absolute; aq. = aqueous; gly. = glycerin; mixt. = mixture; v. = volume.

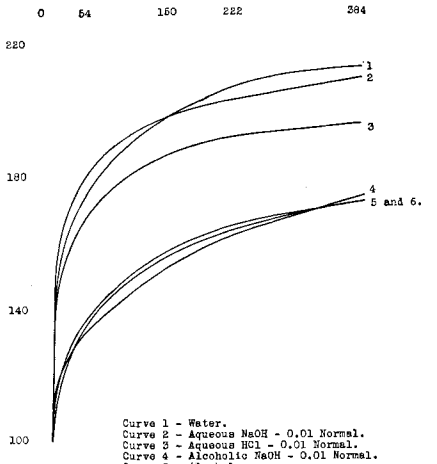
Liquid.	Dry.	After Time Intervals (Hours).							
	0.	6.	12.	24.	54.	83.	150.	222.	384.
Water	100	143	153	166	175	186	195	207	212
Alcohol	100	115	119	128	139	145	157	164	172
Glycerin	100	107	107	116	121	121	132	137	141
Dioxan	100	115	119	124	134	142	157	168	182
Carbitol	100	116	126	138	151	158	172	183	200
Diethylene glycol	100	113	117	126	140	144	156	166	179
Propylene glycol	100	115	115	117	122	126	134	137	144
Ethylene glycol	100	126	128	134	143	150	163	178	189
0.01*N* aq. HCl	100	141	148	162	172	176	185	192	195
0.01*N* aq. NaOH	100	150	159	171	183	188	195	203	209
0.1*N* alc. HCl	100	117	121	129	139	146	158	163	172
0.01*N* alc. NaOH	100	119	121	127	137	141	152	163	173
Mixt. alc. 1 v.—water 1 v.	100	143	153	164	174	177	183	188	188
Mixt. gly. 1 v.—water 1 v.	100	121	126	135	142	149	159	169	182
Mixt. gly. 1 v.—alc. 1 v.	100	123	126	129	139	144	152	163	176
Mixt. gly. 1 v.—alc. 5 v. —water 4 v.	100	135	143	153	166	174	182	188	190
Mixt. gly. 1 v.—alc. 3 v. —water 5 v.	100	140	146	160	174	180	188	194	199
Mixt. gly. 75 v.—alc. 675 v.—water 250 v.	100	134	140	151	166	171	178	183	187
Mixt. gly. 65 v.—alc. 250 v.—water 658 v.	100	138	146	157	172	177	186	191	197

The ternary mixtures of water, alcohol and glycerin penetrate as rapidly as water, while the amount of liquid imbibed is less than that of water and more than that of alcohol (see Graph 10).

The results show that the weight of 0.01*N* aqueous HCl is slightly less than for water while a corresponding quantity of NaOH has practically no effect, with the exception of showing a slightly increased rate of penetration during the first period of imbibition. In alcohol, the absorption is practically unchanged on addition of acid and alkali (see Graph 11).



Graph 10.



Graph 11.

At the end of the experiments, the blocks were cut open and observations made visually as to the indications of completeness of penetration. It was found that glycerin, a mixture of equal volumes of glycerin and alcohol, and propylene glycol were the only liquids which had not completely penetrated the blocks in 384 hours, which was the duration of the experiment. It was found that with glycerin penetration across the grain was only barely perceptible and penetration with the grain was about 1 mm. With propylene glycol penetration across the grain was only barely perceptible and penetration with the grain was about 2 mm. It is interesting to note that in spite of the small distance apparently penetrated by the glycerin and propylene glycol, the imbibition was found to amount to 41 Gm. of glycerin and 44 Gm. of propylene glycol per 100 Gm. of wood.

In order to check more closely the rate of penetration of the various liquids into chestnut wood, blocks were placed in the various liquids and cut open at frequent intervals. In some cases the line of demarcation between the dry and wet portions of the block was rather indefinite, hence penetration experiments were tried coloring the solvents with safranin and methylene blue, respectively. However, it was observed that the dyes penetrated considerably slower than the liquid itself, due most likely to adsorption of the dyes by the wood. It was therefore

concluded that the dyes were inapplicable for this purpose and experiments were made using pure solvents.

Blocks of chestnut wood, averaging 1.75 mm. in thickness and 24 mm. square, were placed in various liquids, and one block from each liquid cut open at various time intervals. In one experiment, blocks with the grain running the long way were used, and in another, blocks with the grain running the short way were used. The liquids, with the time required for complete penetration, are given in Table XIX.

TABLE XIX.—RATE OF PENETRATION OF VARIOUS LIQUIDS INTO CHESTNUT WOOD BLOCKS.

Liquid.	Time for Complete Penetration in Blocks with Grain Running the Long Way.	Blocks with Grain Running the Short Way.
Water	1 day	2.0 hours
Alcohol	2 days (?)	2.5 hours
Dioxan	6 days	6.0 hours
Carbitol	11 days	11.0 hours
Ethylene glycol	14 days	40.0 hours
Diethylene glycol	29 days	70.0 hours
Propylene glycol	Incomplete after 35 days. Penetration about 3 mm. with grain and about 0.5 mm. across grain.	125.0 hours
Glycerin	Incomplete after 35 days. Penetration about 1.5 mm. with grain and not perceptible across grain.	Incomplete after 314 hours.

The results in Table XIX show the comparative rates of penetration of the solvents studied. The results prove definitely that liquids penetrate faster with the grain than across the grain, since the penetration was so much more rapid in the blocks which had the grain running the short way.

Penetration of Various Solvents into Other Woods.—In connection with the tests of swelling on blocks of oak sapwood (see Tables XII–XV) additional measurements were made to compare the absorption of liquids by oak wood, in three conditions, namely, (*a*) fresh, (*b*) dried to constant weight at room temperature, and (*c*) dried to constant weight at 90° C. in an oven. The rates of penetration were determined by weighing in the same manner as in the case of chestnut wood blocks (see "Penetration of Various Solvents into Chestnut Wood").

TABLE XX.—LOSS IN WEIGHT OF BLOCKS OF FRESH OAK SAPWOOD ON DRYING.

	Fresh. After Time Intervals (Hours).								
	0.	3.	10.	24.	46.	240.	528.	720.	1536.
At room temperature	100	97	92	82	70	62	61	61	61
At 90° C. in oven	100	75	68	56	55	55	55	55	55

It is seen that at room temperature the blocks lost 39 per cent of their weight, the constant value being obtained after 528 hours. At 90° C. in an oven, 45 per cent of weight was lost, the constant value being obtained after 46 hours.

The blocks of fresh sapwood of oak absorb 12 per cent additional water. With alcohol, it seems that at first some moisture is removed from the wood by the alcohol as the blocks decrease 4 per cent in weight; later the penetration of alcohol overcomes this effect and after 1536 hours the weight of the blocks is the same as the weight of the original fresh blocks. The large amount of moisture in the oak sap-

TABLE XXI.—ABSORPTION OF LIQUIDS BY OAK SAPWOOD BLOCKS.
(Weight of blocks stated on basis: weight before drying = 100.)

		After Time Intervals (Hours).								
		0.	3.	10.	24.	72.	240.	528.	720.	1536.
Fresh blocks (undried)	Water	100	104	105	107	110	111	111	111	112
	Alcohol	100	98	97	96	98	98	99	99	100
	Glycerin	100	105	107	111	113	113	115	116	117
Blocks dried at room temperature	Water	61	91	96	99	103	106	107	108	
	Alcohol	61	85	90	92	95	96	97	97	
	Glycerin	61	66	70	73	79	85	90	94	
Blocks dried in oven at 90° C.	Water	55	75	87	94	100	103	104	105	
	Alcohol	55	75	82	86	89	91	92	92	
	Glycerin	55	58	59	60	62	65	68	71	

wood apparently allows the entrance of glycerin, as it is seen that the blocks absorb 17 per cent of their weight of glycerin in 1536 hours.

The results show that the imbibition of water and alcohol is somewhat less and of glycerin very markedly less with the blocks dried at room temperature than in the case of the undried and fresh blocks of oak sapwood. Imbibition of water and alcohol is somewhat less and of glycerin very markedly less with the blocks dried in an oven at 90° C. than in the case of the blocks dried at room temperature.

Results similar to those obtained with oak sapwood have been obtained on the wood of an Elberta peach tree and the sapwood of Sassafras variifolium (Salisbury) O. Kuntz (Lauraceæ).

Penetration of Various Solvents into Powdered Belladonna Root.—Studies of the imbibition of solvents by powdered drugs is obviously of importance, since this is the form in which drugs are extracted. There are no data available on the rate or amount of liquid imbibed by powdered drugs.

When obtaining the data on the swelling of powdered belladonna root by the centrifuge method (see Tables XVI and XVII) determinations were also made of the number of cc. of each liquid imbibed by the powdered drug. These data were obtained by reading off the volume of unabsorbed, supernatant liquid in the graduated centrifuge tubes after centrifuging, and subtracting this volume from the known amount of added liquid, which was 8 cc. In the following tables the results are expressed in terms of the volume of solvent in cc. imbibed by 1 Gm. of powdered drug and are based on the average of two determinations.

With the binary mixtures of alcohol and water, it is seen that imbibition decreases as the alcoholic content of the mixture increases. Since only a small proportion of liquid is imbibed after the first 20 minutes it would appear that the powdered drug is rather thoroughly penetrated within that time. The difference in imbibition between 10 and 20 minutes is greater for the liquids consisting largely of alcohol, thus suggesting that for this particular drug penetration by aqueous liquids is more rapid than by alcoholic liquids. Imbibition of glycerin-water mixtures is greater, in the time of the experiment, than of glycerin-alcohol and glycerin-alcohol-water mixtures.

The results in Table XXIII indicate that with increasing fineness of powder, imbibition decreases until No. 80 powder is reached where there is an increase in imbibition. It is possible that the larger particles have a greater proportion of un-

TABLE XXII.—IMBIBITION OF VARIOUS MENSTRUA BY BELLADONNA ROOT IN NO. 40 POWDER.
(Cc. of solvent imbibed by 1 Gm. of powdered drug.)

Menstrua. Volume of: Alcohol.	Water.	Glycerin.	Dry. 0.	Time of Maceration in Minutes. 10.	20.	40.	60.	120.	360.	720.	1440.
0	1	0	0.0	2.6	2.7	2.6	2.9	2.9	3.0	3.2	2.8
1	7	0	0.0	2.6	2.7	2.9	3.0	2.6	2.8	3.0	2.8
1	3	0	0.0	2.3	2.2	2.4	2.4	2.6	2.5	2.6	2.5
1	1	0	0.0	1.8	2.2	2.1	2.2	2.2	2.1	2.0	2.2
7	3	0	0.0	1.8	2.4	2.2	2.1	2.0	2.0	2.0	2.2
5	1	0	0.0	1.5	2.2	2.2	2.0	1.8	1.9	2.0	2.0
9	1	0	0.0	1.5	2.0	2.0	2.2	2.0	2.0	1.9	1.8
1	0	0	0.0	1.4	2.0	1.9	1.9	1.8	1.8	1.8	1.9
0	3	1	0.0	2.6	2.5	2.6	2.6	2.5	2.5	2.5	2.7
0	1	1	0.0	2.5	2.6	2.5	2.6	2.6	2.6	2.5	2.7
0	1	4	0.0	2.4	2.5	2.5	2.5	2.4	2.7	2.7	2.7
3	0	1	0.0	2.0	2.0	2.2	1.8	1.8	2.0	1.9	2.3
1	0	1	0.0	2.3	1.9	1.9	2.3	2.1	2.3	2.1	2.4
1	0	4	0.0	1.7	1.6	1.6	2.3	2.1	2.2	2.4	2.4
250	685	65	0.0	2.0	2.0	2.4	2.2	2.2	2.3	2.5	2.4
500	400	100	0.0	1.8	1.8	1.9	1.9	1.8	2.1	2.0	2.2
675	250	75	0.0	1.8	1.9	1.9	2.0	2.0	2.1	2.0	2.0

damaged cells, and are thus able to hold more solvent in the cell cavities. An opposing tendency, however, arises in the fact that swelling takes place largely near the surface in this type of material, so that small particles show a greater percentage swelling on the basis of this factor taken by itself. It would seem from the results that when the No. 80 powder is reached the increased total surface of the particles allows an increase in imbibition which overbalances the decreased amount of solvent held in cell cavities.

TABLE XXIII.—IMBIBITION OF MIXTURE OF ALCOHOL 5 VOL.—WATER 1 VOL. BY BELLADONNA ROOT OF DIFFERENT DEGREES OF FINENESS.
(Cc. of solvent imbibed by 1 Gm. of powdered drug.)

Powder No.	Dry. 0.	Time of Maceration in Minutes. 10.	20.	40.	60.	120.	360.	720.	1440.
20	0.0	2.2	2.2	2.3	2.1	2.3	2.4	2.7	2.4
40	0.0	1.6	2.0	1.9	1.9	1.8	2.0	1.9	2.2
60	0.0	1.6	1.6	1.4	1.6	1.8	1.6	1.6	1.8
80	0.0	1.6	1.6	1.8	1.8	2.0	1.8	1.9	1.8

Discussion of Results on the Penetration of Various Solvents into Woody Tissues.—The following table lists the solvents used in the penetration study in the order of decreasing rate of penetration into chestnut wood. Along with this are the molecular weights and the amounts of the solvents absorbed by chestnut wood in 384 hours, expressed in moles, grams and cubic centimeters of solvent.

It would seem that smaller molecules should, other things being equal, penetrate in greater amount than larger molecules. The results in Table XXIV show that for those liquids showing complete penetration in 384 hours the amount of liquid which penetrates is inversely proportional in a general way to the molecular weight when the amount absorbed is expressed in moles; when expressed in Gm. or cc. the rule does not hold. However, the rate of penetration is not controlled entirely by the size of the molecule. The slower penetration of larger molecules

would be in accord with a mechanical or sieve theory of penetration, although other factors would enter, such as association of liquids, surface tension, viscosity, vapor pressure, etc.

TABLE XXIV.

Solvent.	Mol. Wt.	Absorbed by 100 Gm. Wood. Moles.	Grams.	Cc.
Water	18	6.22	112	112
Alcohol	46	1.57	72	89
Dioxan	88	0.93	82	79
Carbitol	134	0.75	100	94
Ethylene glycol	62	1.44	89	80
Diethylene glycol	106	0.75	79	70
Propylene glycol*	76	0.58	44	42
Glycerin*	92	0.45	41	33

* Did not penetrate the blocks of chestnut wood completely in 384 hours.

Water and alcohol-water mixture show a rapid rate of penetration with water penetrating in greater amount. Glycerin-water mixture shows a slower rate of penetration than alcohol-water mixture, but a more rapid rate than glycerin-alcohol mixture.

The four glycerin-alcohol-water mixtures used in the U. S. P. and N. F. extractions all show similar rates of penetration and the amount penetrating lies between the amounts penetrated by alcohol and water alone. The results indicate that the variation in the four official menstrua has practically no effect on penetration and imbibition.

The weight of 0.01*N* aqueous HCl is slightly less than for water alone while a corresponding quantity of NaOH has practically no effect. In alcohol the absorption is practically unchanged on addition of acid and alkali.

Penetration of Various Solvents into Fresh and Dried Woods.—The results obtained with fresh and dried wood offer interesting facts. It has been shown that fresh wood takes up considerable water, and that dried wood not only regains the water lost on drying but takes up a further amount of water. This fact may not have received consideration in connection with drug extraction but it has been known to plant physiologists that plant tissues show a water deficit, or unsaturated hydration capacity (4). This condition in the plant is due to the fact that water in the living plant is being used up in metabolic plant processes and is constantly being lost from the surfaces by transpiration; the water available must be divided up among all tissues and accordingly the unsatisfied hydration capacity of a tissue may vary widely according to conditions, for example, fresh oak sapwood absorbed 12 per cent of water, while fresh sassafras wood absorbed 35 per cent of water.

(*To be continued.*)

"The melting point of quinine ethyl carbonate given in the British Pharmacopœia appears to be too high. The melting point of the dried salt of pharmacopœial purity seems to lie between 90° and 92° C. When the salt is purified by recrystallization the melting point may be raised to 91.5° to 92.5° C. The melting point of the substance without previous drying is higher than that of the dried salt and the final point of melting may be above 95° C. The presence of free quinine as an impurity lowers the melting point."—G. R. PAGE, Laboratory British Pharmacopœia Commission.