of castor oil, which is used for both medicinal and technical purposes, was a cultivated crop of some importance in the Middle West during the period following the Civil War until about 20 years ago. Kansas and Oklahoma were the principal producing states and during the early period the beans were crushed in mills located in the Mississippi Valley. In Oklahoma the maximum acreage and production were 2549 acres and 22,481 bushels, respectively, during the early years of this century. According to annual reports of the Kansas State Board of Agriculture that state produced 766,000 bushels from 68,170 acres in 1879. In 1916, the last year included in these reports, only 360 bushels were produced. In 1918 an organized campaign for castor-bean culture was undertaken by the War Department, but the purpose was to supply castor oil for lubricating purposes and, hence, it need not be discussed here. There is at present no domestic commercial production of castor beans.

Two other crops should be mentioned briefly although here again the medicinal use of their products is altogether secondary. Mustard seed is produced in California and Montana in greatly varying amounts. In 1938 the production in these states was 2,600,000 and 15,000,000 pounds, respectively. The other crop is the pungent red pepper of which several varieties are grown in the South and Southwest. Here, as in the case of mustard, its use as a condiment provides the market outlet. From 5000 to 7000 acres, yielding about a million pounds, are grown in southern California, Arizona, New Mexico, Louisiana, Mississippi and South Carolina. These two crops are of some importance in the spice industry but are given only mere mention here because they are not usually considered in connection with medicinal plant crops.

Correlation of the Evaluation of Disinfectants by the Agar Cup-Plate Method and Clinical Experience*

By Rhett G. Harris† *and William A. Prout*‡

Recently the authors were asked to evaluate a series of germicides and determine their efficiency, by *in vitro* methods, for use in the obstetric wards of the Roper Hospital, Charleston, S. C. Usually the criteria for such recommendations are reached by performing tests based upon dilution of the substances under investigation and then determining the time required for the serially diluted material to destroy bacterial growth. Examples of such methods are the Rideal-Walker test, the well-known F. D. A. phenol coefficient and the tissue culture and manometric procedures. If a germicide must diffuse through mucous material to reach the site where its action is desired, as in the birth canal before and after parturition, it is felt by the present authors that methods based upon diffusion would be better than those based upon dilution and simulate more, *in vitro*, the actual conditions under which germicides are used in obstetrics. One such test, the agar cup-plate method which was devised by Himebaugh and published by Ruehle and Brewer in 1931, has been studied by Rose and Miller (1939) in detail, and has been found to yield consistently good results, providing standard procedures are followed. This test was therefore chosen to be used in these investigations.

EXPERIMENTAL

Method of Procedure.—Sterile Petri dishes were poured with 20.0 ml. of melted, cooled nutrient agar (p_H 7.2–7.4) containing in suspension 0.10 ml. of a 24-hour nutrient broth culture of *Staphylococcus aureus*. The plates were allowed to harden after which time test "cups" were cut from the agar with a sterile cork borer having a diameter of 15.0 mm. To this "cup" was added 0.20 ml. of the solution under investigation; the plate was covered with a porous, unglazed porcelain cover, incubated at 37.5° C. for 24 hours at which time measurements of the zones of inhibition were made. The zones produced by the various germicides requested in this investigation are shown in Table I.

Table I.—Widths of Inhibition Zones Produced by Germicides

	Germicide	Zone of Inhibition, Mm.
1.	Merthiolate (Tr. 1:1000)	18.0
2.	Iodine (3.5% solution)	16.0
3.	Iodine (3.5% tincture)	12.0
4.	Mercresin	12.0
5.	Metaphen (Tr. 1:200)	9.0
6.	Mercurochrome (surgical)	9.0
7.	Mercurochrome (4.0% tincture)	8.0
8.	Mercurochrome (4.0% solution)	6.0
9.	Hexylresorcinol (ST 37)	5.0
10.	Amphyl (undiluted)	4.0
11.	Amphyl (2.0% solution)	3.5
12.	Amphyl (5.0% solution)	3.5

The question arising after the completion of such a series of tests is, obviously, of what significance are

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the figures which represent the width of the zone surrounding the test cup? The order of the respective zones may be arranged, as above, to give the most and the least reactive germicides and also determine the relative positions of the intermediate substances. However, what relationship do they bear to one another? In other words, what relationship exists between zones, diffusibility and potency? If we look upon the agar cup-plate method in terms of the amount of material that is rendered sterile per unit volume of germicide, we will be approaching a figure that will give us more nearly the information that we desire. Such a figure, the coefficient of diffusion, may be determined by dividing the volume of material rendered sterile by the volume of germicide added. The latter figure will remain constant

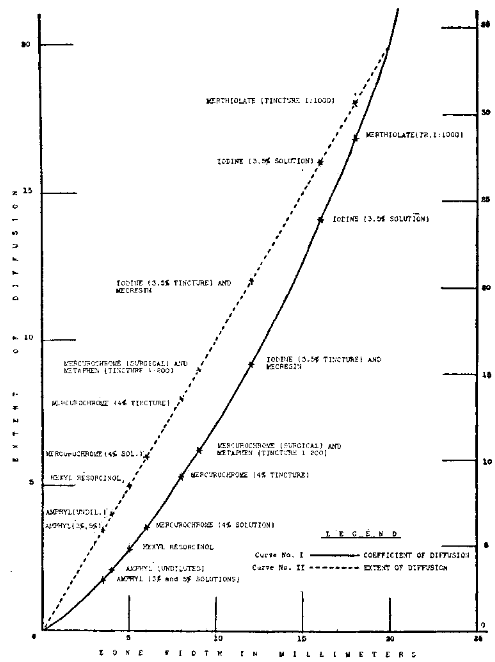

Fig. 1.—Curves Showing Relationship of Coefficient of Diffusion of Germicides to Extent of Diffusion.

in the agar cup-plate method at 200 cu. mm.; the former figure is calculated from the general formula

$$V = \pi h(r_1 + r_2)(r_1 - r_2) \qquad (1)$$

where V = volume of a cylindrical shell
h = altitude of the cylindrical shell
r_1 = radius of the outside ring
r_2 = radius of the inside ring

and is found to be, under the standard conditions of the test to become

$$V = 9.739.x(15 + x) \qquad (2)$$

where x = the width of the zone.
Substituting variables of x in equation (2) and plotting the corresponding calculated values of V against them, we obtain the curve (see Fig. 1) having the slope

$$dy/dx = 146.085 + 9.739.x \qquad (3)$$

which may be proved by differentiating equation (2).

If we calculate, for the substances tested, their respective coefficients of diffusion (see Table II) and place them on the curve plotted above (see Curve II, Fig. 1) we may see the relative position of one to the other. On the other hand, if we merely plot the extent of diffusion, in terms of the zone width, and place the data of Table I upon such a curve (see Curve I, Fig. 1) we note that the relative position of the germicides is much altered, especially in the cases of germicides having a narrow zone. This obviously leads to the overestimation of these substances. The extent of this error is found to decrease with increases in the width of the zone; thus this consideration decreases in importance in testing the more powerful germicides.

Table II.—Coefficients of Diffusion of Germicides

	Germicide	Coefficient of Diffusion
1.	Merthiolate (Tr. 1:1000)	28.92
2.	Iodine (Aq. sol. 3.5%)	24.15
3.	Iodine (Tr. 3.5%)	15.78
4.	Mercresin	15.78
5.	Metaphen (Tr. 1:200)	10.52
6.	Mercurochrome (surgical)	10.52
7.	Mercurochrome (Tr. 4.0%)	8.96
8.	Mercurochrome (Aq. sol. 4.0%)	6.13
9.	Hexyl resorcinol (ST 37)	4.87
10.	Amphyl (undiluted)	3.78
11.	Amphyl (2.0% solution)	3.15
12.	Amphyl (5.0% solution)	3.15

The results shown in Table II are of much interest in that there has been found a direct correlation between the efficiency, as calculated above, and their usefulness in the obstetric wards. No data will be presented in this preliminary report to substantiate this point inasmuch as a detailed study of each substance is now being undertaken in the hospital. The statement is based upon personal communications with Dr. Lester Wilson of the staff of the hospital in which the germicides have been in use, whose years of experience back up these results.

The figures are also of importance in that they show no correlation between the coefficient of diffusion and the Hg content[1] of the mercurials studied. This is congruent with the finding of Miller and Rose (1939) and is to be explained upon the characteristics of the individual germicides.

Most procedures based upon dilution place iodine low in the series, as Bronfenbrenner, *et al.* (1939), whereas in obstetrical practices, providing adequate nursing facilities are available, it is one of the best germicides we know. We find that iodine is more correctly evaluated when tested by this method, that is, placed high in the series superseded only by Merthiolate.

[1] Merthiolate 48% Hg, Metaphen 57% Hg, Mercurochrome 26% and Mercresin 58% Hg.

There is apparently no general relationship that exists between tinctures and solutions of germicides and their efficiency following diffusion, as shown by the conflicting results obtained with such preparations of iodine and mercurochrome. Topley and Wilson, generalizing, state: "Germicides dissolved in alcohol . . . are deprived of the greater part of their power." In this study this seems to hold true only in the case of iodine. Solutions of germicides containing soaps, such as Amphyl, apparently do not diffuse readily through collodial material. This is shown by their low coefficient of diffusion. Two factors probably are important in any consideration of such solutions; first, soaps alter the germicidal powers (Tilley and Schaffer, 1925, and Tilley, 1939) of germicides and, second, as noted in these experiments, the soap brought about changes in the colloidal gel itself thus preventing diffusion through it. Such solutions cannot be accurately judged by the agar cup-plate method, but the fact remains that Amphyl and its solutions have found little value in obstetrics where diffusion through mucous-like materials is desired.

A detailed study involving the various germicides mentioned in this treatise, as well as many others, is now being carried out in respect to diffusibility and clinical usefulness.

CONCLUSIONS

1. The coefficient of diffusion has been explained and its significance discussed.
2. Germicides having a high coefficient of diffusion have been found to be of value in obstetrics; those having a low coefficient were found to be of little value.
3. The agar cup-plate method is recommended especially for the evaluation of germicides where their use will involve diffusion through colloidal material.

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Problems Encountered in the Manufacture of Compressed Tablets*

By L. W. Busse and A. H. Uhl

The chief problems encountered in the manufacture of compressed tablets are binding, picking, capping, sticking and splitting. These problems are particularly annoying because they do not occur until the last step in the process of manufacture; namely, that of compression.

Capping and splitting are alike in the respect that they usually occur together and in many cases may be attributed to the same cause.

Capping is the term applied when the upper surface of the tablet splits off.

Splitting is the term applied when the tablet does not hold together after compression.

In discussing the remedies for capping and splitting, one must of course first know the reason for their occurrence. The reason given by many authors is that of excess powder in the granulation. This excessive amount of fine powder requires a great deal of pressure to form the tablet. It has been said, that this extreme pressure makes the tablet very hard in the center causing the upper surface of the tablet to split off. This fine powder also causes air to be trapped in the powder upon compression and after release of the pressure causes the upper surface of the tablet to split off.

Capping and splitting may also result from a worn upper punch, too much pressure or too damp or too soft a granulation.

It has been our experience, that in most cases capping and splitting were caused by

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