THE BEHAVIOR OF IODINE SOLUTIONS AT LIQUID-SOLID INTERFACES.

II. THE IMPORTANCE THEREOF IN THE PREPARATION OF NEW IODINE ANTISEPTICS.

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DEPENDENCE OF DOSAGE UPON PHYSICAL BEHAVIOR.

Antiseptic solutions depend for their effectiveness first of all upon their chemical fitness for the designated purpose, and, in addition, upon the physical behavior that governs the facility with which they reach the surface that is their assigned site of action.[3] The physical behavior is that of a two-phase system in which an antiseptic solution is the liquid part and the bacteria upon which it acts is a solid or gel phase. The dose which the bacterium receives per unit of weight depends upon the concentration of antiseptic agent per unit of area as governed by the physical behavior of the solution and upon the ratio of the surface to the weight of the bacterium itself.

The surface behavior of an antiseptic solution becomes increasingly important when microscopic organisms are considered: as the size of the organism decreases, its volume changes as the cube of its diameter, whereas the surface changes as its square. The surface per unit of weight therefore increases rapidly as the diameter of the organism becomes less, and consequently the surface behavior of the contact agent becomes more and more important. In the past we have assumed that the dose received upon application of a contact medicinal was entirely dependent upon the concentration of the active agent in the solution applied. That this in general is not a valid assumption is evident from a consideration of the question in terms of the physical chemistry of surfaces. That it is not valid in the specific instance of iodine antiseptics is clear from the investigation of adsorption of iodine upon solid surfaces from various types of solution. This paper is presented in an effort to use the available physical and physiological data to prepare a modified iodine antiseptic, taking advantage of these properties to increase its facility and, if possible, its effectiveness in use.

The iodine solutions now in most extensive use may be classified roughly as follows: iodine in volatile solvents, such as the familiar tincture; iodine in solution in non-volatile organic solvents, such as the glycerol preparations of iodine; and, iodine in aqueous solutions of iodides, such as Lugol's solution.

Of these preparations the volatile solvent class represented by the familiar U. S. P. tincture is the most popular, because of the facility with which iodine in such a solvent can be applied and left in place. It has also been thought that the tincture depended for its penetrating power upon the alcohol that it contains. The objection to preparations of this most used type is that as applied in practice they cause irritation to subcutaneous tissue and that they also often cause excessive sur-

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face irritations, known as iodine burns. The initial irritation giving the pain reaction, usually accepted as characteristic of iodine solutions, may be due to any of the chemical or physical effects of one or all of the several constituents. The excessive irritation causing destruction of tissue is usually due to a lack of adjustment of the dose between the amount of active agent required to give adequate antisepsis and that causing tissue destruction. Dosage is therefore a most important consideration upon which this difficulty depends and it is this factor that we must first consider. The dose applied from a solution in a *volatile solvent* depends first of all on the strength of the solution. This may be readily regulated. It depends finally, however, on the number and depth of the successive puddles of solution that are allowed to *dry* upon the treated surface. This, entirely subject to individual practice, is difficult to control, even when a knowledge of the proper dosage makes possible an intelligent effort to do so. If, however, the solution is *not allowed to dry*, an equilibrium is reached between the antiseptic agent at the surface and in the solution. This concentration ratio has a definite value, depending upon the solution that is applied, and upon the nature of the surface. If it were possible to prepare a solution in which this equilibrium concentration was adequate for germicidal effectiveness, and if this proper dosage would remain after the excess solution was removed, a method of application based upon this equilibrium could be used to insure a certainty of dosage that would be to some degree independent of individual practice.

THE PHYSICALLY DESIRABLE SOLUTION.

The investigation of the adsorption behavior of iodine antiseptics mentioned before, in which the concentrations of iodine at surfaces in several types of solutions have been determined, has given us data from which we can devise an iodine solution basing its dosage upon the equilibrium principle outlined above, which will be most likely to meet the requirements for an antiseptic. It was found that the partial wetting power of free iodine from aqueous iodide solutions is much greater than that from alcoholic solutions of like free iodine strength. For example, it has been found that the iodine dose deposited and adhering to silk fibre from a 3% iodine solution is approximately 10 times as great as that deposited from a solution of like iodine and potassium iodide strength in 70 per cent ethyl alcohol. Glycerin solutions were found to be similar to alcoholic solutions in adsorption behavior. Aqueous iodide solutions which offer the best possibility of securing an adequate and persistent dose of iodine upon a surface, which is independent of the fate of the residual solution, are in turn governed in their behavior by the ratio of iodine to iodide in them. Lugol's solution, which is superior to an alcoholic tincture for this particular type of application, is inferior to a solution of like free iodine strength but containing a decreased amount of iodide ion. We find indeed that by adjusting the ratio of iodide to iodine a 3 per cent solution of iodine can be prepared which will deposit approximately the same amount of iodine on a surface as a 5 per cent Lugol's solution. Assuming that the dose deposited from this 3 per cent aqueous solution is adequate to give germicidal effectiveness, let us recount what we have gained in making such a solution.

First, we have at hand a solution that will give a definite and adequate dose upon a tissue surface that will remain there after the excess of solution is removed.

Secondly, we have eliminated any effects, beneficial or otherwise, that might come from the volatile solvent, such as alcohol.

Thirdly, by decreasing the iodide-iodine ratio we have lowered not only the amount of iodide in the solution, but have also decreased the amount of iodine necessary to deposit a given dose and thereby have materially reduced the chemical and osmotic contributions to pain that the materials would make. In the comparison with 5 per cent Lugol's solution mentioned above, this means an elimination of 40 per cent of the iodine and 70 per cent of the iodide.

THE SOLUTION CHEMICALLY ADJUSTED.

We have by the above considerations made a logical adjustment of the constituents of our solution, eliminating from it, in so far as is possible, those factors which contribute nothing desirable to its physical or chemical behavior.

Those constituents making only an indirect contribution, and which cannot be eliminated, we may adjust further from the chemical standpoint. The most important of these are the positive ions accompanying our indispensable iodide ions. Potassium has been used almost universally in iodide solutions, though it is evident that, if all possible physiological applications of iodine and iodide solutions were considered, a like amount of sodium would be preferable. A solution containing only sodium as its positive metallic ion, having desirable adsorption properties, can be made up to a desired strength using:

Iodine	1.000 part
Sodium iodide	1.180 parts

Indeed, if an iodide solution were to be used in contact with tissue in large amounts for some time, an ion ratio similar to that of the blood would approach the theoretical ideal. Such a solution, theoretically balanced, may be prepared using

Iodine	1.000 part
Calcium iodide hexahydrate	0.044 part
Potassium iodide	0.048 part
Sodium iodide	1.104 parts

The solution can be made to any desired iodine strength in the above ratio.

THE SOLUTION UNDER TEST AND IN PRACTICE.

Clinical trials of solutions of the above type over a period of a year have established the concentrations most suitable for meeting various conditions. For hospital use, for the preparation of operating fields and for direct application to open wounds, a solution of 2 per cent free iodine strength has been found to be most satisfactory. For use in home medicine cabinets and for use in the mouth, 3 per cent strength is to be preferred. In practice, the solution is applied in excess and allowed to remain in place from 15 to 30 seconds. The excess solution may then be removed with absorbent cotton or by washing with water, and the iodine dose will remain behind. A number of arbitrary tests have been made upon solutions of these selected concentrations, and the results thereof will now be recounted along with other properties that have been brought out by clinical observation.

Staining Power.—A striking demonstration of the difference between this aqueous solution and one of similar free iodine strength in alcohol may be made by comparing the amount of iodine remaining on a finger immersed in one solution and washed immediately, with that remaining on a finger similarly treated in the other solution. If the fingers are immersed for 15 to 30 seconds, it will be found after washing with water that a considerable dose of iodine remains on the finger which has been treated with the aqueous solution, while the finger from the alcoholic solution is practically freed from iodine.

Penetration.—The tests of the penetrating power of alcoholic compared with aqueous solutions which have been made, obviously do not duplicate exactly the conditions existing when iodine is applied to live skin or other tissue. They should, however, serve to point out major differences in behavior of the two types of solution. In making the tests freshly prepared dehaired guinea-pig skin membranes were fastened over the end of glass cylinders. The solutions to be tested were placed in tubes suspended in a dilute solution of potassium iodide. Special precautions were taken to maintain the same hydrostatic head with solutions of different specific gravity. The amount of iodine passing through each membrane in a given time was determined by titration. A number of runs alternating the solutions under test were made with each membrane. It was found that with a 3 per cent aqueous solution of iodine the rate of penetration of iodine through the membrane was about twice that of the alcoholic solution of like strength. The difference is undoubtedly due to a combination of physical and chemical causes. Among those that are of interest are the effects of the solvent on the membrane, such as dehydration in the case of the alcohol, and the osmotic effect of the iodide salt in aqueous solution. The difference in iodine concentration at the migrating surface probably plays some part as well.

The fact that the above experiments were made without attempting to remove the natural fat from the skin, makes the test more interesting in the light of the part that the fat solvent action of alcohol has played in the discussions of penetration in the past. Similar determinations of the time required for penetration of alcoholic and aqueous solutions through frog skin, made by an independent investigator, have given results that are in accord with the above findings. In both types of test it was noted that the skin that had been in contact with aqueous solution was much more deeply stained with iodine than that which had been in contact with those containing alcohol.

Pain.—Quantitative estimates of the pain reaction are practically impossible. A wound once treated is so modified that upon receiving a second similar treatment it will not react in the same manner. In addition, we have no standard wound upon which comparisons can be made. Neither do we have a calibrated individual complete in every detail in sensitivity, but completely devoid of pride, whose reactions may be accepted as a standard. Such refinements are not necessary to evaluate the difference between the tinctures and the aqueous solutions, but mention is made of them to demonstrate the futility of attempting to make fine distinctions. Clinical observations of the effect produced by the aqueous solution, while not establishing it as painless, show it to be capable of exhibiting the benefits of iodine without excessive discomfort to the patient.

Iodine Burns.—The efficacy of the controlled dose in preventing iodine burns is

most effectively demonstrated by the fact that after the preparation of fields for abdominal operations no so-called iodine blisters are found, even on the marginal areas where the excess solution from the field collects and usually concentrates.

Effectiveness.—The concentrations mentioned above have been chosen on the basis of their clinical effectiveness, and on further evidence of their bactericidal effectiveness, as judged by accepted means of test. Bacteriological data on the solution in question will be presented with data on other iodine solutions in a later paper by Gershenfeld and Miller. The comparative phenol coefficients of various iodine solutions demonstrate the importance of considering dosage in terms of surface concentration. The aqueous solution in question has a phenol coefficient that is about 15 per cent greater than an iodine solution of like strength made up with alcohol. It is unlikely that this effect is due to the favorable action that alcohol has exhibited on the growth of the bacteria or that it has chemically inhibited the effect of the iodine. When the surface behavior of the iodine in the two solutions is considered, it is more logical to suppose that, even though the alcoholic solution is approaching an aqueous solution at the dilution where the final determination of the phenol coefficient is made, the difference in surface concentration is still appreciable. The importance of surface effects as influenced by the solvent would be much more marked in solutions used without dilution of the solvent. The magnitude of these differences will remain a matter of conjecture pending the development of tests for the bacteriological evaluation of antiseptic solutions under the conditions of use.

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ISOLATION AND STUDY OF THE SAPONIN CONTENT OF THE JUICE AND LEAF OF THE AGAVE PLANT, MAGUEY, MANSO FINO.*

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The saponin occurs in two groups of agaves which are known as the Amoles and Magueys (1). The leaves and roots of the Amoles are sold in the markets as a substitute for soap because of the ability of the saponin content to lather freely in water. The Magueys are known to the Mexicans as Pita Magueys, Mescal Magueys and Pulque Magueys. The latter are grown in the region of Ometusco in the State of

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[1] This paper is the result of investigations undertaken in Mexico City by the writer while on leave from the Alabama Polytechnic Institute.