

Table I.—Per Cent Positive Reactions of Alkyl Sulfates and True Soaps on Human Skin (24 Males and 14 Females; Soap or Alkyl Sulfate Concentration, 0.0225*N*; NaCl, Na₂CO₃ and Na₂SO₄ Concentration, 0.002*N*)

	C-8, Per Cent	C-10, Per Cent	C-12, Per Cent	C-14, Per Cent	C-16, Per Cent	C-18, Per Cent
Sodium alkyl sulfates	5	5	43	24	5	0
Sodium soap	2	19	70	41	4	0
Potassium soap	13	15	89	54	13	10
Sodium alkyl sulfates plus sodium chloride	14	25	57	72	5	0
Sodium alkyl sulfate plus sodium sulfate	14	25	58	67	5	0
Sodium alkyl sulfate plus sodium carbonate	31	47	85	39	8	8

purpose of comparison. While the number of tests should be greater, the results should offer some idea as to the relative power of the different alkyl sulfates to cause skin irritation.

The values for the sodium alkyl sulfates are striking in that they show that the alkyl sulfates are much less irritant to the human skin than the sodium or potassium salts of the pure fatty acids. The results of the sulfates, however, are similar to the results of the others in that lauryl and myristyl derivatives possess the greatest irritant properties. With the addition of minute quantities of the salts of strong acids and strong bases, NaCl and Na₂SO₄, the power to produce irritation in every case except palmityl and stearyl sulfates is decidedly augmented. This increase in activity is pronounced with lower members of the series and reaches its maximum with sodium myristyl sulfate. Since there is the presence of a common ion in sodium which should give a diminution of the dissociation of the alkyl sulfates, the results suggest that the increased amount of the undissociated alkyl sulfate is responsible for the augmentation of the irritant action. Palmityl and stearyl sulfates do not respond because of their low solubility. In the case of the addition of an alkaline salt, Na₂CO₃, the results are somewhat different. Here the augmentation reaches its maximum with lauryl sulfate, and in the case of the lower members, it is much greater than the increase noted with NaCl or Na₂SO₄. Sodium myristyl sulfate in the presence of the carbonate was a jelly while in the presence of the other salts it was not—this should explain the shift in the results. The high values for caprylyl, capryl and lauryl sulfates would be expected since there is not only the presence of a common ion but an increase in the alkalinity as well. Controls of the inorganic salts were negative.

CONCLUSIONS

1. Pure sodium alkyl sulfates are less irritant to human skin than the pure sodium or potassium salts of the saturated fatty acids from C-8 to C-18.

2. Sodium lauryl sulfate is the most frequent cause of skin irritation of the series studied, but it is closely followed by myristyl sulfate.

3. Sodium chloride and sodium sulfate enhance the irritant action of these soap substitutes markedly. This enhancement is greater with sodium carbonate.

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Iodocholeate*

Its Efficiency as a Germicide and Its Clinical Performance

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In the field of disinfection and bacterial control, inorganic iodine, despite its obvious disadvantages, has been used in alcoholic or aqueous solutions practically unchanged for more than a century. However, the extensive use of iodine is limited by its irritation, corrosiveness and other disturbing properties.

As to iodine's effectiveness as a germicide in comparison with modern antiseptics, Gershenfeld and Miller (1) stated in 1931: "From the standpoint of bactericidal action, 3% solutions of iodine were found to be superior to any of the other commonly used bactericidal agents in the dilutions most frequently employed." Nye (2) several years later confirmed in effect their findings.

In 1936 Goedrich brought forth a new iodine compound which was named Iodocholeate. This new compound, the result

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Table I.—Bactericidal Performance

Organism: *Staphylococcus aureus*; 50% horse serum plus germicidal dilution; (1 hour allowed to elapse before running test); temperature 20° C.; method, F. D. A.

Germicide	Dilutions	Contact Time			Phenol Coefficients of Available Iodine
		5 Min.	10 Min.	15 Min.	
Tr. Iodine U. S. P. 7.13%	1/10	—	—	—	Iodine in Tincture, 3.5
	1/15	+	—	—	
	1/20	+	+	+	
Iodocholeate aqueous soln. 2.10%	1/10	—	—	—	Iodine in Iodocholeate, 10.0
	1/15	+	+	—	
	1/20	+	+	+	
Tr. Iodine U. S. P. 7.00%	1/10	—	—	—	Iodine in Tincture, 3.6
	1/15	+	—	—	
	1/20	+	+	+	
Iodocholeate (15% alcohol) 2.46%	1/15	—	—	—	Iodine in Iodocholeate, 11.8
	1/20	+	+	—	
	1/25	+	+	+	

of a partial chemical combination and partial adsorption of iodine with sodium glycocholeate and taurocholeate, as contained in natural bile, obviously overcomes all of the disadvantages of inorganic iodine. It is non-irritating, non-volatile and not as destructive to animal tissues as is inorganic iodine, and even its toxicity by comparison has been considerably reduced. Iodocholeate is easily soluble in water or alcohol. Two and five-tenths per cent solutions of this compound containing 35% alcohol were found to be physically stable and to maintain a permanently high germicidal action.

EXPERIMENTAL

In order to have a basis of comparison of the germicidal action of Iodocholeate with popular proprietary as well as non-proprietary solutions which are ordinarily used as antiseptics, a technique outlined by Nye was followed which consisted of obtaining the minimum concentration necessary to kill a standardized strain of *Staphylococcus aureus* at 37° C. within 5 minutes. Nye's results, obtained by this technique, show that most of the germicides in popular use possess no bactericidal action after a dilution of 1:16. The Compound Solution of Iodine U. S. P. 5% displayed the best performance in his series, showing a killing action in a dilution of 1:256. However, the Iodocholeate 5% aqueous solution, under identical conditions, even exceeded this action, for it displayed a germicidal action over and above a dilution 1:512.

In order to reproduce conditions present during the use of antiseptics in wounds, cuts, etc., wherein large quantities of organic matter such as lymph, blood, tissue fluids, etc., are present and which impede the action of germicides, phenol coefficients were determined using Iodocholeate in the presence of much organic matter (50% horse serum) and compared with those of Tincture of Iodine.

The results of such tests are shown in Table I. Despite the presence of such a large amount of organic matter (50% horse serum) the germicidal ac-

tion of Iodocholeate, as measured in terms of the phenol coefficient of its available iodine, reveals itself to be approximately three times greater than the phenol coefficient of the available iodine in the tincture.

Few antiseptics possess an action against spore-forming organisms, such as *Bacillus subtilis*. Aqueous solutions of Iodocholeate in 4% and 5% concentrations have proved themselves to be lethal to these organisms in *five minutes*. Two and five-tenths per cent solutions of this compound containing 35% alcohol killed the same organisms in a period of ten to fifteen minutes. This action is quite surprising, for further tests have shown that a 7% Tincture of Iodine did not produce an effective action even after two hours' contact, nor did a 20% Solution of Formaldehyde show any killing effect within one hour on these same spore formers.

In recent years infections by fungi, particularly those mycotic infections causing a condition known to the layman as "athlete's foot," have become increasingly prevalent.

This new compound has demonstrated highly satisfactory fungicidal properties. Lever (4) in a series of laboratory tests on common pathogenic fungi with Iodocholeate concluded that this compound had a greater killing power on fungi in the presence of organic matter than Tincture of Iodine. He also proved that the fungicidal power of this compound in Sabouraud's medium (a fungi medium) remained constant within a two-week period, whereas Tincture of Iodine became less potent (Fig. 1).

The photographs in Fig. 1 show the results of tests over a period of 10 days carried out by Deno,¹ using Iodocholeate preparations against *Trichophyton rosaceum*. The clear zone in the center of each plate shows the effective penetration and killing power of Iodocholeate on fungus growths. These results further confirm Lever's findings.

In a study to determine the reason for the germicidal and fungicidal properties of Iodocholeate, it was found, surprisingly, that these properties do not depend alone on its available iodine. For, when

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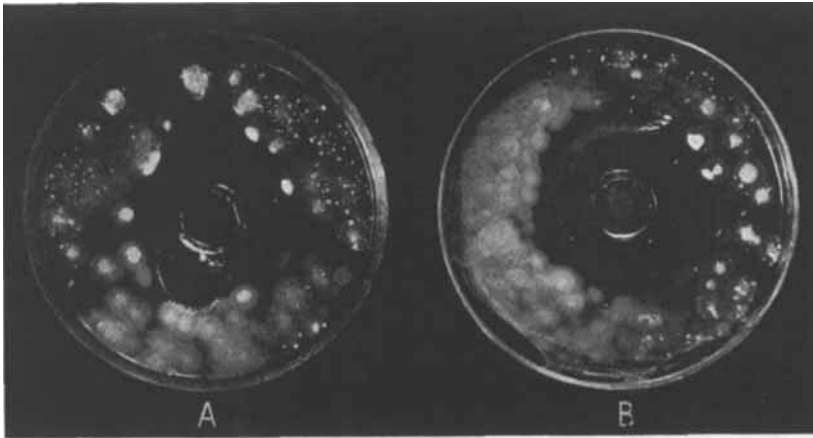


Fig. 1.—Fungicidal Activity. Organism: *Trichophyton Rosaceum*. (A) Iodocholeate Solution, (B) Iodocholeate Concentrated Powder.

this iodine was removed with sodium thiosulfate, the remaining compound was still effective; one part in 10.5 parts of water killed the *Staphylococcus aureus* in less than 5 minutes.

Another interesting fact about Iodocholeate is that it combines much less rapidly with organic matter than iodine and thus affords a more prolonged and better protection. Data to show this are given below. Seventy-five hundredth cc. of a 2.3% Tincture of Iodine and the same amount of an Iodocholeate solution of the same strength were each placed in five cc. of horse serum and then titrated with thiosulfate (after different time intervals) and the following was recorded:

Table II.—Rate of Combination with Organic Matter

Time (Min.)	Tincture of Iodine (% Iodine Remaining)	Iodocholeate Solution (% Iodine Remaining)
2.5	2.8%	59.4%
5.0	1.2%	54.3%
10.0	0.3%	46.0%
15.0	None left	42.1%

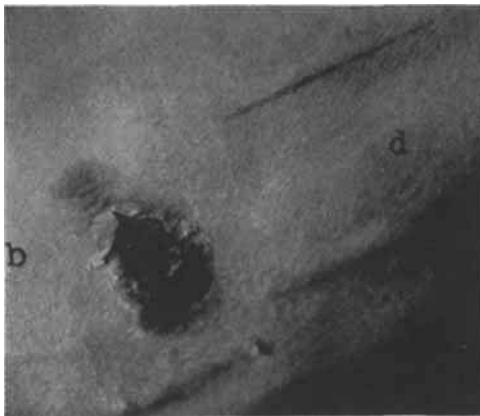


Fig. 2.—Photograph Showing Results of Patch Test on Arm. (b) With 5% Tincture of Iodine Ointment. (d) With 5% Iodocholeate Ointment.

Even though the Iodocholeate has much more available iodine than the Tincture after prolonged contact with organic matter its toxicity is considerably less. To show the low toxicity a 2.6% Iodocholeate solution was administered orally to rabbits of 4¹/₄ lb. weight, and the results are given herewith:

Table III.—Effect of Oral Administration

Type of rabbit used: equal-sized rabbits; weight, approximately 4.5 lbs.; color, white albino

Rabbit	Iodocholeate	Dosage	Result
1	2.62% iodine	2 cc. + 18 cc. water	No ill effects
2	2.62% iodine	4 cc. + 31 cc. water	No ill effects
3	2.62% iodine	8 cc. + 42 cc. water	Suffered loss of appetite for 4 days, then returned to normality
4	2.62% iodine	4 cc. undiluted	No ill effects
5	2.62% iodine	4 cc. undiluted	No ill effects
6	2.62% iodine	10 cc. undiluted	Loss of appetite for 4 days, returned to normality
7	2.62% iodine	10 cc. undiluted	Loss of appetite for 4 days, returned to normality
8	2.62% iodine	16 cc. undiluted	Loss of appetite. Death occurred after 3 days

Then, to demonstrate Iodocholeate's lack of irritation a guinea pig's back was shaved and an incision was made at the shoulder, one-half inch long and a quarter of an inch deep. Into this incision dry Iodocholeate powder (15% available iodine) was then deposited. The wound healed in four days and did not show any sign of irritation (Fig. 2).

In the close-up view of an experiment performed on an arm by Lever, shown in Fig. 2, one can readily note the large amount of necrosis caused by a Tincture of Iodine ointment, while Iodocholeate ointment shows no tissue damage.

Another important property of antiseptic solutions, according to McCulloch (5) as well as Frobisher (6), is the surface tension of these solutions. Germicides having a low surface tension penetrate into minute crevices and broken tissue more readily. Averaging a series of six surface tension results which we obtained in tests on various samples of a 2.5% Iodocholeate solution containing 35% alcohol, the surface tension was found to be 33.8 dynes at 25° C., less than half that of water, which possesses a surface tension of 73 dynes. Hence it is seen that Iodocholeate has high penetrating power.

Because of the physical and chemical properties of Iodocholeate it can be used in many ways in the field of antiseptics. Solutions of this compound have been found to be particularly suited for impregnation of gauze pads and adhesive bandages. On gauze pads, unlike inorganic iodine, Iodocholeate remains stable, non-volatile, does not destroy gauze fabrics and is neither corrosive nor irritating when applied to broken or unbroken skin (Fig. 3).

Figure 3 shows the effect of Iodocholeate ointment, prepared with an oxycholesterol-petrolatum base, and of gauze pads, impregnated with Iodocholeate solution, two of the many convenient forms in which this product can be used. The clear zones in this picture reveal the combined germicidal and penetrating action of Iodocholeate.

Also a surgical dusting or wound powder has been prepared, using bentonite, a clay powder as a base.

With bentonite, containing only 0.8% of available iodine, Iodocholeate, when tested by the F. D. A. agar cup method, demonstrates a far-reaching clear zone of penetration, whereas thymol iodide and iodoform in 100% strength fails to produce any appreciable effect.

In the final analysis the real test for a germicide lies in its clinical performance. Iodocholeate has been used clinically over a long period of time in a variety of cases.

The statement of Dr. A. H. Haskin, of the City Health Department of Newark, N. J., is typical of

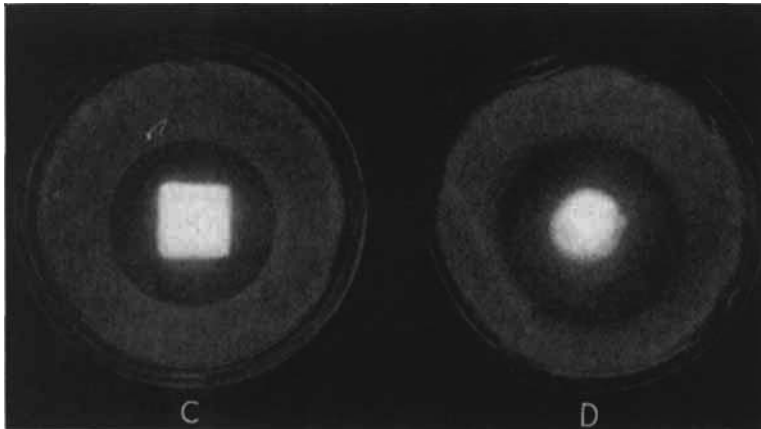


Fig. 3.—Photograph Showing Germicidal Effect of Iodocholeate Impregnated Gauze and Ointment (2.5%). Organism: *Staphylococcus Aureus*. (C) Clear Zone: 11 Millimeters. (D) Clear Zone: 15 Millimeters.

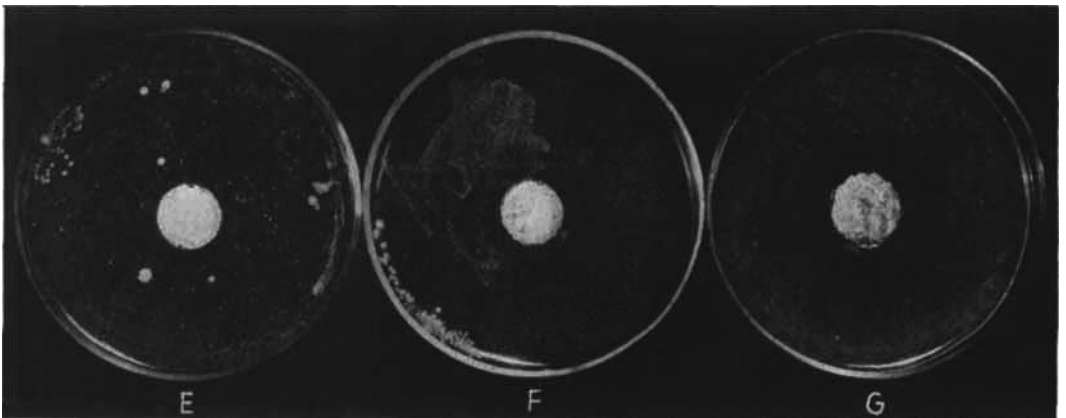


Fig. 4.—Photograph Showing Germicidal Action Compared with Iodoform and Thymol Iodide. Organism: *Staphylococcus Aureus*. (E) Iodoform (100%), (F) Thymol Iodide (100%), (G) Iodocholeate Dusting Powder (0.8%).

many reports that have been received about Iodocholeate.

Quoting him verbatim: "We have been using Solution Iodocholeate for the past two years in the surgical clinic of the Newark Health Department, and have compared its results with those of other antiseptic solutions used in this clinic. The results are gratifying.

"We have treated over 5000 cases with Iodocholeate. Among these were included ordinary lacerations, infected wounds and preoperative sterilization of the skin, and infected lesions in the mouth. In the matter of sinuses, we have placed packs soaked in Iodocholeate solution into the sinus tracts. Bandages may be used on surfaces painted with Solution of Iodocholeate without fear of necrosis.

"In antiseptic properties, we find that Iodocholeate is just as effective as Tincture of Iodine, and yet without its 'burning' properties. It also is less escharotic than Iodine and for this reason is used very effectively on lesions of the mouth, and as packs in large infected wounds. Healing of wounds occurs more quickly when Iodocholeate is used than when the U. S. P. Tincture of Iodine is used.

"It is my opinion that as an all-around antiseptic, it is superior to other solutions commonly used in this clinic."

Lever employed Iodocholeate in the treatment of mycotic infections of the skin, and found that faster improvement was obtained with Iodocholeate than with other fungicidal agents, such as sulfur-salicylic acid ointments, compound ointment of benzoic acid, N. F. and mercurochrome.

One hospital reported the use of Iodocholeate in a diversity of cases such as in appendectomy, hysterectomy, caesarian, perineorrhaphy, removal of rectal fistula and hernectomy. In all the cases in which this preparation was employed, no postoperative infection or tissue necrosis resulted.

These favorable clinical reports comprise but a few typical of many which have been received, and so confirm laboratory findings.

SUMMARY

Further studies on Iodocholeate, the newly discovered iodine-choleate organic germicide, have brought forth the following findings:

Germicidal Efficiency.—Despite the presence of organic matter (50% horse serum) which diminishes the bactericidal effectiveness of all germicides, Iodocholeate demonstrated itself to be approximately three times more effective as a bactericide against vegetative organisms than ordinary solutions of iodine under identical conditions. Against spore-forming bacteria *Bacillus subtilis* it showed a killing action within five minutes.

Fungicidal Efficiency.—It was proved that Iodocholeate had a greater and more prolonged fungicidal power than Tincture of Iodine in the presence of protein.

Double Action.—Even when the available iodine in Iodocholeate was removed, the remaining iodized

choleates demonstrated a remarkable germicidal effect.

Oral Tolerance.—Experiments made on rabbits show that a dose of 2 cc. of undiluted Iodocholeate per pound of body weight produces no lethal effects.

Surface Tension.—Tests reveal solutions of this compound to possess an exceptionally low surface tension giving it a high penetrating and diffusing power.

Versatility.—Because of its absence of irritation and low volatility Iodocholeate has been found to be particularly suited for impregnating gauze pads. It has also been found bactericidally effective in the form of a surgical dusting or wound powder and in ointment form.

Clinical Evidence.—After critical clinical observations Iodocholeate has received highly commendable reports in the field of First Aid, Surgery, Dermatology and related fields.

Further research on Iodocholeate is going to be carried on at Rutgers University, New Jersey College of Pharmacy under a fellowship grant by the Iodocholeate Products Corporation, Newark, N. J.

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NOTICE

It will be appreciated if authors will make tables for illustrations conform to the width of a single column where possible.