When injected intraperitoneally the toxicity of selenium in the form of selenium-cystine is approximately equal to the toxicity of selenium in sodium selenate or sodium selenite. The toxicities of the selenium in the two, above mentioned, inorganic compounds are in the same range as the toxicity of selenium in seleniferous grains. This has been indicated by oral administration of selenium-cystine.

SUMMARY

The minimum fatal dose of selenium in the form of selenium-cystine when injected intraperitoneally into albino rats was found to be 4.0 mg. per Kg. of body weight. This is equivalent to 8.44 mg. of selenium-cystine per Kg. of body weight.

REFERENCES

(1) Franke, K. W., *J. Nutrition*, 8 (1934), 609–613.
(2) Franke, K. W., and Painter, E. P., *Cereal Chem.*, 13 (1936), 67–70.
(3) Horn, M. J., Nelson, E. M., and Jones, D. B., *Ibid.*, 13 (1936), 126–139.
(4) Painter, E. P., and Franke, K. W., *J. Biol. Chem.*, 111 (1935), 643–651.
(5) Jones, D. B., Horn, M. J., and Gersdorf, C. E. F., *Cereal Chem.*, 14 (1937), 130–134.
(6) Painter, E. P., and Franke, K. W., *Ibid.*, 13 (1936), 172–179.
(7) Moxon, A. L., Anderson, H. D., and Painter, E. P., *J. Pharmacol.*, 63 (1938), 357–368.
(8) Franke, K. W., and Painter, E. P., *Cereal Chem.*, 15 (1938), 1–24.
(9) Gordon, J. C., Dissertation, Catholic Univ. of Am. (1935), 43 pages.
(10) Fredga, A., *Svensk Kemisk Tidskrift*, 48 (1936), 160.
(11) Franke, K. W., and Moxon, A. L., *J. Pharmacol.*, 58 (1936), 454–459.
(12) Kondo, S., *Japan J. Med. Sci.*, IV Pharm. (1933), No. 1, 213–232.
(13) Kondo, S., *Japan J. Med. Sci.*, IV Pharm. 9 (1935), No. 1, 29.

The Pharmacology of Soaps

II. The Irritant Action of Soaps on Human Skin

*By Byron E. Emery and Leroy D. Edwards**

In a previous paper (1) the actions of soaps on human red cells and earthworm segments were reported. During the past year, this work has been extended by the study of the irritant action of sodium and potassium soaps made from chemically pure fatty acids on human skin.

The literature gives many conflicting reports as to the component of a soap solution responsible for its irritant action on skin, *i. e.*, free alkali (2), hydrolytic alkalinity (2), free fatty acid (3, 4), acid soap (3), unsaturated acids (5), neutral soaps (3), added ingredients—perfumes (6, 7), antiseptic substances (8, 9), etc. The oils most commonly mentioned as being capable of producing irritant soaps are cottonseed (2, 8), cocoanut (5, 8, 10) and palm (5). Many writers (2, 11, 12) discuss the probability of differences in skin as being a contributing factor to soap irritation. Practically all of these workers used some form of a patch or swab test to determine the results reported.

EXPERIMENTAL

Method Employed.—The patch test, cited above, usually consists of the application to the skin of solid soap or bits of paper or gauze impregnated with a soap solution (alcoholic or aqueous) for some definite period of time. This method is held to be deficient for the following reaons: (1) insoluble soap cannot produce a reaction, (2) a definite volume or a definite concentration of a soap solution cannot remain in contact with the skin, (3) the volume of soap solution is not large enough, (4) paper and gauze have electrical charges which affect the state of a colloidal soap solution, (5) the area of skin covered by a soap solution on paper or gauze is not constant. In order to avoid these difficulties the device as shown in Fig. 1 was developed for use in this study of the irritant action of soaps on human skin. The diaphragm rim was lubricated with a jelly of tragacanth, Irish moss, glycerin, boroglycerin and benzoic acid. Approximately 25 cc. of a soap solution were added to the diaphragm and strapped to the inner surface of the arm or leg.

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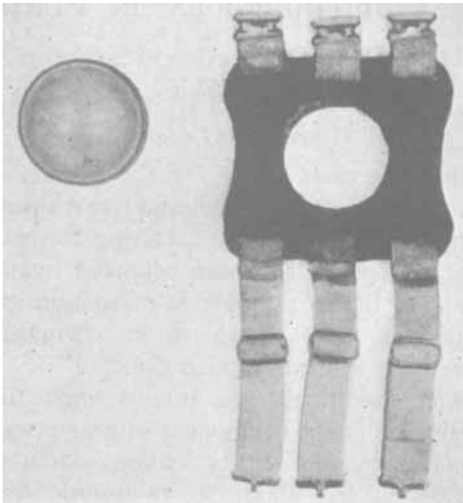

Fig. 1.—Device Used in Skin Tests.

The solution was removed after it had been in contact with the skin for four hours, the area washed with warm tap water, dried and examined at various intervals for signs of irritation. If there was irritation five minutes after the conclusion of the test and this irritation remained for more than two hours (irritation was determined by the presence of redness, itching, pain or any other damage to the epithelium), the result was recorded as "Plus," "Plus-Minus" if irritation was present but disappeared in two hours and "Minus" if no irritation was noted. No detectable differences were observable between the sensitivity of the inner surface of the leg and that of the arm.

In all reports reviewed, the concentrations of the soap solutions employed were expressed in per cent. In this work, in order to put the test on a more scientific basis, an equivalent molarity of each soap has been used. Calculating back from a sodium soap mixture containing 20 to 25% of cocoanut oil, and assuming a lather concentration of 5%, the approximate concentration of sodium laurate in the lather would be 0.5% which is equivalent to 0.0225*M* or 0.0225*N*. Since this concentration of sodium laurate was found to be very irritating to the skin over a four-hour period of time, 0.0225*N* solutions were used for the comparison of the irritant actions of the salts of the pure fatty acids studied. This concentration is further ideal in that soap solutions of this normality exhibit true soap properties and, in addition, such a concentration is above the critical concentration level for all of the salts except for caprylic and capric acids.

In the conduction of p_H control tests on skin it was found necessary to use alkaline buffer salts to maintain the desired hydrion level equivalent to soap solutions because of the neutralization capacity of the skin. Water—p_H 5.8, 0.0225*N* Na_2HPO_4—p_H 8.8, 0.0225*N* Na_2CO_3—p_H 10.9, 0.0225*N* K_2HPO_4—p_H 8.7, 0.0225*N* K_2CO_3—p_H 10.4, gave no evidence of irritation in tests carried out on 24 males and 14 females.

The chemically pure fatty acids, *n*-caprylic, *n*-capric, lauric, myristic, palmitic and stearic, all solid acids at room temperature except *n*-caprylic, were obtained from the Eastman Kodak Company. Linoleic, oleic and ricinoleic, all liquid acids at room temperature, were obtained from Schering-Kahlbaum. The purity of these acids was assumed to be sufficient to indicate possible differences in irritant properties of the resultant soaps. The sodium soaps of all the fatty acids were prepared by adding 0.1 cc. less than the calculated amount of 1*N* NaOH to the acid dissolved in previously neutralized 95% alcohol. The remaining alkali as 0.1*N* NaOH was added dropwise until a drop of the alcoholic soap solution produced a pink color with phenolphthalein. The alcohol was distilled from the soap under reduced pressure, and the powdered soap dried for three hours under vacuum at a temperature of 105° C. The potassium soaps were prepared by the same method.

Results of Soap Tests on Skin.—The sodium and potassium soaps of the above acids were studied as previously outlined. The results given in Fig. 2 were obtained on 24 males and 14 females. A larger number of individuals would, of course, be desirable. When the soaps are compared as to their greatest irritant action on skin, the acids may be arranged in order of decreasing toxicity as follows:

Sodium Soaps: Females—lauric, myristic, linoleic, *n*-capric, oleic, ricinoleic, palmitic, *n*-caprylic. (No reaction: stearic.) Males—lauric, myristic, oleic, *n*-capric, linoleic, ricinoleic, oleic. (No retion: *n*-caprylic, palmitic and stearic.) Combined males and females—lauric, myristic, linoleic, *n*-capric, oleic, ricinoleic, palmitic, *n*-caprylic. (No reaction: stearic.)

Potassium Soaps: Females—lauric, myristic, linoleic, *n*-capric, *n*-caprylic, oleic, palmitic, stearic, ricinoleic. Males—lauric, myristic, linoleic, oleic, *n*-caprylic, palmitic, *n*-capric, ricinoleic. (No reaction: stearic.) Combined male and female—lauric, myristic, linoleic, *n*-capric, oleic, *n*-caprylic, palmitic, stearic, ricinoleic.

When both the potassium and sodium soaps, as per the combined male and female results, are arranged according to decreasing toxicity, the order is as follows: K laurate, Na laurate, K myristate, Na myristate, Na linoleate, K linoleate, Na *n*-caprate, Na oelate, Na ricinoleate, K *n*-caprate, K oleate, K *n*-caprylate, K palmitate, K stearate, Na palmitate, K ricinoleate, Na *n*-caprylate. (No reaction: Na stearate.)

DISCUSSION OF RESULTS

The graphic method of presentation of the irritant properties and the chemical composition of soaps permits a comparison of the activity of one member of a homologous series with that of another. In the case of

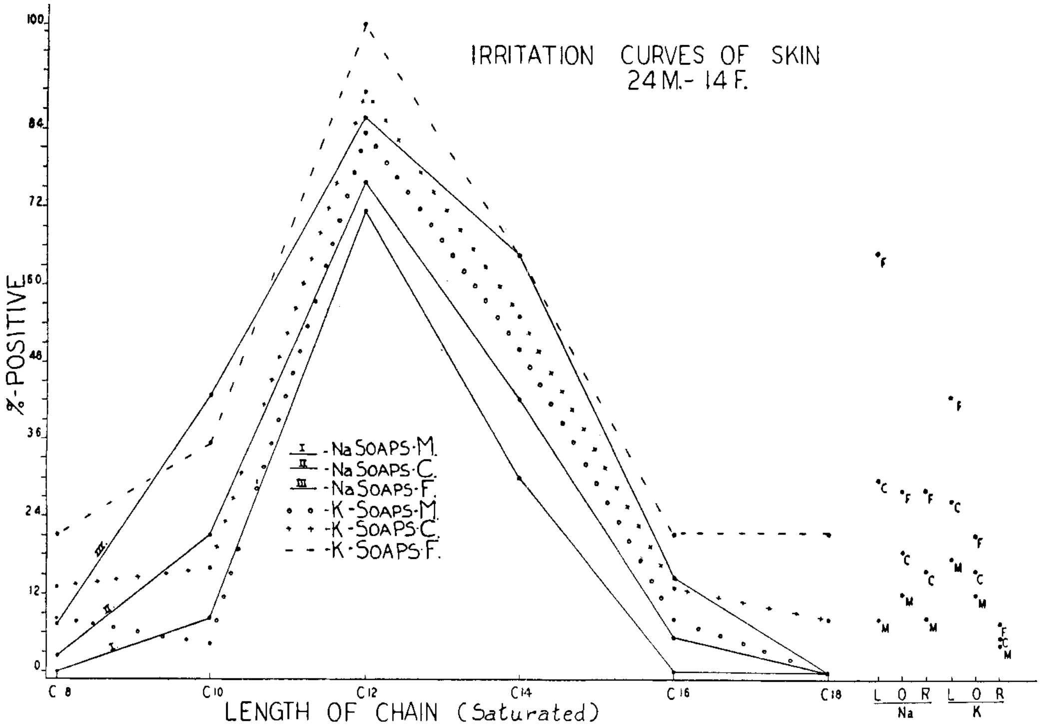

Fig. 2.—Curves of Irritant Action of Soaps on Human Skin.
All soap solutions were 0.0225*N*. % Positive—the per cent of individuals with irritant results. M—males; F—females; C—combined males and females. $\frac{LOR}{Na}$: Sodium soaps of linoleic, oleic and ricinoleic acids. $\frac{LOR}{K}$: Potassium soaps of linoleic, oleic and ricinoleic acids.

the unsaturated acids (linoleic, oleic and ricinoleic) only a single point of the irritation curve has been determined. It is immediately seen that the potassium soaps are more irritant than the sodium soaps on both females and males. Females are more readily irritated than males; hence, the combined curve falls intermediate between the male and female curves. The exceptions to these general statements are that the sodium and potassium soaps of oleic acid are equal in their irritant actions on males and females, and that the potassium soap of ricinoleic acid is less irritant than the sodium soap on both males and females. Lauric and myristic acids, by far, produce the most irritant soaps and are approached in magnitude only by the soaps of *n*-capric and linoleic acids. The left legs of the curves are true representations of the relative irritant properties of the low molecular weight salts. The right legs, however, may be determined in a large way by the low solubility of the high molecular weight salts. It should be pointed out that acids of the same number of carbon atoms (oleic, linoleic, stearic and ricinoleic) show marked differences in irritant properties. These differences cannot be explained on a basis of insolubility alone since ricinoleic and oleic soaps (both highly soluble) are very much less irritant than linoleic soaps (also highly soluble). Undoubtedly the presence of double bonds and substituent groups play an important rôle in determining the irritant properties of these soaps on human skin. Further proof for this statement is for the moment lacking.

The results of the alkali controls on the skin indicate that the hydrolytic alkalinity alone of a neutral soap in solution is not the cause of soap irritation. Another fact not to be overlooked, as noted by several other workers, is that the most irritant solutions, laurates and myristates, have a p_H much lower than the less irritant solutions, stearates and palmitates. The effects of small quantities of excess alkali in a soap or an insufficient amount of alkali to completely saponify the fatty acid on the enhancement or inhibition of the soap's irritant properties have not been thoroughly studied. Since the potassium soaps are more irritant than the sodium soaps and there was no irritation produced by either alkaline buffer control of these cations, it appears that the greater irritant action of the potassium soaps is due to the augmentation of the solubility of the irritant component of the soap by the potassium. The difference in the irritant action of potassium and sodium soaps becomes more marked with the laurates and increases with an increase in chain length. This observation would be expected, as above twelve carbon atom acids the solubility difference is great enough to mean that an appreciable amount of the potassium soap would be in solution but little of the sodium soap would be in solution. Studies of the actions of simple mixtures of these same soaps on human skin are now in progress.

CONCLUSIONS

1. An improved patch test method for the determination of the irritant properties of soap solutions on human skin has been described.
2. The irritant effects of the potassium and sodium soap solutions of nine pure fatty acids common in soaps have been determined on human skin.
3. Lauric and myristic acids produce the most irritant soaps of the nine acids studied.
4. Potassium soaps of the saturated acids have been found to be more irritant than the corresponding sodium soaps.
5. Females are more subject to irritation from soap solutions than males.
6. Soap irritation is not due to hydrolytic alkalinity alone.

REFERENCES

(1) Edwards, L. D., JOUR. A. PH. A., 28 (1939), 209.
(2) Gardiner, F., *Edinburgh Med. J.*, 8 (1912), 514.
(3) Siebert, C., *Med. Klinik*, 18 (1922), 1039.
(4) Blank, I. H., *Arch. Dermatol. Syphilol.*, 39 (1939), 811.
(5) Weber, K. I., *Seifenseider-Ztg.*, 64 (1937), 536.
(6) Luklinski, E., *Ibid.*, 50 (1923), 4.
(7) Schwartz, I., *U. S. P. H. S. Bull.*, 32 (1934), 215.
(8) "Queries and Minor Notes," *J. A. M. A.*, 106 (1936), 644.
(9) Rostenberg, A., and Sulzberger, M. B., *Arch Dermatol. Syphilol.*, 35 (1937), 433.
(10) Beedle, F. C., and Bolam, T. R., *J. Soc. Chem. Ind.*, 40 (1921) 25T.
(11) Mayers, M. R., *Safety Eng.*, 76 (1938) 9.
(12) Sulzberger, M. B., and Finnerud, C. W., *J. A. M. A.*, 111 (1938), 1528.

The Pharmacology of Soaps

III. The Irritant Action of Sodium Alkyl Sulfates on Human Skin

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The sodium alkyl sulfates have recently been introduced on the market in forms of shampoos, washing powders, cosmetics, dentrifices, etc., as substitutes for ordinary soaps. Little can be found in the literature pertaining to the irritant action of these substances on human skin. Carpentar (1) reports irritation of the skin in the case of a hairdresser from daily contact with a "hymolal salt shampoo." Ammonium lauryl sulfate has been claimed to produce skin irritation by Biederman (2). Because of this lack of any definite information concerning the irritant actions of the alkyl sulfates, it was considered advisable to run skin tests similar to those outlined in the preceding paper for true soaps (3).

EXPERIMENTAL

The sodium alkyl sulfates from C-8 to C-18, inclusive were supplied by the Procter & Gamble Company, Ivorydale, Ohio. The concentration of these sulfates employed in the tests was the same as that used in the tests of the pure soaps ($0.0225N$). Since in the commercial production of the alkyl sulfates it is common to add inorganic salts to enhance the detergent properties of these soap substitutes, additional tests were conducted after the addition of $0.002N$ NaCl, $0.002N$ Na_2CO_3, or $0.002N$ Na_2SO_4 to the $0.0225N$ solutions of the alkyl sulfates. The results presented here in Table I were obtained on the same 24 males and 14 females as were the results for the true soaps mentioned above. The per cent positive values for the sodium and potassium salts of the individual fatty acids are included for the

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