in that a significant rise was observed in but one dog, and in view of the present observations, these results must be challenged.

The amounts of histamine obtained from the dog's liver by perfusion of this structure with trypsin solutions are very small, being of the order of 5 to 12 mcg in 30 to 45 minutes of perfusion.

The observed liberation of histamine from isolated guinea pig lungs by perfusion of these structures with trypsin solutions appears to be of no consequence to the toxicity of trypsin in the intact animal in view of the absence of any of the pulmonary effects of histamine when trypsin is injected into the intact animal.

There remains only the observations on the action of trypsin on the blood of rabbits and the action on the intact rabbit which clearly support the histamine hypothesis.

Thus, it is concluded that most of the observations which have been interpreted as supporting the hypothesis that trypsin is toxic because of the action of histamine which it liberates from tissues are susceptible of other interpretation. In addition, such an hypothesis is quite inconsistent with the present observations which indicate that histamine plays no significant role in the toxicity of trypsin.

Summary. It was found that benadryl, a potent antagonist to either injected or liberated histamine, does not modify the lethal action of trypsin in the guinea pig or the dog. It is thus apparent that the histamine hypothesis, relative to the toxicity of trypsin, requires reconsideration.

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Studies on the Adherence of the Epidermis to the Corium.

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In some cases of pathologic blister formation, such as epidermolysis bullosa and pemphigus, the separation of the epidermis from the corium cannot be explained by development of pressure due to accumulation of fluid between these layers. In these cases a change in the adhesive forces holding the 2 heterogeneous layers together must be assumed. Histologic studies with modern methods have failed to demonstrate the existence of a basement membrane at the junction of the epidermis and the corium.[1-3] Lately it has been suggested that a decrease in adhesion between the 2 layers is due to physicochemical changes in the upper corium.[4]

It has been known that treatment of the skin with acids or bases results in separation of the epidermis.[5] These types of separation are accompanied by swelling of the corium. In 1942 Baumberger *et al.* discovered that if excised human skin was warmed up to 50°C for a few minutes on a slide warming table, the epidermis could easily be peeled off.[4] When the skin was cooled, the epidermis became reattached to the corium an indication of a reversible gel-sol formation.

Experimental. With regard to the swelling effect of acids, bases, and neutral salts on collagen[6] and the consequent decrease of its

1 Pautrier, L. M., and Woringer, Fr., *Ann. de Dermatol. et Syph.*, 1930, **7** serie **1**, 985.

2 Szodoray, L., *Arch. Derm. and Syph.*, 1931, **23**, 920.

3 McLeod, J. M. H., and Muende, I., *Pathology of the Skin*, 1940, New York, N. Y., Paul B. Hoeber, Inc.

4 Baumberger, J. P., Suntzeff, V., and Cowdry, E. V., *J. Nat. Cancer Inst.*, 1942, **2**, 413.

5 Wilson, J. A., *The Chemistry of Leather Manufacture*, 1928, New York, N. Y., The Chemical Catalogue Co.

6 Lloyd, D. J., and Shore, A., *Chemistry of the Proteins*, 1938, London, J. and A. Churchill Ltd.

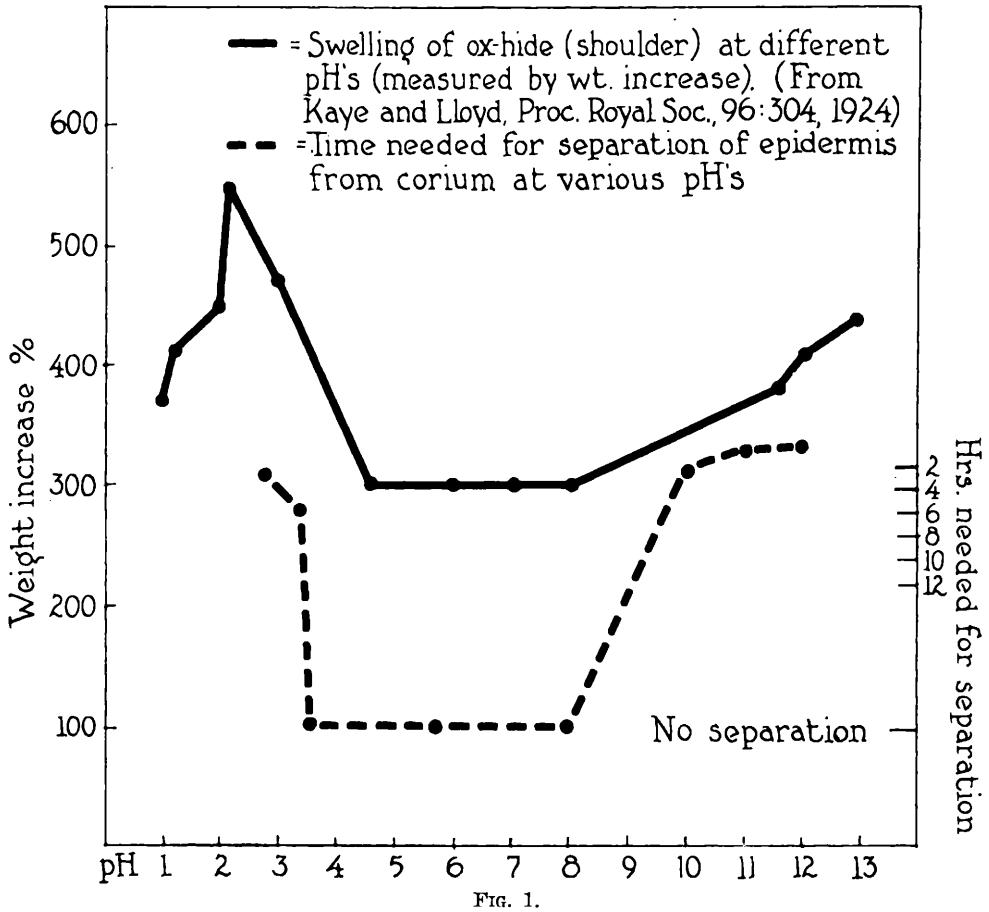

FIG. 1.

cohesive and adhesive properties,[7] an attempt was made to correlate the degree of swelling of the corium to the time necessary for separation of the epidermis. Two millimeter cubes of normal human skin were immersed in various solutions and the time necessary for removability of the epidermis by forceps noted. In acetic acid and sodium hydroxide at various pHs the ease of epidermal separation closely followed the swelling curves for collagen and gelatin. (Fig. 1). Maximum swelling and minimum time of separation occurred at the isoelectric point of collagen (pH 5). On either side of the isoelectric point the depressive effect of 2N salt solutions at neutral pH on swelling and at the same time on the ease of epidermal separation was evident. In neutral salts separation of the epidermis was promoted in the same order that these salts promote the swelling of gelatin (Hofmeister series). 2N solutions of sodium thiocyanate removed the epidermis in 5 minutes; sodium iodide in 14 minutes; sodium chloride in 6 hours and sodium acetate, sulfate and citrate not at all. The latter salts shrink the corium.

Loosening of the epidermis by acids, bases, or heat could be reversed by subsequent immersal of the skin into salt solutions with shrinking effect; there was a solid re-attachment for about 16 hours. Anions that promote swelling facilitated subsequent separation by heat, whereas ions with shrinking properties inhibited heat separation.

Discussion. Swelling of hydrophilic colloids decreases their cohesive and adhesive properties.[7] In human skin the diminution of adhesion between epidermis and corium by swelling is more spectacular than the de-

[7] Wood, T. B., and Hardy, W. B., *Proc. Royal Soc.*, London, 1909, **81**, 38.

crease of cohesion within the collagen. Should the reticular and elastic fibres be involved in epidermal-dermal adherence[2] the great swelling pressure of collagen would be sufficient to rupture these. It is concluded that swelling of collagen in the upper corium may lead to blister formation.

Summary. The ease of separation of the epidermis from the corium by acids, bases, and salt solutions parallels the swelling of collagen in these agents. Separation due to swelling agents can be reversed by shrinking agents. The adherence of normal epidermis to the corium is increased by shrinkage of the collagen.

The author wishes to express his appreciation to Dr. Stephen Rothman and Dr. George Gomori for their aid and valuable advice.

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Distribution of Cholesterol, Cholesterol Esters and Phospholipid Phosphorus in Normal Blood.

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Many observations indicate that not only the absolute amounts of the different lipids, but also the ratios of these lipids to each other in the cells and the surrounding medium are important in physiological and pathological conditions. The most easily accessible system for the study of these ratios is blood. Much work has been done on changes in the individual lipid components in different diseases, but only a few papers deal with their interrelationships. Recently Peters and Man[1] studied the interrelations of serum lipids in normal persons and in patients with different diseases. The study of cell lipids, however, has been comparatively neglected so far, perhaps because the changes that occur there are relatively small when compared to the changes that take place in plasma lipids. In animal experiments (unpublished) we observed that under the influence of different factors the changes in the cell lipids were frequently opposite in direction to those in the plasma lipids. It occurred to us that these changes, although small, might still be significant, and it seemed advisable to investigate under different conditions the cholesterol, cholesterol ester, and phospholipid phosphorus content of both blood cells and plasma, simultaneously. To obtain a baseline for further observations we first determined the various lipid values on a group of normal individuals.

Material and Methods of Analysis. The observations here presented were made on 2 groups of patients. The first group consisted of 10 healthy males and 10 healthy females whose ages ranged from 19 to 35. The second group was made up of 20 surgical patients with no diseases known to affect lipid metabolism. This number was equally divided between the 2 sexes, and their ages were between 70 and 90 years. Two patients whose plasma cholesterol values, (334 mg % and 86 mg % respectively), differed from the mean by more than twice the standard deviation* were excluded and replaced by 2 others.

[1] Peters, J. P., and Man, E. B., *J. Clin. Invest.*, 1943, **22**, 707, 715.

* The standard deviation was calculated by the help of the formula $SD = \sqrt{\frac{\Sigma d^2}{n-1}}$

The standard error can be calculated from this formula as follows: $SE = \frac{SD}{\sqrt{n}}$

Results were considered as probably significant where $m_1 - m_2 > 2\sqrt{SE_1^2 - SE_2^2}$.