B. Acetanilid, antipyrin, phenacetin, picric acid, picrotoxin, pyramidon, salicylic acid.

Experiments with other solvents, and with additional substances of alkaloidal type, will be added to this series.

64 (589)

Notes on Fischer's theory of the influence of acids in the production of edema.[1]

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Several years ago Gies published some of the results of a preliminary study of the effects of acids on tendon collagen.[2] Last December Kantor and Gies reported their observation that collagen fibers from tendon immediately swell markedly in *free* acid but do not swell at all in any strength of *combined* acid[3]—facts on which they base a new microscopic test for free acid. These results naturally led Kantor and Gies to consider the relation of such facts to Fischer's theory of edema, which they were investigating at the time these observations were made. Lately we have gone into this particular phase of the matter with some experiments on fibrin. Similar experiments are under way with other colloids and with various tissues.

Fischer's general conclusion in regard to edema is stated in the following terms:[4]

"A state of œdema is induced whenever, in the presence of an adequate supply of water, the affinity of the colloids of the tissues for water in increased above that which we are pleased to call normal. The accumulation of acids within the tissues,

[1] This study is one of a projected series on *proteins and their combining qualities.* which in turn constitutes a section of a comprehensive plan of research on the composition of protoplasm as well as the structural and dynamic relationships of cell constituents and products. These investigations are now in progress in the Laboratory of Biological Chemistry of Columbia University, at the College of Physicians and Surgeons, and under the auspices of the George Crocker Special Research Fund.

[2] Gies, *Science*, 1907, xxv, p. 462.

[3] Kantor and Gies, *Journal of Biological Chemistry*, 1911, ix; *Proceedings of the American Society of Biological Chemists*, p. xvii.

[4] Fischer, "Edema — a study of the physiology and the pathology of water absorption by the living organism," 1909, p. 99.

brought about either through their abnormal production, or through the inadequate removal of such as some consider normally produced in the tissues, is chiefly responsible for this increase in the affinity of the colloids for water, *though the possibility of explaining at least some of the increased affinity for water through the production or accumulation of substances which affect the colloids in a way similar to acids or through the conversion of colloids having but little affinity for water into such as have a greater affinity must also be borne in mind.*" [1]

Fischer's views on the influence of acid in the production of pathological edemas appear to us to be over-emphasized. Special stress was laid by Fischer upon lactic acid as a causative factor in pathological edema, but apparently no experiments were performed with that acid. The action of electrolytes on the power of lactic acid to excite water absorption by colloids was not ascertained. Acids such as hydrochloric were Fischer's chief reliance in his experiments with acids.

We find, when moist shreds of fibrin are severally suspended in gelatin solution, peptone solution, fresh egg white, blood, milk, and meat juice, that hydrochloric acid solution (0.2 per cent. to 10 per cent.) may be added to the mixture in each case *in any proportion* without inducing visible effects on the fibrin shreds, *unless sufficient acid is added to provide an excess in the* FREE *state.* Very large quantities of acid may be added to such mixtures without appreciable bloating effect.[2] If the colloids in the artificial solutions and protoplasmic liquids enumerated above are combined with any proportion of the acid up to exactly their *maximum* affinity for it (hydrochloric acid), so that the liquids while strongly acid to litmus respond negatively to tests for *free* acid, then moist fibrin shreds can be kept in such acid fluids indefinitely without swelling to any perceptible degree. Warm concentrated gelatin solutions may be put into these conditions of free and combined acidity. After such solutions have been permitted to gelatinize, moist fibrin shreds which have been imbedded in the resultant jellies swell perceptibly, provided the gelatinized mass contains *free* acid, *but the shreds do not appear to absorb water from the medium if its contained acid is only in* COMBINED *form.* It is obvious that such

[1] Special emphasis is laid by us on the part of the quotation which we have italicized.

[2] Similar observations have been made with alkaline mixtures. We expect to describe, in the near future, a new test for free alkali based upon the behavior of fibrin in association with dissolved protein in alkaline media.

facts have an important bearing on any theory of acid causation of edema.

Our experiments do not permit us to deny that acids may be influential factors in the causation of edematous processes. Our results emphasize the fact, however, that the acids which may be produced in, or that are carried into, tissues tend to unite there with non-colloidal basic radicals and with dissolved colloids before combining with suspended colloids. The chemical means and excretory processes by which *living* protoplasm maintains a state of reaction-constancy cannot easily be overcome. In Fischer's published experiments on the bloating effects of acids, *large* excesses of *free* acid were present in all but a few cases. Would Fischer contend that edematous tissues contain *free* acid?

We feel that acids are not the only causes of colloidal water absorption in edema. Results obtained by Berg and Gies[1] several years ago indicate that *enzymes* facilitate any such influence that acids, whether free or combined, may exert; and vice versa. Fischer himself alludes, "in passing" (p. 109), to a result in harmony with that view. The italicized portion of the foregoing quotation from Fischer's book is broad enough to include enzyme influences and all other contributory factors. Experiments along these lines are still in progress.

65 (590)

The relation of the toxic dose of horse serum to the protective dose of atropin in anaphylaxis.

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This study was prompted by the publications of Auer and Lewis,[2] and of Auer,[3] which definitely demonstrated the prophylactic action of atropin sulphat in the asphyxia of immediate anaphylaxis. The results of these writers have been confirmed repeatedly.

[1] Berg and Gies, *Journal of Biological Chemistry*, 1907, ii, pp. 508 and 522.

[2] Auer and Lewis, *Jour. A. M. A.*, 1909, viii, 458; *Jour. Exp. Med.*, 1910, xii, 153; *ibid.*, p. 165.

[3] Auer, *Amer. Jour. of Physiology*, 1910, xxvi, 439.