epidermis is not particularly altered; it is perhaps slightly thickened. In the upper corium there is occasionally very slight exudation. As the disease advances, the number of follicles diminishes, and there appears to be some slight increase in the activity of the sebaceous glands.

The production by nutritional means of 3 scaly dermatoses in rats, each with a different cause, indicates that the factors of nutrition and metabolic disturbance play an important etiologic rôle in similar conditions in man.

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Relative Toxicities and Therapeutic Values of Three Chemotherapeutic Agents of the Sulphonamide Type.

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Since the original report of Domagk[1] on the protective effects of 4'-sulfonamido-phenyl azo-7-acetylamino-l-oxynaphthalene-3, 6-disulfonate of sodium (prontosil) in mice infected with *Streptococcus hemolyticus*, an extensive experimental and clinical literature[2-11] has developed on the use of this and related compounds in streptococcal and other types of infections. Nevertheless, information on the relative toxicity of these several products is either incomplete or relatively limited. Further, their therapeutic efficiencies have been only imperfectly evaluated due to lack of extensive comparative data on the therapy of bacterial infections of standard virulence.

Toxicity. The oral lethal dosages of prontosil and 4-(4'-aminobenzol-sulfonamide)-benzol-sulfonamide (Disulon) cannot be accurately established due to high tolerance and the limited gastric

1 Domagk, G., *Angew. Chemie*, 1935, **48**, 657.

2 Levaditi, C., and Vaismon, A., *Presse med.*, 1935, **103**, 2097.

3 Levaditi, C., and Vaismon, A., *Compt. rend. Soc. de biol.*, 1936, **121**, 803.

4 Colebrook, L., and Kenny, M., *Lancet*, 1936, **1**, 1279.

5 Buttle, G. A. H., Stephenson, D., Smith, S., and Foster, G. E., *Lancet*, 1937, **1**, 1331.

6 Gray, W. H., Buttle, G. A. H., and Stephenson, D., *Biochem. J.*, 1937, **31**, 724.

7 Long, P. H., and Bliss, E. A., *J. A. M. A.*, 1937, **108**, 32.

8 Rosenthal, S. M., *Pub. Health Rep.*, 1937, **52**, 48.

9 Proom, H., *Lancet*, 1937, **232**, 16.

10 Rosenthal, S. M., *Proc. J. Pharm. and Exp. Therap.*, 1937, **60**, 117.

11 Halpern, B. N., and Mayer, R. L., *Presse Med.*, 1937, **40**, 747.

capacities of the animals. However, the M.L.D.'s of these 2 compounds by this route exceed 40 gm. per kilo of body weight, respectively.

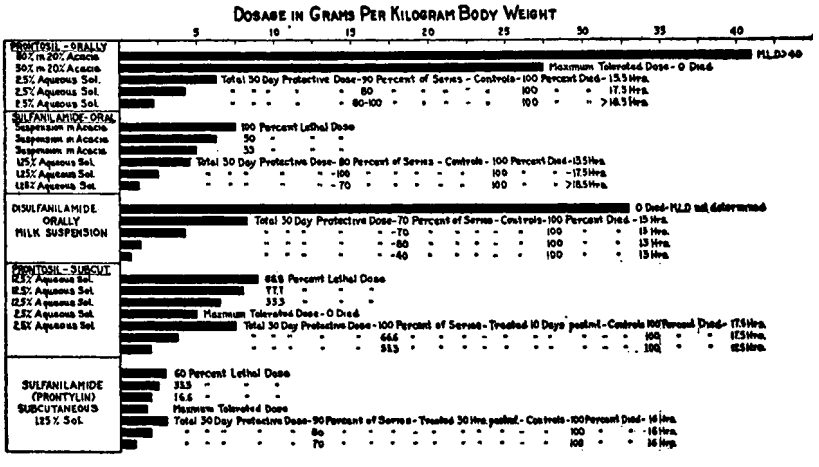
In an acacia-suspension the 50% oral M.L.D. dosage of *p*-amino benzene sulphonamide (prontylin or sulphanilamide) for mice is 6.25 gm. per kilo. Large dosages of this agent can be administered only in the form of a suspension, because of its low aqueous solubility.

For albino mice the M.L.D. of prontosil administered subcutaneously in an isotonic aqueous menstruum lies between 6 and 8 gm. per kilo. The corresponding dosages of prontylin in water, 20% acacia suspension, and olive oil[8] are 2.75, 3.75 and 4.0 gm. per kilo body weight, respectively. The subcutaneous toxicity of disulon, because of its low aqueous solubility, was not determined. Solutions of soluble (sodium or hydrochloride) salts of prontylin are strongly irritant. Reliable toxicological data with such solutions are not obtainable on parenteral administration.

Effect on Growth-rates. The growth-rates of young (50 gm.) rats (maintained on a complete diet) following the subcutaneous administration of prontosil (as a 40% aqueous suspension) in dosages of 2.0 gm. per kilo (16.6% of a single M.L.D.) per day lagged 6.3% behind that of the controls after a 9-week period. The oral administration of 10 gm. per kilo (27% of a single M.L.D.) per day from the 10th to the 12th week inclusive resulted in a 13% lag. This effect was purely a disturbance of alimentation, however, in that the growth-rate of this group 2 weeks after discontinuance of medication exceeded that of the control series by 8.7%. Oral daily dosages of 0.25 gm. of prontylin per kilo (3.3% of a single M.L.D.) over a 9-week period were without influence on the growth rates. Increasing the dosage to 0.75 gm. per kilo (10% of a single M.L.D.) from the 10th to the 12 weeks did not influence the normal growth-curves. P-acetyl-amino-benzene-sulfonamide, the primary conjugation-product of prontylin, in the organism, differed in no respect from prontylin under similar conditions in its effect on the growth-rate.

Therapeutic Efficiency. In our experiments we consider the minimal protective dose to be the total dose, administered over a 10-day period, which protects for 30 days 70 to 100% of animals infected intraäbdominally with 0.3 cc. of a 1:100 saline suspension (800,000 to 1,200,000 bacteria per cc.) of our C-391-2 culture of *β-Streptococcus hemolyticus.* This strain of streptococcus of human origin was obtained at necropsy and subsequently isolated in pure culture.

A high mouse-virulence was maintained by successive passages through mice. Treatment was begun 1 to 2 hours after infection and repeated at 6-hour intervals for the first 24 hours and daily thereafter up to and including the 10th post-infection day.



The figure shows that the minimal protective dose of each product has the following order: prontosil > prontylin > disulon. Moreover, the minimal protective dose varies directly with the virulence of the culture. This point amply confirms the statements of Long and Bliss[7] that effective treatment of experimental streptococcal infections with these chemotherapeutic agents must be predicated on a survival period of reasonable length after institution of therapy (13 or more hours in our experience with mice).

Summary and Conclusions. The anti-streptococcal effects of prontosil on oral administration are somewhat superior to those noted after subcutaneous injection. This confirms Rosenthal.[8]

The chemotherapeutic efficiency of prontylin by the subcutaneous route is superior to that noted after oral medication. This confirms Proom[9] and Rosenthal.[8] The observed differences in efficiency by these 2 routes of administration were not due to the greater volume of fluid administered by the subcutaneous route, in that normal saline injections alone were of no therapeutic value. However, the superiority of the parenteral route from a therapeutic standpoint is open to question, when due consideration is given to the low solubility of the compound and the close similarity between the time intervals, at which the peak blood concentration occurs, after medi-

cation with equal dosages of prontylin by these 2 routes. (Marshall, *et al.*[12])

Prontylin orally appears to be 1.8 times more effective than prontosil for low-grade infections and 1.4 times more effective for high-grade infections. The therapeutic margin of safety of prontosil administered orally, however, is quite superior to that of prontylin.

Disulon orally in dosages of 40 gm. per kilo does not produce symptoms referable to the central nervous system. This compound, due to its lower toxicity, better tolerance and the greater protective efficiency of unit dosages in the presence of infections, has a therapeutic margin of safety quite superior to that of prontylin. The observed superior therapeutic efficiency of disulon as compared with prontylin confirms similar observations of Rosenthal.[10]

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Sodium Chloride Content of Gastro-Intestinal Secretions.*

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The necessity for replacing the sodium chloride carried away when excessive amounts of gastro-intestinal secretions are lost, as by vomiting, or drainage from biliary or intestinal fistulæ, has been repeatedly emphasized. In fact, the value of sodium chloride solutions in such instances is so well known that a definite tendency exists for their use in all patients requiring parenteral fluids. This procedure is not without risk, since the development of edema from the administration of excessive amounts of sodium chloride to sick patients is not uncommon. To avoid this mistake and at the same time provide sufficient salt, the physiologically and chemically minded surgeon knows about the metabolism of these electrolytes and fits his treatment to the needs of the individual patient.

The purpose of this paper is to show the amount of sodium chloride present in various gastro-intestinal secretions obtained from

[12] Marshall, E. K., Jr., Emerson, K., and Cutting, W. C., *J. A. M. A.*, 1937, **108**, 953.

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