

Phytopharmacological Reactions of Blood after Sulfa Compounds.

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Among the commonest reactions following administration of sulfanilamide and its derivatives are skin manifestations of all kinds. The most interesting of these perhaps are such bullous or pemphigoid eruptions as are described by Wien and Lieberthal,¹ Epstein,² Loveman and Simon,³ Bettley,⁴ Omens and Robbins,⁵ and others. Inasmuch as Macht and Pels some years ago reported a specific and characteristic phytotoxic reaction produced by pemphigus blood sera in these PROCEEDINGS⁶ and later in a series of comprehensive papers^{7, 8, 9} reporting results obtained with sera of nearly three thousand patients, it was deemed advisable to inquire whether specimens from patients with pemphigoid lesions effected by the sulfa derivatives would exhibit similar phytotoxicity for seedlings of *Lupinus albus*. Accordingly, a series of experiments was made with regard to the influence on plant growth of rabbit and human blood sera drawn after ingestion of sulfa drugs.

Materials Studied. The compounds studied in 3 sets of experiments were sulfanilamide, neoprontosil, sulfathiazole, sulfapyridine, sulfadiazine, sulfaguanidine and succinyl sulfathiazole. In the first series 0.5 and 1.0 g doses of the respective drugs were given adult rabbits weighing 2 to 3 kg apiece. Such doses ensured a concentration of these drugs in the blood comparable to that effected in humans receiving full doses of the sulfa compounds, as standard biochemical tests demonstrated. Normal blood specimens were drawn before the drugs were given by stomach tube and others were taken 6 and 24 hours afterward. In the second series, blood sera were obtained from cases treated with various sulfa drugs, and their

¹ Wien, M. S., and Lieberthal, E. P., *J. A. M. A.*, 1941, **117**, 850.

² Epstein, E., *Arch. Dermat. and Syph.*, 1940, **41**, 61.

³ Loveman, A. B., and Simon, F. A., *Arch. Dermat. and Syph.*, 1939, **40**, 29.

⁴ Bettley, F. R., and Simon, P., *Brit. M. J.*, 1939, **1**, 1177.

⁵ Omens, D. V., and Robbins, J. B., *Arch. Dermat. and Syph.*, 1939, **40**, 633.

⁶ Macht, D. I., and Pels, I. R., *PROC. SOC. EXP. BIOL. AND MED.*, 1927, **25**, 237.

⁷ Pels, I. R., and Macht, D. I., *Arch. Dermat. and Syph.*, 1929, **19**, 640.

⁸ Pels, I. R., and Macht, D. I., *Arch. Dermat. and Syph.*, 1931, **23**, 601.

⁹ Macht, D. I., *Acta Dermatologica*, 1932, **18**, 126.

phytotoxicity was compared with that of normal human blood. In the third series, the effects of various concentrations of the respective chemicals on the growth of seedlings was studied in plant-physiological saline.

Method of Study. The method employed has been described by the author and associates in numerous publications.^{10, 11} The effect of 1% solutions of blood sera was compared with that of plant-physiological saline or Shive solution on growth of roots of *Lupinus albus* for 24 hours in the dark at 20°C. The phytotoxic index of growth for any unknown solution is expressed by the formula, $\text{Index} = X/N$, or average increment of root growth in unknown solution divided by growth of controls under identical conditions. The author has found the phytopharmacological test quite accurate and reliable in experienced hands, and its results have proven valid on statistical analyses.¹² The laboratory findings have been in striking accord with the final clinical diagnoses of physicians submitting blood sera of pemphigus patients for phytopharmacological examination, as exemplified by the recent paper of Gellis and Glass.¹³

Results. Thirty experiments each were made with (1) blood sera of rabbits, (2) specimens from patients treated with sulfa compounds, and (3) aqueous solutions of the drugs. It was found that blood sera of rabbits receiving massive doses of the various compounds exhibited phytotoxic readings higher than the index given by normal rabbit serum (70%), as shown in Table I.

The figures obtained with sera from human patients treated with sulfanilamide and derivatives are given in Table II. Here again, the figures shown are definitely higher than those obtained with normal human blood serum, the index of which is from 70 to 75%. Experiments made with aqueous or plant-physiological solutions of the

TABLE I.
Effect on *Lupinus* Seedlings of 1% Solutions of Sera of Rabbits Receiving 0.5 g of Respective Sulfa Compounds.

Drug administered	Phytotoxic index %
Sulfanilamide	79
Sulfapyridine	86
Sulfathiazole	81
Sulfadiazine	83
Sulfaguanidine	79
Succinyl sulfathiazole	81
Neoprontosil	96

¹⁰ Macht, D. I., and Livingston, M. B., *J. Gen. Physiol.*, 1922, **4**, 573.

¹¹ Macht, D. I., *Protoplasma*, 1937, **27**, 1.

¹² Macht, D. I., and Macht, M. B., *J. Lab. and Clin. Med.*, 1941, **26**, 597.

¹³ Gellis, S., and Glass, F. A., *Arch. Dermat. and Syph.*, 1941, **44**, 321.

TABLE II.
Effect on *Lupinus* Seedlings of 1% Solutions of Sera of Patients to Whom
Respective Sulfa Compounds Had Been Given.

Drug administered	Phytotoxic index %
Sulfanilamide	76
Sulfapyridine	94
Sulfathiazole	77
Sulfadiazine	85
Sulfaguanidine	83
Succinyl sulfathiazole	78

sulfa compounds in concentration of 1:10,000 on growth of *Lupinus albus* seedlings also yielded interesting results. None of the drugs examined was very toxic for root growth, the phytotoxic indices in concentrations of 1:10,000 ranging from 80 to 90%. Of greater interest were the results obtained with more dilute solutions of the sulfa compounds. When low concentrations of from 1:100,000 to 1:250,000 were employed, a stimulation of root growth was noted. Complete data concerning these plant-physiological experiments will be published elsewhere.

From the standpoint of clinical medicine the above findings with blood sera are significant in that they designate the phytopharmacological test as a convenient means of differentiating true pemphigus from pemphigoid dermatoses effected by sulfanilamide and its derivatives. Plant-physiological experiments with saline solutions of these drugs are of interest in connection with the mechanism of action of sulfa compounds, which is still not completely understood.

Summary. (1) The Macht-Pels phytotoxic test for pemphigus was applied to sera of rabbits and human beings treated with sulfanilamide and 6 derivatives. (2) None of these sera exhibited a greater toxicity than normal blood for seedlings of *Lupinus albus*. (3) The phytopharmacological test thus affords a convenient means of differentiating between true pemphigus and the pemphigoid eruptions produced by sulfa drugs. (4) Hydroponic experiments on *Lupinus albus* seedlings placed in solutions of seven sulfa derivatives revealed a diphasic effect on growth of the roots. Low concentrations stimulated while higher concentrations inhibited root growth.