injections. This was definitely so in my cases, for which hourly temperatures are recorded for 12 hours after each injection; in the apyrexial case to which reference has already been made the temperature registered 101.6° F. (38.7° C.) three hours after the first injection, 102° F. (38.9° C.) ten hours after the second, 99.6° F. (37.5° C.) seven hours after the third, 99.2° F. (37.3° C.) nine hours after the fourth, and 99° F. (37.2° C.) eight hours after the fifth. A further patient who has just started a course developed a temperature of 100.2° F. (37.9° C.) three hours after the first injection. All the temperatures returned to normal in an hour or just over an hour and could have been overlooked with a 4-hourly chart. I have observed on several occasions that mild fever induced by intramuscular injections of "aolan" effects rapid cures in these cases.

The aetiology of the disease is still uncertain. Pleuropneumonia-like organisms have been cultivated in the urethral discharge of 14 out of 84 men suffering from uncomplicated non-gonococcal urethritis, in the cervical secretion of 10 out of 42 women with cervicitis, and in only 3 of 30 of my cases of Reiter's disease. Urethral cultures were also positive in my first case treated with gold eighteen months after apparent cure, and it is worth noting that there had been no subsequent sexual exposure. An examination carried out before the first morning micturition did, however, show the existence of a mild residual abacterial urethritis which may have persisted since the original illness. Cultures were negative in the synovial fluid of two and in the conjunctival secretions of three of my cases. Examination of female contacts of 5 cases in which pleuropneumonia-like organisms were isolated in the urethral discharge yielded negative cultures, but elementary bodies were seen in two. The majority of my cultural examinations have been carried out by Henderson-Begg and Edward.

It is possible that the disease, as I originally stated, is due to a virus. Primary herpetic stomatitis of infants and young children is caused by the virus of herpes simplex, and a virus has recently been shown by Buddingh to be responsible for a similar disease associated with diarrhoea in children. Strains of the virus are maintained by serial passage from cornea to cornea of rabbits, but, unlike primary herpetic stomatitis, no inclusions have been found. In the discussion following Buddingh's paper on this subject Sabin stated that these inclusions would probably be demonstrated in serial sections. On this occasion Dodd also reported that she had obtained positive corneal inoculations in rabbits with vaginal swabs taken from the mothers of the children suffering from the disease. Buddingh had observed similar results with the urethral discharge and oral and conjunctival secretions of a typical case of Reiter's disease.

There would seem, therefore, to be definite room for doubt whether pleuropneumonia-like organisms are the aetiological factor in Reiter's disease. I consider, too, that the efficacy of gold therapy in the treatment of this disease requires further investigation. In view of its dangers I have not used this form of therapy in the treatment of uncomplicated abacterial urethritis (usually a very mild disease) in which these organisms have been isolated.—I am, etc.,

London, W.1.

A. H. HARKNESS.

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"Sulpha-Combination"—A New Chemotherapeutic Principle

SIR,—In the article on "'Sulpha-Combination'—A New Chemotherapeutic Principle," by Drs. A. Rune Frisk, Gösta Hagerman, Sture Helander, and Bertil Sjögren (Jan. 4, p. 7) reference is made to my work on the same subject in a form which creates the erroneous impression that I have suggested only the use of a mixture of sulphathiazole and sulphadiazine. I therefore take the liberty of bringing the following facts to your attention.

My publication to which reference is made by the Swedish investigators appeared in print in January, 1945—that is, one year and three months before these authors published any of their experimental or clinical results with a combination of three sulphonamides; and two years before their article appeared in your *Journal*. The title of my publication—"Inhibition of Drug Pre-

cipitation in the Urinary Tract by the Use of Sulfonamide Mixtures. I. Sulfathiazole-Sulfadiazine Mixture" (*Proc. Soc. exp. Biol.*, N.Y., 1945, **58**, 11)—clearly indicates that the general principle of "sulpha-combination" was investigated and that the sulphathiazole-sulphadiazine mixture represented only the initial phase of this work. This point is further emphasized in Table I of my paper, containing solubility figures of *seven* different sulphonamide combinations, one of these consisting of as much as *four separate constituents*. In addition, several statements in the text of this publication leave no doubt about the recognition of the general principle and the direction of further research.

I quote: "Since even closely related sulfonamides, when present simultaneously in the same solution, do not influence each other appreciably with regard to their particular solubilities, the danger of intrarenal drug precipitation from the sulfonamides comprising the mixture should be only as great as if each compound had been administered alone, and in the partial dosage contained in the mixture. . . . Sulfathiazole and sulfadiazine were selected for the initial series of experiments, because these compounds are at present most frequently employed, have almost the same therapeutic indications, and cause renal complications in about the same percentage of cases. . . . The findings of the solubility study summarized in Table I indicate that many other sulfonamide combinations should be investigated as to their ratio of renal toxicity and bacteriostatic activity." Since then I completed experiments on the combinations of sulphadiazine-sulphamerazine, and sulphadiazine-sulphathiazole-sulphamerazine early in 1946, and submitted my work to the American Medical Association in February, 1946, for presentation at its 95th Annual Session at San Francisco on July 3, 1946. The title of this presentation was "The Prevention of Renal Complications by the Use of Sulfonamide Mixtures" (Announcements: *J. Amer. med. Ass.*, 1946, **131**, 306, and *ibid.*, **131**, 1141).

Further references to the general principle of sulphonamide mixtures can be found in three clinical publications. In the *Journal of Urology*, 1946, **55**, I stated on p. 565: "With regard to its potentialities and to possible future developments, however, treatment with sulfonamide mixtures seems to hold the promise of an efficiency which might dispense with the necessity of any other preventive measure." In the *Journal of Pediatrics*, 1946, **29**, we explained on p. 284: "Experimental work and preliminary clinical trials suggest that for the treatment of meningitis, sulfadiazine should be combined with a sulfonamide, such as sulfamerazine, which diffuses better than sulfathiazole through the hematocephalic barrier. . . . Our results suggest that the simultaneous employment of two or more sulfonamides should replace the use of single compounds, since mixtures combine a high therapeutic efficacy with a significantly lowered toxicity."

Flippin *et al.* published "An Evaluation of Sulfonamide Mixtures and Various Adjuvants for Control of Sulfonamide Crystalluria" in the *Annals of Internal Medicine*, 1946, **25**, 433. I quote from the discussion of this paper: "An alternative method, proposed by Lehr^{14,15} avoids exceeding the critical concentrations at which crystallization will occur by using two or more sulfonamides simultaneously. Our preliminary observations indicate that this approach is as effective as the administration of sodium bicarbonate at the rate of 12 grams per day."

In summary then: The use of sulphonamide mixtures for the prevention of renal complications was conceived independently in our laboratory as the result of extensive animal experimental investigations on "Methods which Inhibit or Prevent Intrarenal Precipitation of Compounds of the Sulfonamide Series" carried out since 1941. I published complete experimental proof for the validity of the sulphonamide mixture principle one year and three months before the Swedish investigators announced their "new chemotherapeutic principle" in *Nordisk Medicin*, 1946, **29**, 639, based on their first animal experimental study. Previous to this publication the authors, according to their own statement, had done only preliminary clinical work with a mixture containing equal parts of sulphathiazole and sulphadiazine. Even if my publication, to which reference is made by the Swedish authors, was the only one available to them when their article was written, they must have been aware of the fact that I did not merely suggest the use of a sulphathiazole-sulphadiazine mixture, as the reference in your *Journal* implies, but that I had offered valid animal experimental proof for this new concept of sulphonamide therapy. On the basis of the evidence presented I am forced to conclude, with regret, that the Swedish authors, in quoting my publication, did not cite the facts properly and completely. Hence, they have failed to give due credit to my work in this field.—I am, etc.,

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