

salicylate, acetylsalicylic acid and salicylosalicylic acid (diplosal) was compared in each of three human individuals. Small doses of 0.5 gm. to 1 gm. were used. The mean total excretion of sodium salicylate was 80 per cent., which agrees with the results obtained with very large doses (12 gms.) previously reported. On the other hand, the mean total excretion of salicyl after the administration of the salicyl esters was distinctly less, namely, 60 per cent. Special treatment of the urines for detection and estimation of the undecomposed esters gave contradictory results. Unchanged esters appeared to be present to a small extent only in some urines, absent in other urines. Ethereal extractives of the urines after the administration of methyl salicylate possessed a fruity odor, indicating the presence of the unchanged ester. Larger doses of the esters may give more conclusive evidences along this line. Since all urines were collected until excretion of salicyl was completed, the salicyl unaccounted for appears to have been destroyed, and this is confirmative of previous results with large doses of sodium salicylate. The mean duration of excretion of sodium salicylate and the esters was practically the same, namely, about 48 hours; only the methyl salicylate showing a tendency to somewhat more prolonged excretion (55 hours).

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**The effect of the administration of salvarsan in combination with various colloid substances on its toxicity.**

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In some unpublished articles it has been shown that the ill effects following salvarsan administration may be divided into two types; first, an immediate reaction from which the animal dies suddenly in a convulsive seizure as a result of embolism of its agglutinated red cells, and second, a late death occurring in from two days to as many weeks, which is the result of degenerative lesions in the kidneys and liver. As the former has been

shown to be the effect of the physical properties of the salvarsan solution, while the later is the result of its chemical constitution, we have suggested the terms "physical" and "chemical" toxicity for these two types of ill effects. We have also studied the protective action of various colloids on the process of agglutination of red cells in vitro and found that there is a marked inhibition of the agglutination from salvarsan by certain of these substances.<sup>1</sup>

Recently the effect of the administration of salvarsan in mixture with these protective colloids has been studied. An almost complete removal of the physical toxicity of salvarsan has been found. Under our standard conditions an animal rarely survives the injection of more than .27 gram per kilo of 2 per cent. disodium salvarsan. Yet we have repeatedly given doses of .40 gram per kilo of a similar preparation mixed in a 3 per cent. solution of gelatin with no immediate ill effects. Such animals die from the late chemical toxicity of this tremendous dose in the course of a few days.

The late chemical toxicity of salvarsan is also lessened. Under the conditions of our experiments the maximum tolerated dose of salvarsan was found to be .09 gram per kilo, the majority of animals receiving such a dose surviving two weeks. When administered in 3 per cent. gelatin solution, the maximum tolerated dose was found to be .14 gram per kilo. Administration in acacia solution and in serum was found much less effective in reducing the toxicity, the maximum tolerated dose in the former case being .10 gram per kilo.

Repeated injections of large doses are also better tolerated if the salvarsan is administered in gelatin solution. In some previous experiments animals were given .10 gram per kilo every three days. All the animals died, the majority after the second injection, and on microscopic examination showed marked necrosis of their kidneys. Three rabbits receiving the same dose in gelatin solution withstood 4, 6 and 7 doses and lived 9, 16 and 24 days respectively. The kidneys of these animals showed in the first case a slight parenchymatous degeneration with some necrosis, while in the other two no definite lesions were found.

<sup>1</sup> These articles will appear in an early number of the *Journal of Pharmacology and Experimental Therapeutics*.