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The relative therapeutic efficiency of arsphenamine and gelatin-arsphenamine[1].

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Under certain conditions of H ion concentration compounds are formed between di-sodium arsphenamine and hydrophile colloids. The amount of arsphenamine bound varies with the nature of the colloid and the P_H of the medium in which the reaction occurs. The relative affinity of arsphenamine for certain of these colloids, stated in a descending series, is: gelatin, globulins, gum arabic and egg albumin. A similar union between arsphenamine and the plasma proteins, especially the globulins, may be demonstrated *in vivo* following the intravenous administration of arsphenamine, and it may be further shown that this union is the mechanism by which the animal is protected from the agglutinating action which arsphenamine shows towards the red cells of the blood. If a large amount of arsphenamine is administered, the plasma proteins are "saturated," free arsphenamine is bound by the red cells and agglutination of them results. Under such conditions the compound of plasma globulins, including fibrinogen, with arsphenamine, is found to be no longer coagulable by either heat or thrombin. The shed whole blood from such an animal does not coagulate on standing[2].

From these facts it would seem that the administration of arsphenamine previously bound to such a colloid as gelatin would augment the protecting factors and result in a lower toxicity of the drug. As we have reported[3] such is found to be the case. The immediate or physical toxicity, due to embolism from agglutinated red cells, is lowered to such a degree that relatively enormous doses are well borne. The late, or chemical, toxicity

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[2] Publications in press.

[3] PROC. SOC. EXP. BIOL. AND MED., 1922, xix, 304.

is also lowered, the ratio of the minimum lethal dose of arsphenamine to that of gelatin-arsphenamine being as 10 is to 14.

The relative therapeutic action of arsphenamine and gelatin-arsphenamine was next examined. A priori it may be argued that the gelatin will "protect" the parasite in the same manner as it does the blood cells and tissues of the host. On the other hand, our experiments have shown that the gelatin-arsphenamine is more slowly excreted, and that therefore a higher concentration of it persists in the blood stream and tissues than after the administration of an equal amount of arsphenamine. The therapeutic efficiency of gelatin-arsphenamine would be the resultant of these two opposing factors.

In testing the therapeutic efficiency we have followed the method described by Voegtlin[4]. *Trypanosoma Brucei* were used. Rats showing from 150,000 to 300,000 trypanosomes per c.mm. of blood were given increasing doses of the two substances intravenously. The blood was examined after 24 hours for the presence of parasites and every day for 3 weeks.

The result of 50 experiments may be summarized as follows: Arsphenamine and gelatin-arsphenamine have the same minimum effective dose of 10 mg. per kilo. Such a dose frees the blood stream of parasites in 24 hours. The minimum sterilizing[4] dose[5] which prevents relapses for 21 days is also the same with the two drugs, 20 mg. per kilo.

The chart compares these findings to the results of similar experiments of Voegtlin and of Schamberg, Kolmer and Raiziss with arsphenamine and neo-arsphenamine. It will be noted in comparing the minimum effective doses that the ratio of the indices of therapeutic efficiency, $\frac{\text{minimum lethal dose}}{\text{minimum effective dose}}$, of gelatin-arsphenamine is 1.4 times greater than that of arsphenamine. As will be seen under Voegtlin's findings, this figure is slightly larger than the corresponding ratio of neo-arsphenamine to arsphenamine. Gram for gram, however, gelatin-arsphenamine is twice as effective as neo-arsphenamine and equally effective as arsphenamine.

[4] *Public Health Reports*, 1922, xxxvii, 1627.

[5] Schamberg, Kolmer and Raiziss, *Amer. Journ. Med. Sciences*, 1920, clx, 25.

The minimum sterilizing dose gives similar results. The therapeutic index $\frac{\text{maximum tolerated dose}}{\text{minimum sterilizing dose}}$, of gelatin-arsphenamine is 1.4 times that of arsphenamine and corresponds in this regard to Kolmer's findings with neo-arsphenamine. Gram for gram, gelatin-arsphenamine is almost twice as effective as neo-arsphenamine.

These relations may be summarized as follows: Gelatin-arsphenamine is as effective as arsphenamine and 5/7 as toxic. It is 1.9 times as toxic as neo-arsphenamine, arsphenamine being 2.4 times, and twice as effective.

As used above "toxicity" refers to the late chemical toxicity of the drug. An even more striking contrast is shown if the immediate physical toxicity of arsphenamine and gelatin-arsphenamine is considered. Considerable evidence has been advanced indicating that the "reactions" occurring during or soon after the injection of arsphenamine are due to this physical toxicity[6] [7]. Practically speaking, gelatin-arsphenamine has no immediate toxicity. The immediate toxicity of arsphenamine varies with the condition of the individual. For these reasons no exact ratios can be established, but it can be stated that whereas on account of its physical toxicity, a resulting "acute reaction" is always a possibility during the injection of arsphenamine, it seems unlikely from the experimental evidence on hand that such acute mishaps could occur with gelatin-arsphenamine under any conditions or with any dosage.

MINIMUM EFFECTIVE DOSE

Arsphenamine and Neo-Arsphenamine—Voegtlin

$$\text{Therap. Index Arsphen.} \frac{\text{M. L. D. (206)}}{\text{M. E. D. (9.9)}} = 20^{1}.$$

$$\text{Therap. Index Neo-Arsph.} \frac{\text{M. L. D. (438)}}{\text{M. E. D. (20.6)}} = 24^{1}.$$

$$\text{Ratio} \frac{\text{Therap. Index Neo-Arsphen.}}{\text{Therap. Index Arsphen.}} = 1.2.$$

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[6] Karsner and Hanzlick, *Jour. Pharm. and Exp. Therap.*, 1920, xiv, 479.

[7] Oliver and Yamada, *Jour. Pharm. and Exp. Therap.*, 1922, xix, 393.

$$\text{Ratio}\ \frac{\text{M. E. D. Arsphen.}}{\text{M. E. D. Neo-Arsph.}} = .48.$$

Arsphenamine and Gelatin-Arsphenamine

$$\text{Therap. Index Arsphen.}\ \frac{\text{M. L. D. (100)}}{\text{M. E. D. (10)}} = 10.$$

$$\text{Therap. Index Gel. Arsp.}\ \frac{\text{M. L. D. (140)}}{\text{M. E. D. (10)}} = 14.$$

$$\text{Ratio}\ \frac{\text{Therap. Index Gel. Arsp.}}{\text{Therap. Index Arsphen.}} = 1.4.$$

$$\text{Ratio}\ \frac{\text{M. E. D. Arsph.}}{\text{M. E. D. Gel. Arsph.}} = 1.$$

MINIMUM STERILIZING DOSE

Schamberg, Kolmer and Raiziss

$$\text{Therap. Index Arsphen.}\ \frac{\text{M. T. D. (105)}}{\text{M. S. D. (23)}} = 4.5.$$

$$\text{Therap. Index Neo-Arsph.}\ \frac{\text{M. T. D. (254)}}{\text{M. S. D. (40)}} = 6.3.$$

$$\text{Ratio}\ \frac{\text{Therap. Index Neo-Arsphen.}}{\text{Therap. Index Arsphen.}} = 1.39.$$

$$\text{Ratio}\ \frac{\text{M. S. D. Arsphen.}}{\text{M. S. D. Neo-Arsph.}} = .57.$$

$$\text{Therap. Index Arsphen.}\ \frac{\text{M. T. D. (90)}}{\text{M. S. D. (20)}} = 4.5.$$

$$\text{Therap. Index Gel. Arsph.}\ \frac{\text{M. T. D. (130)}}{\text{M. S. D. (20)}} = 6.5.$$

$$\text{Ratio}\ \frac{\text{Therap. Index Gel. Arsph.}}{\text{Therap. Index Arsph.}} = 1.4.$$

$$\text{Ratio}\ \frac{\text{M. S. D. Arsphen.}}{\text{M. S. D. Gel. Arsp.}} = 1.$$

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[1] The greater magnitude of these ratios as compared to our figures and those of Schamberg *et. al.* is the result of the high lethal dose. This is doubtless due to the shorter period of observation, 48 hours instead of two weeks, which Voegtlin used.

M. L. D. = minimum lethal dose. M. S. D. = minimum sterilizing dose.
M. E. D. = minimum effective dose. M. T. D. = maximum tolerated dose.