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The Inhibition of Anaphylactic Shock by the Intravenous Injection of Neoarsphenamine.*

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We have been particularly interested in the prevention or modification of anaphylactic shock by intravenous injection of colloidal substances into the sensitized animal before reinjection of the antigen, in connection with our studies on the rôle of the reticulo-endothelial system to various immunity phenomena.[1] Extensive studies on the effect of a large number of various colloids (India ink, trypan blue, collargol, casein, etc.), when introduced by the intravenous route into sensitized guinea pigs shortly before reinjection of the antigen, have in our hands, contrary to the findings of other investigators, led uniformly to negative or doubtful results. We have been able, however, to amplify the interesting contributions of Freud[2] and Walbum[3] in a similar field by observing that tuberculous guinea pigs frequently survived a fatal dose of tuberculin when this was preceded (a few hours) by an intravenous dose of India ink. More significant results, of which the following is a brief report, have recently been obtained with the intravenous administration of neoarsphenamine in sensitized guinea pigs shortly before reinjection of the specific antigen.

In one experiment 20 guinea pigs, weighing from 250 to 350 gm., were sensitized by the subcutaneous injection of 0.01 cc. of normal horse serum. The minimum dose of antigen, capable of producing after intravenous injection death from acute anaphylactic shock within 3 to 5 minutes, was determined in 4 animals, 3 weeks later, and found to be 0.3 cc. The remaining 16 animals, in groups of 4, were given at the same time, 1 cc. of a 1:50 dilution of neoarsphenamine intravenously, preceding the intravenous reinjection with 0.3 cc. of normal horse serum at intervals of 5 minutes, 15 minutes, 30 minutes and one hour. The 4 animals which had received the antigen 5 minutes after the injection of the arsenical showed no immediate symptoms, but died from protracted shock within 20 to 35 minutes. Of those injected after the 15 minute interval, 2 survived

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without exhibiting more than transitory dyspnea and slight anaphylactoid symptoms such as were seen in normal guinea pigs from the dose of neoarsphenamine employed; the other 2 died with ill-defined symptoms within 10 to 20 minutes. With the 30 minute interval, one animal survived and 3 died more suddenly, while in the last group, which had received the neoarsphenamine one hour previously, death occurred in all animals with typical anaphylactic shock within 3 to 5 minutes. With the exception of the last group, autopsy of the dead animals did not reveal the characteristic inflation of the lungs. The 3 surviving animals of this series were reinjected intravenously 24 hours later with 0.5 cc. of normal horse serum in order to determine the presence of anti-anaphylaxis. All survived without exhibiting any symptoms whatsoever.

In another experiment 12 guinea pigs of the same weight were sensitized passively by the intraperitoneal injection of 1 cc. of an anti-horse rabbit immune serum, which gave a marked precipitin reaction with the antigen up to 1:2000 dilution. The minimum dose of horse serum, producing actual fatal shock after intravenous injection, was determined 24 hours later in 4 animals and found to be 0.05 cc. The remaining 8 animals, in groups of 4, were given at the same time intravenously 1 cc. of a 1:50 dilution of neoarsphenamine 15 and 30 minutes, respectively, before the intravenous injection of 0.05 cc. of normal horse serum. Of the 4 animals receiving the antigen 15 minutes after the drug, 3 survived, showing only slight initial dyspnea, one died within 25 minutes in protracted shock; of the 4 injected after the 30 minutes interval, 2 survived and 2 died within 10 to 20 minutes. The surviving animals were tested the following day for antianaphylaxis and were found to be fully protected against 0.5 cc. of normal horse serum.

Although the number of animals in these 2 experiments is too small to draw definite conclusions, it appears that the intravenous injection of neoarsphenamine into actively and passively sensitized guinea pigs, if given 15 to 30 minutes before the introduction of the specific antigen, was capable of saving at least 50% of the animals, while the rest died during prolonged prostration from a modified shock which did not include the classical symptoms of acute anaphylaxis. It is difficult to determine accurately at present the mechanism of this inhibitory action. The fact that the surviving animals were antianaphylactic 24 hours later points to a specific desensitization which makes an explanation based solely on a temporary disturbance of the blood colloids somewhat unlikely. The production of an effect analogous to a blockade of the histiocytes, for which the drug undoubtedly has a strong affinity,[4] or an action

on other susceptible tissue cells, seems to be highly improbable since the protective effect of the neoarsphenamine appeared to be definitely limited to the time during which the drug is present in the circulation at the maximal concentration. An adsorption of complement cannot be considered more than possibly a contributing factor inasmuch as we found that even as strong an adsorbent as yeast cells, when introduced intravenously into a sensitized guinea pig, did not protect against a subsequent shocking injection, but rather, on the contrary, provoked in itself in some cases very marked symptoms resembling true anaphylactic shock. In view of the pronounced anticoagulant properties of the arsphenamines, one might be tempted to assume such an action as the cause for the observed protection, were it not for the fact that recent studies by Hanzlik, Butt and Stockton,[5] Reed and Lamson[6] and Hyde[7] have apparently refuted the earlier claims of Kyes and Strauser[8] and Williams and van de Carr[9] on the shock-preventing action of heparin. Finally, one might think of a denaturizing effect of the arsenical on the antigen which would entail a change of the immunological specificity of the latter, since the injection of an *in vitro* prepared mixture of antigen and neoarsphenamine was likewise tolerated by some sensitized animals, without being followed by death from anaphylactic shock. Such an hypothesis would seem to be supported by the earlier work of Swift[10] and Landsteiner,[11] and would find an interesting analogy in the more recent studies of Steppuhn, Zeiss and Brychonenko,[12] Schmidt,[13] Makarowa and Zeiss,[14] and Iwanoff[15] on the shock preventing and biological properties of "Germanin" (Bayer 205).

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