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Toxin-antitoxin mixtures as immunizing agents.

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Ehrlich early suggested that injections of partially neutralized diphtheria toxin produced active immunity. This was demonstrated by Wernicke, Dreyer and Madsen, Morgenroth, ourselves and others. Smith in a recent article suggested the use of such mixtures in the immunization of children. The possibility of such a practical application has suggested to us some experiments with especial reference to the safety and effectiveness of the injections.

The proportion of toxin to antitoxin in the mixture required to produce immunization. — In May, 1903, one of us reported some experiments in which one set of horses were injected with mixtures containing toxin .66 of L+ dose for each unit of antitoxin and another with .66 of L+ for each 4 units of antitoxin. Three large injections produced in the first series an average of 150 units, in the second an average of 3 units in each c.c. of serum.

Smith injected three guinea pigs with 1 unit plus 1 L+ dose, 2 units plus 1.3 L+ dose, and 2 units plus 1 L+ dose respectively. The litters born from the first and second animals showed marked immunity at the end of eight months. The litter from the third animal showed slight immunity at three months and none at six months.

These experiments indicate that while even a proportion of 6 units of antitoxin to 1 L+ of toxin produces slight immunity, the toxin must be in proportion of more than 1 L+ dose to 2 units to give marked and lasting effects.

This brings us to the question of the safety of such mixtures. The work of Morgenroth suggests that mixtures which are toxic for one species are toxic for all. There is a difference, however, among animals as to the amount of natural immunity and perhaps therefore as to the development of serious symptoms or death from a given quantity of toxin-antitoxin mixture. Even if all guinea pigs lived, therefore, there would be a slight uncertainty in infants.

In a series of tests we found that the least proportion of diphtheria toxin which was necessary to give lasting immunity was not quite harmless in guinea pigs. Thus of four guinea pigs receiving a mixture of 1 unit plus $\frac{1}{2}$ L+ the two larger remained permanently well, while the two smaller finally died of paralysis. Four guinea pigs receiving one half the quantity of the same mixture all remained alive. Two other series receiving still larger quantities of the same mixture acted as the first lot. Some of these guinea pigs received six months later two fatal doses of toxin without serious poisoning.

It is interesting to note that three of these animals received repeated injections of toxin in increasing amounts, until finally 6,000 fatal doses were given in one injection. The blood of the animals at this time contained from 25 to 30 antitoxin units per cubic centimeter. It is possible that the toxin used in these experiments which was produced by Culture No. 8 may have more tendency to promote late paralysis than that from other cultures such as used by Smith.

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Antiperistalsis in its relation to tubercle bacilli and other bacteria in the alimentary tract.

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Fifteen years ago Grützner showed that charcoal, starch and similar substances when introduced in normal salt solution into the rectum, ascended in the intestinal tract and after from four to six hours could be demonstrated in the stomach. His work was confirmed by some and refuted by others. This problem has of late assumed a new aspect inasmuch as some workers have claimed that when bacteria are introduced in the same way, within a short time they ascend by means of the antiperistaltic action of the alimentary tract to the stomach, œsophagus and thence into the respiratory tract. The most recent report of this phenomenon comes from the Kaiserliche Gesundheitsant, which concludes that this antiperistaltic movement must be considered, not only in exper-