as have been demonstrated with the colon-paratyphoid group and other organisms. Rabbits inoculated with 3-day filtrates were not affected. One rabbit inoculated with an 8-day filtrate had a severe diarrhea within one hour after injection. A guinea pig received intravenously 1 cc. of the filtrate of the same strain which affected the rabbit, but showed no signs of discomfort. Rabbits injected with filtrates of another strain of *B. Friedlander* which was not virulent for mice were not affected.

The results indicate that with an organism highly virulent for mice when injected into the peritoneum, injections of filtrates of culture 18 hours to 20 days old could not be shown to be toxic for these animals when injected into the same body cavity. The effect of the filtrate of *B. Friedlander* appears to be less constant in its action in rabbits when given intravenously than that reported with other organisms.

3104

Heparin. II. Investigation of possible antigenic action.*

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In a previous paper[1] were reported details of experiments on the intravascular use of heparin[2, 3, 4] in etherized dogs. These experiments, together with other experiences in preservation of blood samples used for various physical and chemical analyses, have demonstrated the value of this material in laboratory work. It seemed advisable, therefore, to investigate the possibilities of its use in transfusion when, for any reason, there might be delayed injection.

* Part of the expense of this investigation was borne by a grant from the American Association for the Advancement of Science.

1 Reed, C. I., *Am. J. Physiol.*, 1925, lxxiv, 79.

2 Howell, W. H., *Am. J. Physiol.*, 1918, xlvii, 328.

3 *Ibid.*, 1922, lxiii, 434.

4 *Ibid.*, 1925, lxxi, 553.

Numerous experiments were undertaken in which large doses of heparin—5 to 60 mg. per kilo of body weight—were injected intravenously in normal dogs and rabbits. In no instance was there any demonstrable gross disturbance of any body function.

It occurred to us, however, that the effects of repeated injections should be investigated. For this purpose, 20 mg. per cc. of heparin were dissolved in Ringer solution and injected into the peritoneal cavity of adult healthy guinea pigs, in relatively large doses, 20 to 60 mg. In a few instances symptoms characterized by prostration and weakness occurred within a few minutes after the first injection. After periods varying from 2 to 3 weeks, transcutaneous and intracutaneous tests were made with a similar solution of heparin, all of which proved negative. A second injection of a comparable dose of heparin was now made. In most cases this proved entirely negative, but in a few instances there occurred symptoms suggestive of anaphylaxis.

These results, together with those noted following the first injection, suggested two possibilities: 1. There might be a protein fraction in the heparin that sensitized certain more susceptible animals. 2. The heparin possessed toxic properties of undetermined nature.

Subsequent employment of fresh lots of heparin uniformly failed on both first and second injections to produce either toxic or anaphylactic symptoms, so that it is possible that the particular lot first used had not been satisfactorily purified.

Several lots of material from various stages in the purification of heparin were secured.† Some of these were highly toxic, both first and second injections producing immediate symptoms from which all the animals recovered. The most highly purified material, like heparin, gave entirely negative results after both first and second injections.

In another series, heparin was injected, and after 3 weeks relatively large doses of normal horse serum were injected intraperitoneally with negative results.

In still another series a sensitizing dose of horse serum was injected, and after 3 weeks a large dose of heparin. These were also negative.

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† These fractions, as well as part of the pure heparin, were generously supplied by the manufacturers, Messrs. Hynson, Westcott, and Dunning, Baltimore, Md.

The net result of 58 experiments was a complete failure to demonstrate by cutaneous or systemic reactions any antigenic properties for heparin.

The power of heparin to *modify* the antigenic action of horse serum is still under investigation.

3105

An attempt to locate cells of kinaesthetic sensibility in extraocular eye muscles.

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Experimental work on dogs, cats, and pigs has thus far yielded the following positive findings. The cells of the III, IV, and VI cranial nuclei of the dog and cat can be separated into two distinct sizes, hitherto unrecognized, both having "motor" tigroid substance, and being in general diffusely intermingled throughout the nuclei. The smaller cells do not preponderate in any portion of the III, IV, or VI nuclei, nor in any of the subnuclei of the III, except Perlia's median nucleus which, in the dog, is made up entirely of the smaller cells. In the dog, the proportion of the sizes of the cells by actual count correlates roughly with the sizes of fibers in the peripheral trunks, more especially in the case of the third cranial pair. There is in the dog an excess of cells in the central nuclei of the extraocular muscles over the number of fibers in the peripheral homologous trunks, roughly, 30 to 40 per cent for the Nn. III and IV, and 10 per cent for the N. VI. Adequate clumps of cells along the peripheral nerves for the mediation of kinaesthetic sense of the extraocular muscles have not been demonstrated. The accumulated evidence of experiments with degenerations thus far indicates the possibility that the smaller cells in the central nuclei may mediate kinaesthetic sense of the extraocular muscles. The problem is being attacked further.