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### Relation of Hypophysis to Spleen. III. Hypophysectomy and Resistance to *Trypanosoma lewisi*.

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Hypophysectomized animals are less resistant to the effects of anesthetics, drugs, toxins and spontaneous infections (Perla<sup>1</sup>). The decrease in general resistance is associated with involutinal changes in the suprarenal glands. The alteration in natural resistance to poisons such as histamine<sup>2</sup> is attributed in part to the withdrawal of the adrenotropic hormone of the hypophysis, since it may be restored by the administration of suprarenal cortical hormone (Perla<sup>3</sup>), emulsions or extracts of dried anterior hypophysis rich in adrenotropic factor<sup>4</sup> and heated acid extracts containing only active adrenotropic hormone.<sup>5</sup>

The removal of the hypophysis is associated with a drop in natural resistance to both spontaneous bacterial and to induced protozoan infection (*Trypanosoma lewisi*) (Perla,<sup>1</sup> Culbertson and Molomut<sup>6</sup>). A drop in resistance to infection of this type is in part due to the effect of hypophysectomy on the spleen and lymphoid tissues (Perla<sup>5</sup>). Perla and Marmorston and Taliaferro, Cannon and Goodloe<sup>7</sup> observed that removal of the spleen in *Bartonella*-carrier or *Bartonella*-free rats disturbs the production of trypanolysins and reproduction-inhibitory antibodies and a more severe and more prolonged trypanosome infection occurs. Suprarenalectomy, on the other hand, lowers the resistance but does not alter the course of the infection in those surviving the toxemia (Perla and Marmorston<sup>9</sup>). Since removal of the hypophysis results in atrophy of splenic and lymphoid tissue it seemed reasonable to anticipate an alteration in

<sup>1</sup> Perla, David, *Proc. Assn. for Research in Nervous and Mental Diseases*, 1936a, **17**, 471.

<sup>2</sup> Perla, D., and Rosen, S. H., *Arch. Path.*, 1935, **20**, 222.

<sup>3</sup> Perla, David, *Proc. Soc. Exp. Biol. and Med.*, 1935, **32**, 797.

<sup>4</sup> Perla, David, *Proc. Soc. Exp. Biol. and Med.*, 1935, **33**, 121.

<sup>5</sup> Perla, David, *Proc. Soc. Exp. Biol. and Med.*, 1936, **34**, 751.

<sup>6</sup> Culbertson, J. T., and Molomut, N., *Proc. Soc. Exp. Biol. and Med.*, 1938, **39**, 28.

<sup>7</sup> Taliaferro, W. H., Cannon, P. R., and Goodloe, S., *Am. J. Hyg.*, 1931, **14**, 1.

<sup>9</sup> Perla, David, and Marmorston, J., *The Spleen and Resistance*, Williams and Wilkins, 1935, Baltimore.

response to infection with *Trypanosoma lewisi*.<sup>\*</sup> It was suggested (Perla<sup>8</sup>) from experimental evidence that a spleen-stimulating factor exists in the anterior hypophysis. In the present communication further data on the effect of hypophysectomy in rats on infection with *T. lewisi* is presented. The effects of extracts of the pituitary was determined both on hypophysectomized infected and unoperated infected animals.

In the experiments of Culbertson and Molomut<sup>6</sup> all the hypophysectomized rats succumbed in an average period of 5.4 days after injection of the trypanosomes.† The intensity of infection, however, did not exceed that of the controls as determined by the number of trypanosomes at the peak of infection. Some of the operated controls also died of the infection and only a few were protected by anterior pituitary extract (Squibb, in amount of 10 rat units daily‡).

*Methods:* All the rats were of Bartonella-free stock, 6 to 8 weeks of age. They were injected 2 to 3 weeks after hypophysectomy with 50,000 trypanosomes. Some were treated with daily injections of acid or alkaline extracts of dried anterior pituitary substance from the day of operation.

TABLE I.  
Effect of Complete and Partial Hypophysectomy in the Rat on Course of Infection with *Trypanosoma lewisi* (All infected 2 to 3 weeks after hypophysectomy).

Operation	No. rats	Treatment	Avg No. trypanosomes at peak	No. days from injection to peak	Duration of infection in days
Complete hypophysectomy	10	None	741,000	7.3	27.4
Partial hypophysectomy	11	"	526,000	7.5	18.7
Unoperated controls	10	"	524,200	6.8	19.2
Complete hypophysectomy	10	Alkaline extr. of ant. lobe*	573,500	6.2	18.8
Complete hypophysectomy	7	Acid extr. of ant. lobe†	1,126,000	7.8	26.8

\*The alkaline extracts were prepared as follows: 10 gm of dried powder was extracted with 100 cc of 0.5 N sodium hydroxide over night. The fluid was brought up to pH 7.8, centrifuged and filtered through a Zeiss filter. 1 cc of this extract was injected daily intraperitoneally.

†The acid extract of dried anterior hypophysis was prepared by the method of Loeb.<sup>5</sup> 10 g of dried powder was extracted with 100 cc of ½% acetic acid over night. The fluid was brought to pH 6.8, centrifuged and then brought to 7.8 and filtered through a Zeiss filter.

\* The evidence of the relation of the spleen to resistance is reviewed in a monograph by Perla and Marmorston.<sup>9</sup>

<sup>8</sup> Perla, David, *J. Exp. Med.*, 1936, **63**, 599.

† All received 1 million trypanosomes intraperitoneally.

‡ The nature of the rat unitage is not mentioned.

*Results:* From Table I, it is seen that the infection in the hypophysectomized animals extended for a period 50% longer in duration than that in either the unoperated rats or the partially hypophysectomized animals. Partial hypophysectomy had no effect on the course of the infection. The intensity of the infection as determined by the number of trypanosomes at the peak of the disease was somewhat greater in the hypophysectomized rats than in those of the control groups with intact hypophysis. None of the animals died.

The duration of infection in the hypophysectomized rats treated with alkaline extracts was approximately the same as in the control groups. The duration of the infection in the hypophysectomized rats treated with acid extracts was as long as that of the untreated hypophysectomized rats. The intensity of the infection as estimated by the number of trypanosomes at the peak was more severe in the rats treated with acid extract than in those of all the other groups.

The number of days from the day of injection to the height of infection was approximately the same in all groups. Reproduction forms were not present in the blood after the first 8 to 10 days in any group. From these observations it is probable that the reproduction-inhibiting factor, ablastin, was normally produced in the hypophysectomized animals. The prolongation of the infection following hypophysectomy suggests some impairment in the production or activity of trypanolysins. When a rat does not form ablastin in infections with *T. lewisi*, the parasite produces a lethal infection. Splenectomy in animals does not abolish the formation of ablastin but in some instances only it may inhibit its production. It does, however, prolong the duration of the disease.<sup>9</sup> Since hypophysectomy decreases splenic activity and growth but does not completely abolish its function, the effect of hypophysectomy need not be as severe as splenectomy on the course of infection with *T. lewisi*.

The results reported by Culbertson and Molomut<sup>6</sup> may be attributed to the fact that a much greater infecting dose of trypanosomes was employed in their experiments and the disease, therefore, may have proved fatal. The animals, in their experiments, were infected within one week after operation at a time when the resistance of such animals is known to be lowest (Perla and Rosen<sup>2</sup>). In the

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§ In Culbertson's experiments, though death occurred, it cannot be concluded that ablastin was not produced, since the rats died prior to the time when the peak of infection occurs in control rats. Further, the number of trypanosomes at the time of death did not exceed that of the controls. In other words, death was not necessarily an expression of impairment of immune processes but of enhanced susceptibility to the toxic effects of infection.

present work the animals were not infected until 2 to 3 weeks after operation at a time when the general resistance is not as severely affected but the spleen and lymphoid tissue have undergone pronounced atrophy (Perla<sup>8</sup>). The results of these experiments is further proof of the effect of hypophysectomy on the functional response of splenoid tissue.

*Summary and Conclusions.* Hypophysectomy in rats was followed by a decrease in resistance to a protozoan infection such as *Trypanosoma lewisi*. The infection was prolonged and the intensity of the infection exceeded that of the controls. The administration of alkaline extracts of anterior lobe, rich in spleen-stimulating factor restored the resistance to the normal level.

It is likely that the altered resistance to protozoan infection in hypophysectomized rats is in part attributed to impairment of the function of the splenoid tissue.

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### **Comparative Experimental Studies on Symptomatology and Anatomical Changes Produced by Anoxic and Insulin Shock.**

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Thirty-eight rabbits were exposed to anoxia for short periods during which the oxygen percentage in the mixture with nitrogen was so slowly decreased as to avoid excitement, though in some instances the anoxia was prolonged until respiration ceased. This slow deprivation of oxygen is termed anoxic shock. The rabbits were exposed to from 1 to 51 anoxic shocks during a period of from 1 to 60 days. The duration of a single shock varied from 15 to 60 minutes. Twenty-nine other rabbits were injected with insulin sufficient to produce coma and convulsions.

The symptoms of the insulin and anoxic shock were similar except that those due to anoxia occurred on a more rapid time scale. Anoxia was characterized by increase of the respiratory rate, dilatation of the ear arteries, muscular weakness, somnolence and finally decrease of the respiratory rate and complete cessation of respiration, though the heart continued beating. In insulin shock muscular weakness and somnolence also occurred before convulsions and coma. Here, too, respiratory arrest was observed. With