

note that *Trypanosoma brucei*, although equally susceptible to the photodynamic action of eosin, cannot be preserved by this treatment.

The fact that *Trypanosoma brucei* can be well preserved morphologically by the photodynamic action of methylene blue even at incubator temperature for a considerable length of time, and that a large quantity of such treated organisms can be easily obtained by the method described, offers the possibility of studying active immunization in susceptible animals with a vaccine. Since the protective property of heat-treated trypanosoma vaccine has not been satisfactorily demonstrated such a method is worthy of further investigation.

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Observations on the "Latent Period" in Experimental Diabetes Insipidus.*

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The "latent period" as designated and described by Fisher, Ingram, and Ranson¹ was encountered by us without exception in upward of 30 experiments in the dog where permanent d.i. of varying severity has followed hypothalamic lesions. The operation was usually followed immediately by a polydipsia and polyuria which was invariably interrupted by a return of the water exchange toward normal, usually reaching to below normal, in a matter of 2 to 6 days. The more or less abrupt onset of the permanent phase of polydipsia and polyuria occurred on the seventh to eleventh postoperative day. Our series differed from the Fisher series in that the d.i. of the temporary phase was, as a rule, greater in magnitude than that of the permanent phase.

In view of the evidence indicating that a functioning pars anterior of the hypophysis is essential for the occurrence of d.i. *in its maximal form*, it seemed possible that the events of the latent period might be explained on the basis of the operative procedure produc-

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¹ Fisher, C., Ingram, W. R., and Ranson, S. W., *Arch. Neurol. and Psychiat.*, 1935, **34**, 124.

ing in addition to an immediate and lasting impairment of the anti-diuretic secretory mechanism also a transitory depression of the pars anterior, the onset of the permanent phase signaling the returning function of this tissue.

This explanation seemed at first particularly possible because the essential characteristics of the latent period have been duplicated in a series of dogs in which total hypophysectomies were attempted and, after a lapse of several days, anterior pituitary extract was administered (see upper graph, Fig. 1). There occurred in these

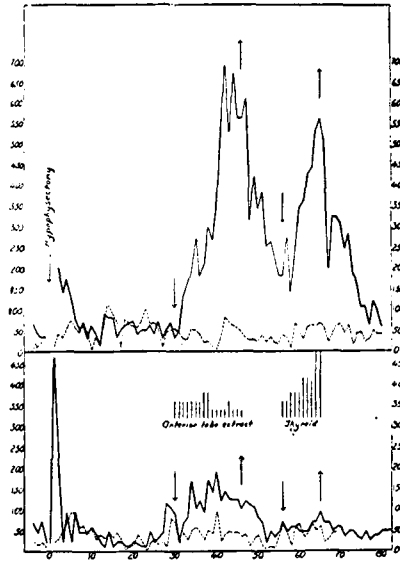


FIG. 1.

Solid line—water intake. Stippled line—food intake. Ordinate—cc. and gr. per kilo. body weight. Abscissa—days after operation. Upper curves—dog 192, wt. 5.5 kilo. Lower curves—dog 193, wt. 4.2 kilo. The magnitude of the polydipsia on the first day in 192 was not determined because of its water being contaminated with feces. Both dogs were operated the same day and received the same dosage of anterior pituitary extract (.5 to 1.5 cc. per day subcutaneously) and thyroid (1 to 4 gm. U.S.P. powder per day by capsule) irrespective of body weight. In dog 192 there was no gross involvement of the hypothalamus but the hypophysectomy was incomplete in that fragmentary islets of tuberalis cells remained attached to the hypothalamus and a remnant of the pars intermedia remained in the base of the pituitary fossa associated with the posterior lobe artery. In dog 193 the larger portion of the tissue of the hypophyseal stalk remained intact as well as remnants of pars intermedia and anterior.

dogs on the first day after operation a striking (500 cc. per kilo) though moderate d.i. which on succeeding days became progressively reduced either to normal (approx. 50 cc.) or to a level intermediate between normal and that of the immediate transitory phase (200 cc.). (If the spontaneous consumption of water and food is pre-

vented as by prolonged anesthesia or a very sore head, this transitory phase may not be detected.) Whether or not the water exchange returned to normal or leveled off above normal, a subsequent daily administration of anterior pituitary extract over a period of several days elicited characteristically a striking d.i. (see upper curve, Fig. 1).

The return of the water exchange to normal following an attempted total hypophysectomy is indicative, we believe, that a functional remnant of antidiuretic secretory tissue remains intact. This belief is based on our findings in a group of dogs in which only partial hypophysectomy was performed in that the hypophyseal stalk was purposely left attached to the brain.[†] In these animals there was also usually an immediate transitory d.i. after which the water exchange always returned quickly to normal or below and in addition the preparations were subsequently resistant to anterior pituitary extract. (See lower curves, Fig. 1.) By taking special care in severing the body of the gland, previous to its removal, from the stalk as by a clean cut with scissors the immediate transitory d.i. has in instances been avoided. We interpret the immediate transitory d.i., when it appears in such an animal, as being due to a temporary traumatic paralysis of the secretory tissue of the stalk. The fact that such a preparation can be prepared without transitory d.i. occurring would seem to indicate that this tissue normally secretes the antidiuretic principle in the intact animal; that is, there is no reason to believe that it assumes this function after the operation.²

Assuming that there is a complete absence of the antidiuretic principle in the presence of *total* hypophysectomy, the immediate³ transitory d.i. which follows this procedure may well be explained in terms of the evidence that d.i., at least in its maximal form, is dependent upon thyroid activity and on the basis of the known difference in latencies of action of the antidiuretic and thyroid substances. Thus one would expect in the presence of a simultaneous abrupt removal of the antidiuretic and the thyrotropic principles that the effects of the former would appear before the latter. The pars anterior deprivation effect in this respect seems, however, already evident on the first day after operation because the magnitude of the

[†] This procedure in the dog is equivalent to "hypophysectomy" as it has been practiced in the rat as well as probably in most instances on record for other species.

² Sato, G., *Arch. f. exp. Path. u. Pharm.*, 1938, **131**, 45.

³ a. Howet, F., *C. R. de la Soc. de Biol.*, 1936, 798; b. Richter, C. P., *A. R. N. M. D.*, 1938, **17**, 392.

water exchange on this day in these experiments has never approached that encountered following hypothalamic lesions. On the basis of our observation we suspect that in the situation of a complete absence of the antidiuretic principle in the presence of an intact pars anterior that the water exchange would be a liter or more per kilo.^{3b} Again the presence of a persistent submaximal d.i. in the total absence of the pars anterior is consistent either with the view that d.i. is wholly dependent upon thyroid activity⁴ or with the possibility that a low grade d.i. is possible in the total absence of thyroid tissue,⁵ thyroid activity being essential only for the occurrence of d.i. in its maximal form. Even if d.i. is entirely dependent upon thyroid activity, one would expect a mild or moderate form of d.i. to persist following total hypophysectomy because it is known that removal of the pars anterior results in marked hypothyroidism but not athyroidism.⁶

The possibility that the events of the latent period are due to a transitory depression of anterior pituitary functions is immediately questioned when it is recognized that a *permanent*, but submaximal, d.i. does occur in the complete absence of the pars anterior.⁷ This being true, even in the complete absence of the antidiuretic principle as well as the pars anterior, the lowest level that the water exchange could reach (unless other factors entered) would be considerably above normal. Actually in our series the water intake was frequently reduced to below normal, even to zero, for a day or two just prior to the onset of the permanent phase.

In order to test this possibility in a more specific way, anterior pituitary extract of established potency and dosage⁸ was administered daily during the immediate postoperative period to 8 dogs in which it was deliberately attempted to precipitate d.i. by hypothalamic lesions. An immediate moderate, though well marked, d.i. developed in 5 and a mild d.i. in 2 of these dogs. Without exception there was a transitory return of the water exchange to or near to normal, there being no detectable gross change in the characteristics of the latent period. The experiment on dog 215 is typical of the series. Its essential features are graphed in Fig. 2.

Conclusion. In the light of the foregoing analysis it seems that

⁴ a. Barnes, B. O., Regan, J. F., and Buano, J. G., *Am. J. Physiol.*, 1933, **105**, 559; b. Mahoney, W., and Sheehan, O., *Am. J. Physiol.*, 1933, **112**, 250.

⁵ a. Fisher, G., and Ingram, W. R., *Arch. Int. Med.*, 1936, **58**, 117; b. Findley, T., *An. Int. Med.*, 1937, **11**, 701.

⁶ Houssay, B. A., *Endocrinol.*, 1934, **18**, 409.

⁷ a. Reichert, F. L., and Dandy, W. E., *Bull. Johns Hopkins Hosp.*, 1936, **58**, 418; b. Mahoney, W., and Sheehan, D., *Brain*, 1936, **59**, 61.

⁸ Keller, A. D., *PROC. SOC. EXP. BIOL. AND MED.*, 1937, **36**, 787.

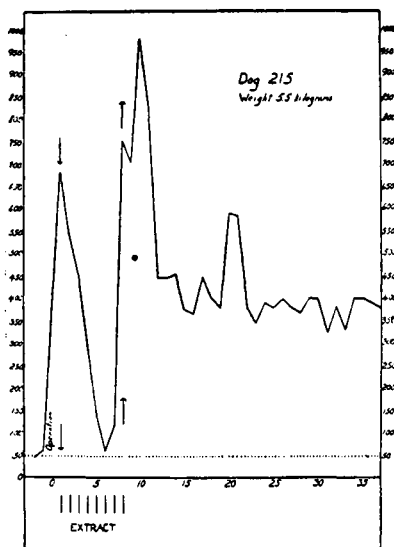


FIG. 2.

Food and water intake as in Fig. 1. Anterior pituitary extract 1 cc. daily subcutaneously. Note that in this experiment the food consumption (Baloration) was maintained constant.

the early temporary alleviation of d.i. which invariably occurs when prolonged d.i. is precipitated by hypothalamic lesions is not due to a fleeting depression of anterior pituitary function.‡

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Total Creatinine, Phosphates, Calcium and Potassium in Normal and Infarcted Myocardium of the Dog.*

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In 1934 and 1935 with the help of Decherd, the authors studied the mobilization of creatine in experimental myocardial damage¹

‡ We are indebted to Dr. Oliver Kamm of Parke, Davis & Co. for the generous supply of "anterior pituitary total extract" which we used in these studies. Although it is now going on the second year since the lot was prepared, it is still satisfactory in potency, as evidenced by experiments executed at the present time (December 1).

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¹ Herrmann, G., and Decherd, G., *PROC. SOC. EXP. BIOL. AND MED.*, 1934, **32**, 477.