various types of spinal cord neurones, and has found it not to affect interneurones, Renshaw cells or motoneurones. The latter two observations are in accord with the results presented here, and it is possible that those interneurones studied by CURTIS were all of the type which have been found to be uninfluenced in the present experiments also. The results which have been obtained here would suggest that a possible explanation of the action of applied 3-hydroxytyramine reported earlier[1], is that it leads to the excitation of inhibitory interneurones which make synaptic contact with the motoneurones of the cord.

Zusammenfassung. «Direkte» Hemmung monosynaptischer spinaler Reflexe in Katzen wird durch Administration von DCI nicht verhindert, obwohl die Hemmung nach Reizung der bulbären retikulären Formation ausbleibt. 3-Hydroxytyramine, dessen reflexhemmende Wirkung bei direkter Applikation am entblössten Rückenmark früher gezeigt wurde, verursacht eine gesteigerte Erregbarkeit mancher Interneurone der retikulospinalen Leitungsbahn, wodurch seine hemmende Wirkung erklärt werden könnte.

H. MCLENNAN

Department of Physiology, University of British Columbia, Vancouver (Canada), March 12, 1962.

Antidiuretic Hormone Concentration in Blood Perfusing the Adenohypophysis

The concept of the antidiuretic hormone (ADH, vasopressin) as a physiological stimulus for adenohypophysial ACTH secretion has been questioned recently[1-4]. An argument often employed against this once attractive hypothesis is based upon the fact that the concentration of injected Pitressin or vasopressin which stimulates ACTH secretion is much larger than that mimicking physiological antidiuresis. Because a high concentration is not normally encountered in peripheral blood, this action of vasopressin on the adenohypophysis is interpreted as pharmacologic. Implicit in this interpretation is the assumption that high adenohypophysial and low peripheral blood concentrations of ADH are physiologically mutually exclusive.

The purpose of this paper is to demonstrate that both conditions do, in fact, normally exist. Our reasoning follows and is based on a calculation of the ADH content in blood leaving the neural lobe and directly perfusing a major portion of the adenohypophysis. The data used in our calculations are our own measurements of neural lobe blood flow[5], coupled with GINSBURG's estimate of the half-life of circulating ADH[6], HELLER's measurements of the resting ADH level in the rat[7], and DE WIED's data for the ADH response to haemorrhage in the rat[8].

The resting level of ADH in the adult albino rat is 2.3 μU/ml whole blood[7]. A 300 g rat with about 15 ml blood volume therefore has a total circulating ADH content of about 35 μU. According to GINSBURG[6] the half-life of circulating ADH in a rat under similar conditions is about 42 sec. Assuming that the neural lobe is the only source of ADH, this means that this gland must add 2.5×10^{-5} U to blood perfusing it each minute. If the blood flow fraction through the neural lobe is 5×10^{-5} times the cardiac output, which is about 90 ml/min in our unanesthetized rats, the blood flow through the gland is about 4.5×10^{-3} ml/min[5]. The concentration of ADH in the neural lobe effluent of the resting rat must therefore exceed that in the arterial input by

$$2.5 \times 10^{-5} \text{ U/min} / (4.5 \times 10^{-3} \text{ ml/min}) = 5.6 \times 10^{-3} \text{ U/ml}.$$

During the last 20 sec of a substantial haemorrhage (5 ml in 90 sec) DE WIED's data indicate that the change in peripheral concentration of ADH is approximately 3×10^{-2} U/2×10^{2} ml whole blood/20 sec or 4.5×10^{-4} U/ml whole blood/min[8]. Repeating the earlier calculations, the amount of ADH added to the general circulation under these circumstances must be $15 \text{ ml} \times 4.5 \times 10^{-4}$ U/ml/min or 6.75×10^{-3} U/min. Since the neural lobe blood flow is 4.5×10^{-3} ml/min the concentration of ADH in this blood must exceed that in the arterial input by

$$(6.75 \times 10^{-3} \text{ U/min}) / (4.5 \times 10^{-3} \text{ ml/min}) = 1.5 \text{ U/ml}.$$

Correction for the half-life of ADH in the general circulation would raise this value by some 25%, or close to 2 U/ml. This represents a 300 fold increase in ADH output over the resting level; and, since ADH can be suppressed below this level, the dynamic range of the ADH secreting mechanism should be in excess of 300.

The adenohypophysis has no (or almost no) direct arterial supply, instead receiving its vascular input from a group of elegantly controllable parallel portal systems draining parts of the neurohypophysis[9-12]. That a substantial fraction of the adenohypophysis receives its input from the neural lobe has also been established[13]. Since it is reasonable to expect all neural lobe effluent—whether portal or systemic—to carry the same concentration of ADH, this fraction of the adenohypophysis must indeed 'see' a very high ADH concentration, which is subsequently diluted more than 20000 times in the general circulation.

In view of our calculations, interpretations suggesting a pharmacologic (as opposed to physiologic) action of vasopressin on ACTH secretion which are based primarily on responses to systemic injections must be reevaluated. The phenomena occurring between the neurohypophysis and adenohypophysis are local and not reproducible by events occurring in the general circulation. In order to achieve, by peripheral intravenous injection, levels of local vasopressin or Pitressin concentration equivalent to those here calculated it would be necessary to administer heroic doses: in a 300 g rat, 80 mU for the basal state, 28 Units for extreme stress. The first dose is well within the range

[1] M. SAFFRAN and J. SAFFRAN, Ann. Rev. Physiol. *21*, 403 (1959).
[2] B. NICHOLS, Jr., Yale J. Biol. Med. *33*, 415 (1961).
[3] C. FORTIER and J. DE GROOT, Progr. in Neurol. and Psychiat. *14*, 256 (1959).
[4] W. F. GANONG and P. H. FORSHAM, Ann. Rev. Physiol. *22*, 579 (1960).
[5] H. GOLDMAN and L. A. SAPIRSTEIN, Amer. J. Physiol. *194*, 433 (1958).
[6] M. GINSBURG, J. Endocrinol. *16*, 217 (1957).
[7] J. HELLER, Physiol. bohemoslov. *10*, 167 (1961).
[8] D. DE WIED, Endocrinology *68*, 956 (1961).
[9] J. LANDSMEER, Neuroendocrinology Symp. Miami (1961), in press.
[10] H. DUVERNOY, Neuroendocrinology Symp. Miami (1961), in press.
[11] P. M. DANIEL and M. M. L. PRICHARD, Quart. J. exp. Physiol. *41*, 215 (1956).
[12] W. C. WORTHINGTON, Jr., Endocrinology *66*, 19 (1960).
[13] H. GOLDMAN, M. ALPERT, S. LEVINE, and A. WETZEL, Endocrinology, in press.
[14] *Acknowledgement.* This work was supported in part by United States Public Health Service Grants A2530 and M5323.

provoking ACTH release[2]; the latter, lethal. Clearly, events within the hypophysis are more appropriately studied by such methods as local implantation of crystalline or highly concentrated solutions of vasopressin[14].

Zusammenfassung. Der antidiuretische Hormon-(ADH, Vasopressin)Gehalt des die Adenohypophyse durchströmenden Blutes wird für die Ruhephase mit 6 mU/ml und nach schwerem Blutverlust mit 2 U/ml berechnet. Die bisher allgemein vertretene Auffassung, nach welcher das ADH in einer für die normale Stimulation der adenohypophysären Sekretion des ACTH ungenügenden Konzentration vorhanden ist, kann nicht aufrechterhalten bleiben.

H. GOLDMAN und L. LINDNER

Research Division, Columbus Psychiatric Institute and Hospital, The Ohio State University College of Medicine, Columbus (Ohio, U. S. A.), March 5, 1962.

Pyruvate Metabolism in Epileptic Tuberculous Patients

Introduction. In a recent paper[1] we have studied the prevention of the convulsant and lethal effects of isoniazid by pyruvic acid. We have shown that isoniazid reduces the levels of blood pyruvate, combining with it to form an hydrazone, and that this reduction was responsible for the acute toxicity of that drug.

The convulsant effect of isoniazid has been known since the first studies on its toxicity[2], as well as the risks involved in the treatment of tuberculous epileptic patients with that drug[3]. The fact that epileptic seizures are aggravated by isoniazid, together with our own results on its convulsant effect, led us to study the pyruvic acid content of the blood of epileptic tuberculous patients and its modification during isoniazid-therapy.

Material and Methods. The results we are about to describe were obtained from epileptic tuberculous patients from the San Sebastian Sanatorium of Rio de Janeiro (Brazil), a control group of non-epileptic tuberculous patients having been examined on the same occasion.

Pyruvic acid was assayed according to FRIEDEMAN and HAUGEN[4]. Blood samples were collected as described by these authors, from the fasting patients and, whenever possible, immediately after the crisis.

Clinical notes on the patients under examination: (a) *Epileptic patients.* GRS, female, 34 years; grand mal epileptic seizures since childhood, presently very frequent. Therapeutic scheme: *p*-aminosalicylic acid (15 g/day), isoniazid (300 mg/day) and streptomycin (1 g/day). – NAS, female, 27 years; frequent epileptic seizures since childhood. Therapeutic scheme: *p*-aminosalicylic acid (15 g/day), isoniazid (300 mg/day), and streptomycin (1 g/day).– DA, female, 22 years; occasional epileptic seizures since childhood. Therapeutic scheme: Isoxyl[5] (3 g/day). (b) *Non-epileptic patients.* DMM, female, 32 years. Therapeutic scheme: *p*-aminosalicylic acid (15 g/day), isoniazid (300 mg/day) and streptomycin (1 g/day).–AS, female, 38 years, and MD, female, 31 years. Therapeutic scheme: Isoxyl (3 g/day).–NC, female, 24 years, and EO, female, 16 years. Therapeutic scheme: thiosemicarbazone (100 mg/day) and *p*-aminosalicylic acid (10 g/day).

The epileptic status of patients GRS and NAS was confirmed by psychiatric examination and EEG tracings, which were nearly normal for patient DA. Treatment with Luminal was suspended during the experiment.

Results and Discussion. Pyruvic acid was assayed in blood samples collected from epileptic and non-epileptic patients during a period of 42 days (September–October 1961), at different intervals, according to the case. The non-epileptic patients of the control group were examined once a week, epileptic patients NAS and DA twice a week and patient GRS, due to the high frequency of seizures, had blood samples drawn every morning and after each crisis.

The results obtained from non-epileptic and from epileptic patients NAS and DA are shown in the Table. All the results quoted in the Table are from fasting subjects, and it can be seen that, for the non-epileptic patients, the concentration of blood pyruvate keeps well within the normal levels[6,7].

As for epileptic patients NAS and DA, there was a sharp increase in blood pyruvate coinciding with each crisis. In the case of patient NAS it can be seen that the concentration of blood pyruvate dropped steadily afterwards, till normal levels were attained. At this point a

[1] R. C. R. BARRETO and D. B. MANO, Biochem. Pharmacol. *8*, 409 (1961).
[2] S. Y. P'AN, L. MARKAROGLU, and J. REILLY, Amer. Rev. Tub. *66*, 100 (1952).
[3] K. I. FETTERHOFF, C. X. HOLMES, and G. E. MARTIN, Amer. Rev. Tub. *66*, 501 (1952).
[4] T. F. FRIEDEMAN and G. E. HAUGEN, J. biol. Chem. *147*, 415 (1943).
[5] 4-4'-diisoamyloxythiocarbanilide (Continental Pharma, Brussels).
[6] T. D. R. HOCKADAY, Biochem. J. *80*, 31 P (1961).
[7] H. KÄSER, Clin. chim. Acta *6*, 337 (1961).

Pyruvate levels in the blood of epileptic and non-epileptic tuberculous patients (C = crisis)

Name	Period of observation (days)																	Notes
	1	2	3	8	11	13	15	17	23	26	28	30	36	39	40	41	42	
NAS	0.31	C	0.89	0.62	0.45	C	0.71	0.51	0.48	C	—	0.75	0.39	C	1.55	—	—	Epileptic
DA	0.35	—	0.45	0.45	0.45	—	0.35	0.45	0.40	—	C	0.71	0.35	—	—	C	0.75	Epileptic
EO	—	—	—	0.53	—	—	—	—	0.37	—	—	—	0.42	—	—	—	—	Non-epileptic
DMM	0.45	—	—	—	—	—	0.45	—	0.51	—	—	0.37	0.35	—	—	—	—	Non-epileptic
AS	0.53	—	—	0.53	—	—	0.45	—	0.37	—	—	0.47	0.42	—	—	—	—	Non-epileptic
MD	0.53	—	—	0.53	—	—	0.45	—	0.45	—	—	0.45	0.35	—	—	—	—	Non-epileptic
NC	0.53	—	—	0.53	—	—	0.53	—	0.38	—	—	0.55	0.37	—	—	—	—	Non-epileptic