(rabbits) or renal artery (dogs) 24 hours previously. The aortic and renal arterial installations were successful: the base-line had not shifted appreciably and the calibration curves agreed with those obtained in acute experiments. The renal venous installations were unsuccessful because of shrinkage and distortion of the vein.

Summary. A thermostromuhr is described which differs principally from that of Rein in substituting storage battery for high frequency current. Its use is thereby vastly simplified. It has been calibrated on arteries and veins of living animals and gives promise of yielding quantitative information as to blood flow in unanesthetized animals.

We are anxious to express our gratitude to Dr. D. W. Bronk for his frequent helpful advice, and to Mr. A. J. Rawson of his department who has made for us the more perfect models of the instrument.

8368 C

Effect of Adrenalin on Blood Sugar and Lactic Acid in Addison's Disease and in Adrenalectomized Dogs.

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The hypothesis has recently been put forward that in adrenal insufficiency there is an inability of the muscles to produce lactic acid normally. Buell, Strauss and Andrus[1] found that in autolyzing pulverized skeletal muscle removed from cats suffering from experimental hyperthyroidism or adrenal insufficiency there was an inhibition of lactic acid formation, and suggested that the reason for the high blood lactate values found after exercise in patients suffering from hyperthyroidism or Addison's disease might be due to an impaired ability to metabolize the lactic acid formed rather than to an overproduction of lactic acid by the contracting muscles. Buell and Strauss[2] showed that in rats suffering from experimental hyperthyroidism the liver does not convert absorbed d-lactic acid into glycogen as readily as it does in normal animals, and the same

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1 Buell, M. V., Strauss, M. B., and Andrus, E. C., *J. Biol. Chem.*, 1932, **98**, 645.

2 Buell, M. V., and Strauss, M. B., *Bull. Johns Hopkins Hosp.*, 1934, **4**, 220.

has been shown to be true for rats suffering from chronic adrenal insufficiency (Buell, Strauss, and Anderson, unpublished data). It was considered of interest to find whether there was any similar disturbance of liver function (A) in patients suffering from Addison's disease, and (B) in dogs after double adrenalectomy.

(A) *Observations on patients with Addison's disease.* Two means of presenting d-lactic acid to the liver were considered—the injection of d-lactate, or the injection of adrenalin, which would cause a breakdown of muscle glycogen to lactic acid and raise the level of the blood lactic acid. The second method was chosen since it also allowed the response of the liver to an increase in the blood sugar to be observed. Cori[3] concluded that subcutaneous injection of adrenalin could be used with impunity in experiments to study the physiological effects of adrenalin, and this method was chosen in preference to continuous intravenous infusion. The dosage required to give a marked elevation of the blood lactic acid level was found to be 0.018 mg. of adrenalin per kilo body weight, and this dose was used in all the following experiments.

Three female patients suffering from Addison's disease were observed, 2 of whom (J. H. and F. B.) were being maintained on sodium chloride by mouth, while one (L. K.) required injections of adrenal cortical extract in addition, to maintain normal sodium and chloride levels in her blood. Three female patients, convalescent from lobar pneumonia, toxic arthritis, and malarial therapy for syphilis of the central nervous system, respectively, and of approximately the same weight as the patients with Addison's disease, were used as controls. The patients were all fasted for 12 hours before the experimental period and also during the experiment. A sample of blood was removed, and the appropriate dose of adrenalin injected subcutaneously. Further blood samples were taken 15, 30, 60, 90, 120, 180 and 240 minutes after the injection. The pulse rate and blood pressure were also taken at the same time as the blood samples. Blood lactic acid was determined by the method of Friedmann and Kendall[4] and blood glucose by the method of Hagedorn and Jensen.[5]

The results of individual experiments are shown in Table I. Since the individual results when plotted gave curves of approximately the same contours for each group, composite curves were constructed by averaging the individual values for each of the 2 groups (Fig. 1).

[3] Cori, C. F., *Physiological Reviews.*, 1931, **5**, 143.

[4] Friedmann, T. E., and Kendall, A. I., *J. Biol. Chem.*, 1929, **82**, 23.

[5] Hagedorn, H. C., and Jensen, B. N., *Biochem. Z.*, 1923, **135**, 46.

TABLE I.
Time in Minutes After Adrenalin Injection.

		0	15	30	60	90	120	180	240
(1) Normals									
1. R.L.	Blood glucose	106	154	165	171	160	131	115	92
	" lactate	21	69	48	21	23	23	16	12
	Pulse rate	66	82	78	76	74	70	68	70
	Blood pressure	140/88	104/58	112/68	116/80	104/72	108/66	106/68	110/78
2. B.E.	Blood glucose	—	178	208	205	149	114	143	99
	" lactate	30	50	66	61	36	36	25	24
	Pulse rate	76	84	98	108	112	108	94	94
	Blood pressure	106/68	148/98	130/80	112/60	94/64	98/64	96/62	92/62
3. F.H.	Blood glucose	88	127	167	203	194	158	124	88
	" lactate	10	23	32	38	28	29	14	19
	Pulse rate	62	62	74	80	86	80	76	78
	Blood pressure	106/68	174/68	170/68	114/60	112/64	108/64	104/64	106/58
(2) Addison's Disease									
1. L.K.	Blood glucose	89	139	161	186	164	117	81	73
	" lactate	9	30	31	31	34	34	17	17
	Pulse rate	66	68	90	94	92	86	72	70
	Blood pressure	124/86	188/90	150/82	108/66	120/74	114/72	114/78	108/74
2. F.B.	Blood glucose	93	128	130	186	150	152	123	97
	" lactate	9	17	26	25	27	25	21	15
	Pulse rate	78	78	82	82	84	74	84	86
	Blood pressure	86/54	110/78	114/78	100/66	92/66	110/74	90/62	86/60
3. J.H.	Blood glucose	66	107	133	142	180	149	100	66
	" lactate	22	36	45	—	40	47	—	26
	Pulse rate	74	76	80	80	84	80	88	86
	Blood pressure	92/56	106/66	96/52	98/56	88/52	90/60	82/58	86/58

The blood glucose and blood lactate values are in milligrams per 100 cc. blood.

The normal individuals showed a blood lactate curve which rises rapidly, reaching a maximum within 30 minutes after the injection of adrenalin and falling more slowly to reach the basal level within 3 hours. In the patients with Addison's disease, the blood lactate curve, starting from a lower basal level, rose almost as sharply as in normal individuals, but instead of falling rapidly, remained elevated and did not return to the basal level in 4 hours. The absolute increase in blood lactate was slightly less than in normal individuals, 20 mg. % as against 27 mg. %.

The blood sugar curves showed approximately the same contour in the 2 groups, reaching a maximal level within one hour and falling

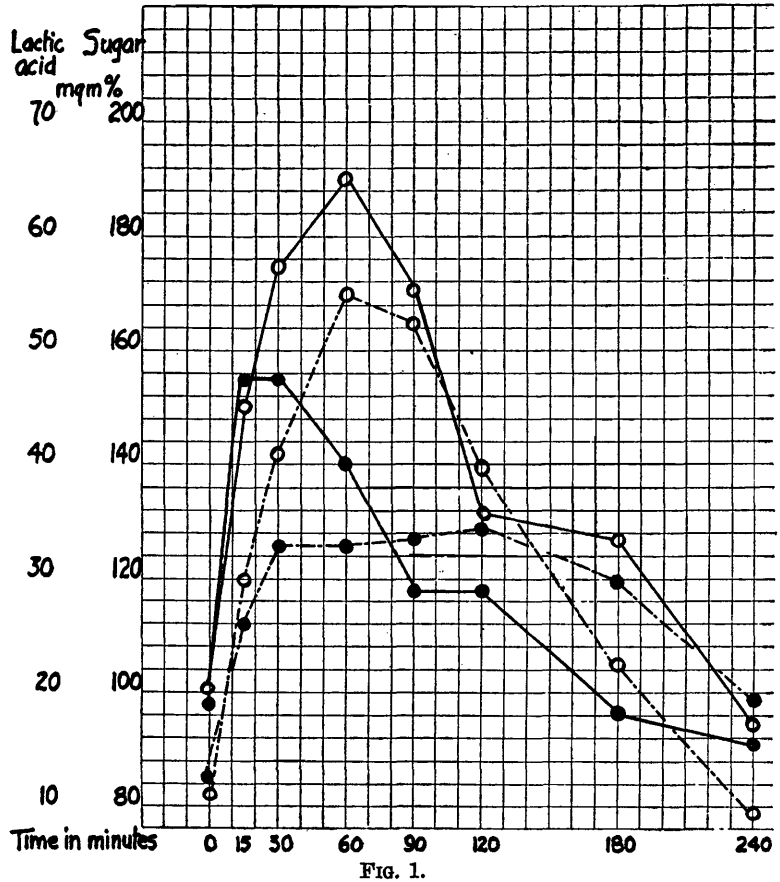

FIG. 1.

Blood sugar and blood lactate curves following subcutaneous injection of adrenalin—0.018 mg. per kilo body weight in normal individuals and in patients with Addison's Disease—composite curves (three cases in each group).

Sugar—normal o——o Sugar—Addison's o - - - - - o
Lactic acid—normal ●——● Lactic acid—Addison's ● - - - - - ●

to basal level in 4 hours. The initial basal level was significantly lower in the patients with Addison's disease, 83 mg. % as against 97 mg. %, but the absolute increase showed little difference: 88 mg. % as against 96 mg. % in the normals.

The continued elevation of the blood lactate curve in the patients with Addison's disease was not due to slower absorption of adrenalin from the subcutaneous tissues owing to low blood pressure, since the blood sugar curve did not show a corresponding contour; also 2 of the normal controls had blood pressures within the range of those found in the patients with Addison's disease. It was noted that in the 2 cases of Addison's disease with hypotension (F. B. and J. H.) the increase in pulse rate and blood pressure was markedly less than in the 2 normal controls (F. H. and B. E.) who also had hypotension and who received approximately the same total amount of adrenalin. This would appear to indicate that in Addison's disease there is a lessened sensitivity to the cardio-accelerator and pressor effects of adrenalin.

It would appear that in patients suffering from Addison's disease who are kept in approximately normal health by means of sodium chloride or sodium chloride plus adrenal cortical extract, adrenalin can cause a conversion of muscle glycogen to lactic acid as readily as in normal individuals. The delay in the disappearance of the accumulated lactate from the blood seen in such patients may be due to a sluggishness on the part of the liver to convert lactic acid into glycogen, as was found in rats suffering from chronic adrenal insufficiency.

The power of the liver to synthesize glycogen from blood sugar is evidently not impaired, as the disappearance of the blood glucose formed from liver glycogen under the action of adrenalin was just as rapid in the cases of Addison's disease as in the normal individuals.

B. *Observations on adrenalectomized dogs.* The effect of adrenalin on the blood sugar and blood lactate of adrenalectomized dogs was studied by 2 experiments on the same animals, one before and the second after the removal of the second adrenal gland in the 2-stage operation for bilateral adrenalectomy, it being assumed that animals with one intact adrenal gland would give a normal response to adrenalin injection, since both their general condition and the concentration of arterial plasma electrolytes were normal. After the second gland had been removed, the dogs were allowed to develop adrenal insufficiency to make sure that both glands had been completely removed, and were then restored to approximately normal

condition by the administration of adrenal cortical extract as described by Harrop *et al.*[6] The second adrenalin experiment was not performed until the animals were in good condition as judged by their weight and the chemical findings in the heparinized arterial plasma.

It was decided to give the adrenalin as a single intravenous injection, since this would shorten the experimental period during which the animals had to be kept as quiet as possible, although it was recognized from the work of Markowitz *et al.*[7] that the injected adrenalin would be rapidly destroyed in the tissues. The dose of adrenalin required to produce a marked elevation of blood lactate was found to be 0.036 mg. per kilo body weight. The dogs were accustomed to being fastened down on a table, and at the beginning of the experimental period, previous to which no food had been given for 12 hours, they were tied down, and a sample of blood removed from the jugular vein, after which the appropriate dose of adrenalin was injected, and blood samples removed after 5, 15, 30, 45, 60 and 90 minutes, the dog being returned to its cage during the intervals between the taking of the last 3 samples.

Two such experiments have been performed, the results of one of which are shown in Fig. 2. The blood lactate curve in the control experiment (single adrenalectomy) showed the same rapid rise as was found in the human controls, but the descent of the curve was more prolonged and the basal level had not been reached in 90 minutes. After bilateral adrenalectomy, the blood lactate curve showed a flattening of its contour, the increase in blood lactate being only 13 mg. % as against 26 mg. % in the control experiment. It also showed a tendency towards a prolongation of the elevated level, though this was not nearly so striking as in the patients with Addison's disease.

The blood sugar curve after bilateral adrenalectomy showed a slower rise to the maximal level than in the control experiment, and a flattening of the contour of the curve, the increase in blood sugar being only 32 mg. % as against 51 mg. % in the control experiment. In neither case had the basal level been regained in 90 minutes, but the descent of the curve was slightly slower in the animal after bilateral adrenalectomy, only 13 mg. % of blood sugar disappearing in the last hour of the experiment as against 37 mg. % in the control. This affords some evidence of delay in the removal of glucose

[6] Harrop, G. A., and Weinstein, A., *J. Exp. Med.*, 1933, **57**, 305.

[7] Markowitz, J., and Mann, F. C., *Am. J. Physiol.*, 1929, **89**, 176.

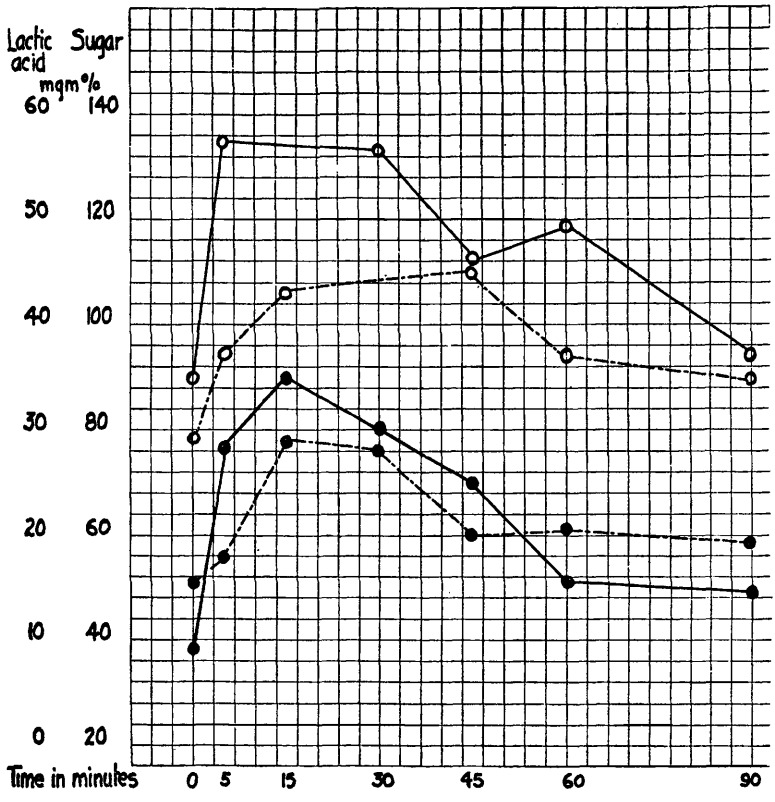

FIG. 2.

Blood sugar and blood lactate curves following intravenous injection of adrenalin (0.036 mg. per kilo body weight) in a dog after (1) unilateral adrenalectomy, and (2) bilateral adrenalectomy.

Unilateral—blood sugar o——o Bilateral—blood sugar o - - - - o
adrenalectomy—blood lactate ●——● adrenalectomy—blood lactate ● - - - - ●

from the blood stream, as was noted by Fernandez *et al.*[8] in dogs 48 hours after bilateral adrenalectomy, in which 2 gm. of glucose per kilo body weight were injected intravenously.

The second experiment gave substantially similar results.

Summary. 1. The effect of adrenalin on the blood sugar and blood lactate was studied: A. in patients with Addison's disease. B. in adrenalectomized dogs. 2. In patients with Addison's disease, the subcutaneous injection of adrenalin produced a similar increase in the blood sugar to that observed in the controls, and the blood sugar curve showed approximately the same contour in the 2 groups. The blood lactate curves differed, however. Both showed a similar

[8] Fernandez, R., Foglia, V. G., Leloir, L. F., and Novelli, A., *Compt. rend. soc. Biol.*, 1934, **115**, 334.

sharp rise, but in the patients with Addison's disease, the curve remained elevated, and had not returned to basal level in 4 hours, whereas in the normal controls, it had reached basal level again within 3 hours. 3. It is suggested that the delay in the disappearance of the accumulated lactate from the blood seen in patients with Addison's disease may be due to a sluggishness on the part of the liver to convert lactic acid to glycogen. 4. The blood sugar and blood lactate curves, following a single intravenous injection of adrenalin in adrenalectomized dogs, are both lower and tend to remain elevated longer than in the same dogs before removal of the second adrenal gland.

8369 C

Suspension Stability of Erythrocytes in Solutions of Globulin.*

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Fahraeus[1] showed that the most rapid sedimentation of erythrocytes took place in solutions of fibrinogen, less rapid in solutions of globulin, and least rapid in solutions of albumin. He concluded that the rapidity of sedimentation and the increased percentage of serum globulin and fibrinogen occurring coincidentally "stand in direct causality."[2] In confirmation of the thesis of Fahraeus, Westergren[3, 4] obtained the following coefficients of correlation between the *sedimentation rate* and fibrin, globulin, and albumin:

$$r_{SR\text{-}F} + 0.82,\ r_{SR\text{-}G} + 0.50,\ r_{SR\text{-}A} - 0.46, \text{ and } r_{SR\text{-}FGA} + 0.87$$

Using a modification of the Linzenmeier[5] technique, Lucia and coworkers[6] obtained a correlation coefficient of —0.27 between *sedi-*

*Assisted by a grant from the Christine Breon Fund.

1 Fahraeus, R., *Acta. Med. Scand.*, 1921, **55**, 1.

2 Fahraeus, R., *Physiol. Rev.*, 1929, **9**, 255.

3 Westergren, A., Theorell, H., and Widstrom, G., *Z. f. d. g. Exp. Med.*, 1931, **75**, 668.

4 Westergren, A., Juhlin-Dannfelt, C., and Schnell, R., *Acta. Med. Scand.*, 1932, **77**, 469.

5 Linzenmeier, G., *Arch. f. Gynaekologie*, 1920, **113**, 608.

6 Lucia, S. P., Blumberg, T., Brown, J. W., and Gospe, S. M., to be published.