THE REGULATION OF EXCRETION OF WATER BY THE KIDNEYS. I.

By J. S. HALDANE, M.D., F.R.S. and J. G. PRIESTLEY, B.M., Captain R.A.M.C., *Beit Memorial Research Fellow*.

Numerous observations tend to show that the excretory process by which the kidneys regulate the composition of the blood-plasma is most delicately regulated. It is known, for instance, that a very slight excess of urea, or sodium chloride, or water, or acid or alkali, introduced into the body will produce a compensatory excretion of these substances. A very slight increase in the percentage of sugar in the blood will cause an abundant excretion of sugar, although practically no sugar is normally excreted, in spite of its constant presence in the blood. Similarly, a salt-free diet will rapidly cause the practical disappearance of chlorides from the urine, in spite of their continued abundant presence in the blood.

The stimulus to the excretion or retention of this or that substance by the kidneys is presumably a slight increase or diminution in its concentration in the blood-plasma; but quantitative data on this subject are as yet hardly existent. We therefore determined to set about the task of obtaining, as regards excretion by the kidneys, the same sort of information as we succeeded, some years ago, in obtaining with regard to the regulation of breathing by small changes in the CO_2 content of the blood.

The first question taken up has been the excretion of water. Our immediate object was to ascertain what dilution of the blood with water corresponds to a given rate of excretion of water by the kidneys. As a measure of dilution of the blood we at first took the hæmoglobin percentage, since, if the blood is diluted with an excess of water during diuresis, there will presumably be a fall in the hæmoglobin percentage. For obvious reasons the experiments were made on man.

As a means of increasing the excretion of water we adopted the method of simply drinking large quantities of water. To diminish the excretion we employed prolonged sweating in a respiration chamber kept at such a wet-bulb temperature as to produce a maximum amount of sweating without any considerable rise of body temperature.

For determining the effects of these procedures on the concentration of the blood the Gowers-Haldane hæmoglobinometer was used, the samples of blood being taken from a finger in the usual way. By this method the hæmoglobin can, with careful work, be determined to within 1 % of the normal concentration[1]. In some of the experiments we used the rather more delicate method of comparing the tints in two ordinary test-tubes, as described by Haldane and Lorrain Smith[2]. The results are given in terms of the Gowers-Haldane scale. The specific gravity of the urine was measured with an ordinary urinometer standardised by us beforehand, the observations being made at the temperature for which the instrument was standardised.

The percentage of hæmoglobin in the blood of any individual varies appreciably, within certain limits, and is affected by muscular exertion, as recently shown by Schneider and Havens[3], and by Boothby and Berry[4]; but control experiments showed that if disturbing causes, such as meals, were avoided, it remained nearly steady during a stay in the laboratory of a few hours.

In each of the first two experiments two litres of water were drunk in 15 minutes. The results were as follows:

Time	Hb % on scale	Urine passed in c.c.	Mean rate of secretion since urine last passed in c.c. per hour	Sp. gr.	Remarks
Exp. I.					
10.45 a.m.	—	—	—	—	Bladder emptied
11.0	108	—	—	—	
11.25—11.40	—	—	—	—	2 litres of water drunk
11.45	108	—	—	—	—
12.15 p.m.	109	—	—	—	—
12.30	—	530	303	1004	—
12.45	106	—	—	—	—
12.50	—	400	1200	1002	—
1.30	—	500	750	1003	—
2.0	—	320	640	1003	—
2.15	108	—	—	—	—
2.30	—	235	470	1005	—
Exp. II.					
2.0 p.m.	108	—	—	—	—
2.20	—	—	—	1023	Bladder emptied
2.20—2.35	—	—	—	—	2 litres of water drunk
3.55	—	670	425	1002	—
4.0	108	—	—	—	—
5.0	—	760	701	1002	—

[1] This *Journal*, XXVI. p. 497. 1901.
[2] *Ibid.* XXV. p. 331.
[3] *Amer. Journ. of Physiol.* XXXVI. p. 239. 1915.
[4] *Ibid.* XXXVII. p. 418. 1915.

Of these experiments, the first gave a very slight and doubtful diminution of the hæmoglobin during the height of the diuresis, while the second gave no diminution. A third experiment in which five litres of water were drunk gave the following results:

Exp. III. Time	Hb % on scale	Urine passed in c.c.	Mean rate of secretion since urine last passed in c.c. per hour	Sp. gr.	Remarks
10.30 a.m.	108	—	—	—	—
10.45	—	—	—	1021	Bladder emptied
11.0	—	—	—	—	1 litre water drunk
11.10	—	—	—	—	½ " "
11.30	—	—	—	—	½ " "
11.45	—	175	175	1009	½ " "
12.0	—	300	1200	1003	½ " "
12.10 p.m.	108	—	—	—	—
12.30	—	380	760	1003	½ litre water drunk
12.45	—	325	1300	1001	½ " "
1.0	—	265	1060	1001	½ " "
1.15	106	265	1060	1001	½ " "
1.35	—	310	930	1001	—
1.45	108	—	—	—	—
2.0	—	440	1056	1003	—
2.30	—	380	760	—	—
3.0	—	365	730	1003	—
3.15	108	—	—	—	—
3.30	—	375	750	1003	—
4.0	—	335	670	1003	—
4.30	—	—	—	—	2 cups of tea = 500 c.c. drunk
4.55	—	595	650	1002	—
6.0	—	655	605	1002	—
7.0	—	275	275	1003	—
8.30	—	60	40	1023	Dinner 7.0—7.30

In spite of the increased amount of water drunk in this experiment there was again no definite fall in the hæmoglobin percentage. During the diuresis, between 10.45 a.m. and 7.0 p.m., 5460 c.c. of water had been excreted, while 5500 had been drunk. This volume of water (exceeding by about a third the volume of the blood) had been passed through the circulation without any appreciable dilution of the blood in the process, and possibly also without appreciable increase in the volume of the lymph and tissues.

The maximum rate of excretion of urine was about 25 times an average normal rate, but was hardly greater in Exp. III than in Exp. I, in spite of the far greater amount of water drunk in Exp. III. There were also indications that the maximum rate could not be kept up by the kidney, owing to fatigue. In order to test this point further, the following experiment was made, in which the water-drinking was spread out over a long period. The urine was also measured at short intervals.

Exp. IV.

Time	Hb % on scale	Urine passed in c.c.	Mean rate of secretion since urine last passed in c.c. per hour	Sp. gr.	Remarks
10.7 a.m.	—	—	—	—	Bladder emptied
10.31	—	14	35	—	—
11.0	108	15	31	—	—
11.30	—	17	34	—	—
11.35	—	—	—	—	250 c.c. water drunk
11.40	—	6	36	—	—
11.45	—	—	—	—	250 c.c. water drunk
11.50	—	6·5	39	—	—
11.55	—	—	—	—	250 c.c. water drunk
12.0	—	8·5	51	—	—
12.5 p.m.	—	—	—	—	250 c.c. water drunk
12.10	—	15·0	90	—	—
12.15	—	—	—	—	250 c.c. water drunk
12.20	—	24	144	—	—
12.25	—	—	—	—	250 c.c. water drunk
12.30	—	71	426	—	—
12.35	—	—	—	—	250 c.c. water drunk
12.40	—	118	708	—	—
12.45	—	—	—	—	250 c.c. water drunk
12.50	—	122	732	—	—
12.55	—	—	—	—	250 c.c. water drunk
1.0	—	136	756	—	—
1.5	—	—	—	—	250 c.c. water drunk
1.10	—	148	888	—	—
1.15	—	—	—	—	250 c.c. water drunk
1.20	—	146	876	—	—
1.25	—	—	—	—	250 c.c. water drunk
1.30	—	148	888	—	—
1.35	—	—	—	—	250 c.c. water drunk
1.40	—	140	840	—	—
1.45	—	—	—	—	250 c.c. water drunk
1.50	—	144	864	1001	—
1.55	—	—	—	—	750 c.c. water drunk
2.0	—	130	780	—	—
2.5	—	—	—	—	750 c.c. water drunk
2.10	—	130	780	—	Shivering. Nausea on drinking
2.15	—	—	—	—	750 c.c. water drunk
2.20	—	140	840	—	—
2.25	—	—	—	—	750 c.c. water drunk

Time	Hb % on scale	Urine passed in c.c.	Mean rate of secretion since urine last passed in c.c. per hour	Sp. gr.	Remarks
Exp. IV (*continued*).					
2.40 p.m.	108	256	768	1001	Shivering
2.50	—	120	720	1001	—
3.0	—	118	708	1001	—
3.12	—	150	720	1001	—
3.20	—	112	840	1000	—
3.30	—	112	672	1000	—
3.40	—	112	672	—	—
3.50	—	130	780	—	—
4.0	—	136	816	1000	—
4.10	—	130	780	—	—
4.30	—	256	768	—	—
5.0	—	374	748	—	—
5.30	—	384	768	—	—
6.0	—	370	740	—	—
6.30	—	352	704	—	—

In this experiment the diuresis was pushed up gradually, and reached a maximum of only 888 c.c. per hour, after which there was a distinct decline, in spite of the fact that three times as much water was being drunk, and that the excess of water within the body was rapidly accumulating. The kidneys appeared to be unable to keep up a water diuresis of more than about 750 c.c. per hour. Four hours after the last water had been drunk the diuresis was still unchecked, and only 4700 out of the 5500 c.c. of water drunk had been excreted.

Exps. I to IV were all made on the same subject (J. G. P.). Another experiment was therefore made on a different subject (J. S. H.). It will be seen that the results confirm those previously obtained.

Time	Hb % on scale	Urine passed in c.c.	Mean rate of secretion since urine last passed in c.c. per hour	Sp. gr.	Remarks
Exp. V.					
1.28 p.m.	—	—	—	1029	Bladder emptied
1.40	96	—	—	—	—
1.58	97	28	56	—	—
2.0—2.32	—	—	—	—	2 litres water drunk
2.15	—	14	49	—	—
2.32	—	20	70	—	—
2.47	94	21	84	—	—
3.2	—	37	148	—	—
3.8	94	—	—	—	—
3.17	94	82	328	1001	—
3.32	—	157	628	1001	—
3.47	96	165	660	—	—
4.2	96	188	752	1001	—
4.20	96	204	680	—	—
4 38	—	161	536	—	—

In none of these experiments, nor in a further one which we need hardly quote, was there a diminution of the hæmoglobin percentage parallel with the diuresis, and it seems clear that a diminished hæmoglobin percentage, or increased volume of the blood, has nothing to do with the diuresis produced by drinking water. It was clearly necessary to seek elsewhere for the change in the blood which excites the excretion, so we decided to examine the conductivity of the serum. The results are given in the succeeding paper. The fact that the hæmoglobin percentage remains constant during even extreme water diuresis is nevertheless of great significance in enabling us to exclude certain mechanical factors to which the diuresis might be attributed. The urine secreted during water diuresis is of course no mere filtrate, and whatever changes in the composition of the blood lead to the enormous increase in the excretion of water, these changes are evidently very slight, and are comparable to the very minute changes in hydrogen ion concentration which cause enormous changes in the breathing.

As no diminution in the hæmoglobin percentage was produced by drinking water, we determined to try the effects of drinking dilute salt solution. In the first experiment 0·6 % solution of NaCl was employed, and two litres were drunk in 15 minutes. Nausea was at once produced, and 800 c.c. were vomited, so the hæmoglobin estimations were abandoned. Nevertheless a considerable diuresis followed, and the interesting observation was made, that the specific gravity of the urine fell rapidly to a value below that of the salt solution. At the height of the diuresis, with a rate of secretion of 604 c.c. per hour, the specific gravity of the urine was 1002, as compared with 1004 for the salt solution. In the succeeding paper further experiments with more palatable salt solutions are recorded, and show that, apart from other blood changes, a marked fall in the hæmoglobin percentage occurs.

Owing to the war, we were only able to make very limited observations on the influence of sweating. As regards the influence of sweating on the hæmoglobin percentage, several observations, made at the Oxford Physiological Laboratory, have already been recorded by E. H. Hunt in an interesting paper on "The Regulation of Body-Temperature in extremes of dry heat[1]." He found that in two subjects, each of whom had lost 2·3 kilos. during an exposure of 2½ hours to dry heat in a Turkish bath, the hæmoglobin percentage was the same before and after the exposure, although no liquid had been drunk. He also found that, when collected with due precautions, the sweat

[1] *Journn. of Hygiene*, XII. p. 479. 1913.

contained only about ·21 % of NaCl, even after prolonged sweating without liquid being drunk.

Our first observation was a preliminary one, in which J. G. P. remained for 2¾ hours in a chamber with the wet-bulb at about 30°. The loss of weight was only 870 grms., and the hæmoglobin was 109 before going in, and 111 half an hour after coming out.

In a second experiment he stayed about 4½ hours in the chamber, and lost 1·78 kilos. (of which only about ·02 kilo. could be accounted for by respiratory exchange). The hæmoglobin was 108 before going in, 115 shortly after coming out, and 108 3½ hours later, about 1600 c.c. of water having been drunk in the interval. There was thus a distinct fall in the hæmoglobin percentage after the sweating, though the fall would only account for about a sixth of the liquid lost. During the sweating, and including a period of 40 minutes before entering the chamber, 133 c.c. of urine had accumulated in the bladder, with a specific gravity of 1029. The mean rate of secretion during the sweating was thus a little under 30 c.c. per hour—a considerable diminution from the normal.

Another experiment, made on J. S. H., gave the following results:

Time	Mouth temperature	Temperature in chamber Wet bulb	Dry bulb	Urine passed in c.c.	Rate of secretion since last passed in c.c.	Sp. gr.	Hb % on scale	Remarks
11.55 a.m.	—	—	—	—	—	—	—	Bladder emptied
12.45 p.m.	—	—	—	—	—	—	91	
1.0	—	—	—	50	46	1026	—	
1.30	—	—	—	—	—	—	—	Entered chamber. Wt=76·48 kilos. after bladder emptied
1.40	98·9° F.	27·5° C.	43·5° C.	—	—	—	—	—
1.50	—	29·5°	42°	—	—	—	—	—
2.15	99·4°	30·5°	38°	—	—	—	—	—
2.30	—	31·5°	38°	34	34	1028	—	—
3.0	99·5°	32·0°	37°	—	—	—	—	—
3.30	99·6°	30·5°	36°	—	—	—	—	—
3.45	—	32·0°	37°	20	16	1028	—	—
4·30	99·7°	31·8°	37°	—	—	—	—	Left chamber. Wt=75·35 kilos.
4.35	—	—	—	14	16	1028	—	—
4.55	—	—	—	—	—	—	91	—
6.5	—	—	—	27	18	—	—	—

In this experiment the gross loss of weight was 1·13 kilos. during the sweating. Of this loss, however, ·05 was due to the urine passed, and about ·009 to respiratory exchange. The net loss, due to sweating and evaporation, was thus 1·07 kilos. The hæmoglobin, as in Hunt's experiments, had not altered. After the first hour the rate of secretion of urine had fallen to about a third of the normal, but its specific gravity was only slightly increased. There was no sign of total stoppage of urine secretion. The rate of loss by sweating was somewhat disappointing. A greater rise of body-temperature seemed to be needed in order to produce the maximum of sweating.

The last experiment shows clearly enough that, just as no fall in the hæmoglobin percentage need accompany a great rise, due to ingestion of water, in excretion of water by the kidneys, so no rise in the hæmoglobin need accompany a fall, due to withdrawal of water from the body, in the excretion of water. We must seek elsewhere than in mere alterations of the volume of the blood for the causes of increased or diminished excretion of water by the kidneys.

CONCLUSIONS.

The enormous diuresis caused by ingestion of water is not dependent on general dilution of the blood with liquid.

The diminished excretion of urine following great sweating is not dependent on general concentration of the blood, although some general concentration may occur.