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NOTES ON THE RETENTION OF UREA ELIMINATION TO FEVER.

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FOR some years we have been much interested in the relations of Fever and Urea, and had hoped to publish an elaborate memoir upon the subject. The growing press of more urgent professional duties seems, however, to render this impossible; but we think we have done enough work to justify the putting upon record our reflections and experimental results, although these are more or less fragmentary.

Every one knows that increase of the bodily temperature in man which is commonly spoken of as "Fever," is especially associated with an increase of the elimination of urea, and probably most physiologists believe that the increase of nitrogenous elimination is the direct result of the fever process. It seems to us, however, not yet definitely decided whether the increase of urea elimination is an integrant part of the fever process, or whether it is an indirect outcome, caused by the action of the excessive heat upon certain organs, or by some of the various disarrangements of the bodily functions produced by fever.

The latter theory gains probability from the experiments of Schleich (*Archiv f. exper. Path. u. Pharma.*, Bd. iv.), and of Naunyn (*Berlin klin. Wochenschr.*, 1869) upon dogs, in which the artificial elevation of the animal temperature was followed by an increase of the eliminated urea: results which agree with those of Bartels (*Greifswalder med. Beiträge*, Bd. iii., 1864), who found that the production of urea was increased nearly four grammes in man by raising the temperature artificially by a vapor bath, but disagree with those of Dr. C. F. A. Koch (*Hoffmann and Schwalbe*, 1885), who was not able to produce any increase of urea elimination by artificially raising the temperature of the animal. Further careful, thorough investigation of the effects of external warmth upon urea elimination seems necessary.

The facts in regard to the relations between urea elimination and bodily temperature which appear to have been established by the concordant results of different experimenters, are:

*First.* That in fever the increase in the elimination of urea is not necessarily proportionate to the bodily temperature, so that very slight increase of temperature may be associated with great increase in the elimination of urea, or very great increase in the temperature may be associated with very slight increase in the urea elimination, and especially when disease of the liver exists there may be a marked rise of the bodily temperature, with a discharge of urea that is less than the norm. See Ernst Unruh (*Virchow's Archiv*, 1869, Bd. xlviii.); Keith Anderson (*Centralblatt f. d. med. Wissenschaft*, 1866, No. 19); Thomas Oliver (*Brit. Med. Jour.*, 1886, vol. ii.); Paul Lewis (*Paris Thesis*, 1877); R. du Castel (*Paris Thesis*, 1878), in which theses, also, may be found various abstracts of other confirmatory researches.

*Second.* In the crisis of the fever there is very apt to be an extraordinary elimination of urea, although the temperature may be much below the point which it has reached during the continuation of the fever, when the urea elimination was much less, or even below the normal. As proof of this, we make reference again to the works of Unruh, Keith Anderson, Lewis, Hirtz, Charcot, Gubler and others.

*Third.* In certain diseases with low temperature, such as cancer, scorbutus, diabetes, gout, rheumatism, and especially various affections of the liver, a low bodily temperature may coexist with a great increase in uræa elimination. See Ernst Unruh, Keith Anderson, Paul Lewis.

Especially interesting at this point is the question of uræa elimination in cases of hepatic fever, produced by the presence of gall-stones in the gall-bladder or ducts. The first, and the only sufficiently extended study of such a case to be of value with which we are acquainted is that made by Regnard, 1873 (in the *Memoirs Soc. Biologique*, page 339). A number of cases have been published, especially by Prof. William Pepper, in which it has been found that high hepatic fever may co-exist with a small elimination of uræa, but in these cases the uræa elimination in the non-febrile days has not been sufficiently examined to make the records valuable for our present purpose, that is, for the determination whether fever in these cases does or does not increase uræa elimination; for it may well be that the discharge of uræa is in these cases habitually so far below the norm that in fever days it fails to reach the norm, although there is an increase in the output of the uræa as contrasted with that of the non-febrile day. The study by Regnard seems to have been a very complete one; and he further states that although it was impossible to determine the exact quantity of nitrogen taken each day by the patient, the same regimen was enforced in the febrile and non-febrile days, and there was no notable difference in the amount of nitrogen taken. Regnard's results are tabulated by him as follows:

	1	2	3	4	5	6	7	8	9
Temperature...	37.4°	(40.8°)	(38.6°)	37.4°	36.8°	(39°)	36.6°	37.6°	(39°)
Urea ....	14	( 4 )	( 9 )	11	14	( 4 )	15	12	( 7 )

  

	10	11	12	13	14	15	16	17	18
Temperature...	37°	36.8°	(40.4°)	36.8°	(40.5°)	37.5°	(39.8°)	36.8°	(40.6°)
Urea.....	13	15	( 9 )	12	( 7 )	16	(12 )	18	( 7 )

The dates are in August. The fever days in parenthesis. Average temperature given every day.

We have had an opportunity for making a study of the urea elimination in one very severe protracted case of hepatic fever, with nearly or altogether complete closure of the common duct. The patient was a man about sixty years old, who had suffered from repeated attacks of gall-stones. The diet at the time during which the study was made, was almost exclusively milk, and was nearly uniform, a little less nitrogen being taken on the febrile than on the non-febrile days. We place the results which we have reached, in the form of tables, in which F. D. stands for febrile day, and N. D. for normal day, the minimum and maximum temperature of each day being given, with the amount of urine passed in c. c.; followed by the amount of urea :

N. D.	F. D.	N. D.	F. D.
97.°	103.°	98.°	98.°
99.5	98.5°	99.°	103.2°
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1370 c. c.	1295 c. c.	800 c. c.	1687 c. c.
11.09 grms.	12.82 grms.	7.71 grms.	13.17 grms.

A glance at these experiments show that there was much irregularity of the temperature of the patient, even upon those days which we term "normal." This irregularity was present for some weeks, or even months, in the case. The days which we term "normal" were as near a normal day as could well be obtained, but were always the twenty-four hours following an attack of fever. The results certainly indicate that in hepatic fever, although the total elimination of urea is less than the average passed, it is more than that eliminated on non-febrile days by the same patient upon the same diet.

In order to show still more clearly the relation between temperature and urea elimination, we took five consecutive periods of twelve hours, shown in the accompanying tables. In the first column the maximum and minimum temperatures are given; in the second, the average temperature for the twelve hours :

## 12 HOUR PERIODS.

1.	99.8° 100.8°	100.1°	}	.....	6.66 grms.	Urea.
2.	98.° 99.°	98.6°	}	.....	3.65 grms.	Urea.
3.	98.° 98.5°	98.3°	}	.....	4.06 grms.	Urea.
4.	99.2° 103.2°	101.3°	}	.....	7.02 grms.	Urea.
5.	98.° 99.2°	98.6°	}	.....	6.15 grms.	Urea.

The results which we have reached in this way are, upon the whole, concordant with the idea that even in hepatic fever a distinct rise of temperature is usually accompanied with an increase of the elimination of urea.

There is a very natural tendency to use the facts which have thus been demonstrated by the joint labors of clinicians and chemists as to the relations between temperature and urea as the basis upon which theories can be constructed concerning the relations between fever and nitrogenous waste in elimination. There is, however, one very important fallacy which must be guarded against, namely, the tendency to consider temperature as a measure of fever. Of course, if the term "fever" be simply used to express bodily heat, temperature and bodily temperature are synonymous; but if the term "fever" is used as it ought to be, as the name of the nutritive process whose outcome is so often elevated temperature, it is certain the two are not synonymous; for the nutritive process may be in a state of continuous activity at a time when the bodily temperature is below the norm.

The calorimetrical experiments made many years ago by Dr. H. C. Wood, if they proved nothing more, certainly proved that in any case of fever the temperature of the body at a given time is no indication of the activity of the

nutritive disturbance, *i. e.*, of heat production at that time. If increase of the urea elimination be, in fact, an inevitable factor of the fever process, it is the result of increased heat production, and is not directly connected with the increase of temperature. It is evident that for further progress there is needed at present, most urgently, careful calorimetical studies in which the comparison is made between heat production and urea elimination.

A fact which was especially noteworthy in Dr. Wood's early calorimetical studies was, that often in advanced stages of fever, when the bodily temperature was rapidly falling, and was even much below the norm, heat production was extraordinarily active, and it is extremely probable that in the crisis of a human fever, the heat production reaches far out beyond where it has been during the continuance of the disease, although the temperature may be near to or even below the norm. If this be true, it is readily to be seen why, in the crisis of a fever, urea elimination should be increased.

The experiments of Huppert and Riesell (*Archiv der Heilkunde*, 1869, Bd. 10) seem to show, chemically, that the urea of fever is chiefly the result of the destruction of bodily albumen; coinciding with the views reached by Dr. Wood in calorimetical studies, that there are two distinct sources of bodily heat: one the stored tissues of the body, the other the food stuffs taken into the body; and it is probable that in the crisis of a fever there is a rapid wasting of bodily albumen.

If these probabilities be correct, it is easy to see that the urea discharge in any case of fever, and not the temperature, is the real index to the activity of the nutritive disturbance, so that its study may be of the greatest importance in the treatment and prognosis of a case.

A very important question, for which there has hitherto been no answer at all, is, as to whether intense fever, with great increase of the heat production, can exist without corresponding increase of urea elimination. We have made experiments, which appear to answer this question in the affirmative, and in consequence, to suggest the further

question, whether there is not under such circumstances some chemical destruction of nitrogenous material entirely beyond the ken of modern science. These experiments were made by allowing the dog to go without food for twenty-four hours, so as to reduce the food urea to the least possible point; then for twelve hours, measuring the urea elimination; then dividing the medulla at its junction with the pons in such a way as to avoid injury to the vaso-motor centres; and then, when fever developed itself, measuring the urea elimination. It will be remembered that it was proven by Dr. Wood formerly that this intense, brief fever is accompanied by a most extraordinary increased production of animal heat. The successful experiments were two in number.

#### EXPERIMENT NO. 1.—LARGE RED AND WHITE SETTER.

Section at 3.30 P. M., followed by immediate arrest of respiration, but after ten or fifteen minutes of artificial respiration (by simply compressing of the chest), very deep, slow, regular respiration came on.

TIME.	REC. TEMP.	
3.55.....	103.7	Paralysis complete.
4.00.....	103.9	
4.37.....	104.2	
4.45.....	103.9	
5.00.....	104.	
5.37.....	105.3	
6.35.....	105.8	Cheyne Stokes.
7.35.....	108.3	
8.05.....	108.	Breathing fast.
8.30.....	107.	
9.00.....	106.4	Breathing very fast, nearly regular.
10.35.....	106.4	Respiration 60 per minute.
10.55.....	106.	
11.37.....	105.4	

11.45 P. M. Animal killed; autopsy immediate; no meningeal or other clot of any considerable size in the brain. The knife had passed through the cerebellum and

had also wounded the extreme posterior edge of the left cerebral hemisphere, striking the pons at its junction with the medulla; it had cut entirely through on the right side. In the centre a film of fibres about a half line in thickness, on the extreme inferior or anterior portion of the pons was, left uncut. In the extreme left edge of the nerve mass a portion about a line in width was left uncut through the whole thickness of the pons and medulla.

#### EXPERIMENT NO. 2.—LARGE CUR.

Section at 5.55 P. M., followed by immediate intense rigidity of the whole body, without arrest of respiration. In a few minutes the rigidity was replaced by absolute paralysis, the breathing becoming very deep and regular.

TIME.	REC. TEMP.
6.00.....	102.4
6.30 .....	104.2
6.50 .....	104.8
7.45 .....	107.
8.10.....	105.8
8.35 .....	108.7
9.05.....	110.3

At the time of the taking of the last temperature the animal was breathing very well and regularly, appearing as though it would live for many hours. Dr. Wood was now called out of the building, leaving the dog in care of a servant. On his return at 10.15 there was marked post-mortem rigidity of the whole animal, and the rectal temperature was 109°. According to the report of the servant, death occurred suddenly. It was probably caused by paralysis of the respiratory centre by heat; so that the animal may be said to have died of a thermic fever or sunstroke produced by nerve section.

*Autopsy.*—At the base of the brain some small scattered, rather thin meningeal clots. The section was through the middle portion of the pons; the knife had passed so as to wound the extreme anterior portion of the cerebellum, and had divided the pons in its middle region almost entirely

through, leaving, however, everywhere on the lower aspect a thin layer of fibres half a line in thickness, and at each extreme edge a thicker band.

The experiments for urea, as made by Dr. John Marshall, were as follows :

		UREA.	PERIOD.
White Dog.	{ Before .....	10.482	12 hours.
	{ After.....	0.964	8.50 "

Cord cut at pons, Tuesday, 3 P. M. Dog died, Tuesday, 11.30 P. M.

		UREA.	PERIOD.
Black Dog.	{ Before ..	8.345	12 hours.
	{ After .....	2.107	6.5 "

Cord cut at pons, Tuesday, 3 P. M. Dog died, Tuesday, 9.30 P. M.

The blood of each dog was examined after the section, but no urea could be detected in it.

We have made a series of experiments upon the excretion of urea, after section of the spinal cord, high up. The experiments were all conducted in the same manner. The dog was fed heavily the evening of one day. From twenty-two to twenty-four hours afterward the bladder was emptied by catheter, and the urine carefully collected for the ensuing twenty-four hours, during which time no food at all was allowed the dog. After this first collection, the dog was fed all he would take. Twenty-two hours subsequent to this the operation was performed upon the spinal cord, and the urine collected for twenty-four hours, as before. One point which should have been attended to was not, namely, the weight of the dog was not given.

The temperatures given in the table are rectal temperatures, taken at the close of the twenty-four hours after section of the cord.

The results obtained are so discordant that we can only conclude from them that section of the cord has no direct constant effect upon the secretion of urea, although by shock, interference of the abdominal circulation, etc., it probably greatly influences such secretion, the result being a varying one, according as the indirect consequences of the operation vary.

		Quantity of urea in grammes.	Volume of urine in c. c.	REMARKS.
Black Dog.	Before	243.	20.339	Cord cut Tuesday, between 7th and 8th vertebræ, 4 P. M. Temp., Wednesday, 12 M., 88.2° F., and at 4 P. M., Wednesday, 88° F.
	After	155.	11.163	
Pup.	Before	92.	7.749	Cord cut Tuesday, between 7th and 8th vertebræ, 4 P. M. Temp., Wednesday, 12 M., 96.8°, and at 4 P. M., Wednesday, 94° 7°.
	After	115.	8.178	
White Dog.	Before	240.	6.612	Cord cut Tuesday, between 6th and 7th vertebræ, 0.852 at 4 P. M. Temp., Wednesday, 4 P. M., 88°.
	After	14.7	0.852	
Brown Dog.	Before	325.	2.782	Cord cut Tuesday, between 8th and 9th vertebræ, at 4 P. M. Temp., Wednesday, 4 P. M., 101.4°.
	After	54.	1.923	
Black and White Dog.	Before	210.	10.539	Cord cut Tuesday, between 8th and 9th vertebræ, at 4 P. M. Temp., Wednesday, 4 P. M., 89°.
	After	350.	25.296	
Black Dog.	Before	505.	12.555	Cord cut Tuesday, between 10th and 11th verte- bræ, at 4 P. M. Temp., Wednesday, 4 P. M., 97°.
	After	330.	19.739	

### HYSTERICAL APHONIA.

Dr. Clemens, in the "Therapeutische Monatshefte," reports the cure of a case of hysterical aphonia by galvanization of the muscular nerves of the accessorius. B. M.

### THE SURGICAL TREATMENT OF INSANITY.

In the "Internationale klinische Rundschau," Dr. Burkhart contributes an article on cortical excision in the treatment of psychoses. He reports the results of operation in five cases. Four of the patients in various stages of dementia were much improved mentally by having a portion of the cortex of their left frontal convolutions removed. In the fifth case, which was one of delusional insanity, the greater part of the cortex of the left temporal convolution was removed, word deafness following the operation. The author thought the bad result in this case due to the fact that the same amount of care was not taken in the technique of the operation as in the other cases. B. M.