FEVER: ITS METABOLIC CHANGES.[1]

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Krehl and his pupils have stated that the material which is oxidized in the fever generated by puncture of the thermogenic center is different from that oxidized in infectious fevers. In neurogenic fever (puncture of thermogenic centers) they infer that the fever is due to an increased metabolism of glycogen, while the increased metabolism of proteids in it is due not to the puncture but to the high temperature. In infectious fever, on the contrary, there is a toxic metabolism of the proteids, since the excitant of fever acts upon all the tissues of the body and in that way increases the metabolism of proteids. Hirsch and Rolly have shown in the neurogenic fever and the infectious fever that the liver has the highest temperature. Hirsch and Rolly have shown that in curarized animals puncture of the nerve centers causes an elevation of the temperature.

Manassein found that in fever and in hunger the amount of glycogen present was considerably diminished and finally completely vanished.

Rolly determined the diminution of glycogen in the liver and in the muscles in neurogenic fever and in the fever of infection. Rolly found the amount of glycogen diminished in toxic and in neurogenic fever, in strong muscular work, and in fasting of the animal.

Hirsch and Müller have shown that as the liver has the highest temperature, in the liver must be found the greater metabolic changes. The question then arose, whether after puncture of the thermogenic centers in animals freed of glycogen there ensued an

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elevation of temperature. Rolly found that in twenty-one rabbits with no glycogen in the muscles or liver, puncture of the thermogenic center did not cause an elevation of temperature. In two rabbits only was there a rise of 0.4 and of 0.2° Fahrenheit. To animals free of glycogen he fed simple syrup to produce glycogen again; puncture of the brain then produced fever. In glycogen-free animals the injection of bacteria (pneumococcus and bacterium coli) produced a fever; hence in glycogen-free animals infection generates fever, but in the same animal thermogenic puncture does not.

Rolly also found that albumoses and peptones do not generate fever in glycogen-free animals. One of us long ago[2] proved that they generated fever in animals in normal condition.

Rolly also found that there was no increase (or only a small one) of urinary nitrogen after thermogenic puncture in glycogen-free animals. Hence Rolly supports Krehl and Schultz in their theory that the small increase of urinary nitrogen after brain puncture is due to the hyperthermia and is not a direct result of the puncture of the thermogenic center. In the glycogen-free animals not only does the thermogenic puncture produce no fever, but the increase of urinary nitrogen does not take place to any extent. Rolly believes that in neurogenic fever the increase of urinary nitrogen is due to the hyperthermia and not to the irritation of the thermogenic nerves. The greater increase of urinary nitrogen in fever generated by bacteria is due to an increased destruction of proteid, produced by the infection itself. In infectious fever there is from the beginning an abnormal destruction of proteid.

Hirsch, Müller and Rolly hold to the theory that in fever we have two parallel processes: (1) a specific breaking up of the proteid by the bacteria, and (2) a central excitation in the sense of a neurogenic fever.

Aronsohn has opposed this view. He believes that the increased destruction of proteid is dependent upon the nerves and ferments. The theory of a toxic destruction of proteid is without foundation. An increased destruction of proteid ensues according to him (1) where there is a paucity of glycogen and fats; (2) in toxic fever

[2] *Jour. of Physiol.*, 1887, viii, 218.

and in excessive irritation of the nerves, and (3) in cachexias. The increased destruction of proteid for Aronsohn is a result of the fever-process due to heightened innervation of the cells—an irritation of a thermogenic center.

It occurred to us to study the effect of an agent, beta-tetra-hydro-naphthylamin, upon glycogen-free animals. This body is a pure nervous agent in the production of fever. One of us has in another place[3] shown that it acts only when the corpus striatum and tuber cinereum are present. If only the corpora striata are removed, still the irritations of the thermogenic centers in the tuber are sufficient to produce a fever. The first experiment shows the effect of beta-tetra-hydro-naphthylamin in normal rabbits. The second experiment shows that there is a rise after a transverse section of the brain behind the corpora striata. The third experiment shows that there is no rise after section behind the tuber cinereum.

Experiment 1.—Black rabbit.

Time.	Temperature.	
2:45 P. M.	102.4° F.	
2:50		.05 gram of naphthylamin per jugular.
2:55	103.1	
3:00	103.4	
3:10	104.0	
3:25	104.3	
3:35	104.8	
3:40	105.0	
3:55	105.6	
4:10	106.2	
4:30	106.8	
4:40	107.1	
4:50	107.3	+ 4.9° F.

Experiment 2.—Rabbit was etherized and jugular prepared; brain exposed.

4:30 P. M.	101.8° F.	Transverse section on a line behind the corpora striata.
4:31		½ drop of beta-tetra-hydro-naphthylamin per jugular.
4:35	102.2	
4:43	102.5	
4:46	102.8	
4:51	102.9	+ 1.1° F.

[3] *Med. Bull.*, 1898, xx, 411.

Experiment 3.—Rabbit; transverse section through the tuber cinereum.

2:20 P. M.	Before section.	101.8° F.	
2:35	After section.	101.0	.005 gram of naphthylamin injected per jugular.
2:40		101.1	
2:45		101.2	
2:55		101.2	.055 gram of naphthylamin.
3:00		100.6	
3:05		100.6	.010 gram of naphthylamin.
3:30		100.2	
3:50		100.2	
4:00		100.1	
4:05		100.1	

We next proceeded to make rabbits free of glycogen. The animals received water but no food for four to five days. They then received subcutaneously one cubic centimeter of a .01 per cent. solution of sulphate of strychnia at intervals of fifteen minutes, until spontaneous convulsions ensued. These convulsions were kept up by sensory irritation and injections of strychnia. If the convulsions could not be provoked another injection of strychnia was made. This was kept up about four hours. They were then permitted to rest for a while, when they received intra-muscular injections of adrenalin. In some cases intra-muscular injections of adrenalin were made before the use of strychnia. After a rest of about twenty hours they received hypodermic injections of naphthylamin, when the temperature was noted. To determine the amount of glycogen present we proceeded as follows: The animal was killed by a blow on the neck. The liver was removed, weighed and quickly thrown into a boiling (1.7 per cent) solution of potash. The boiling was kept up for about a half hour, until the pieces of liver were dissolved. A definite quantity of this alkaline solution was neutralized with hydrochloric acid, and the hydrochloric acid and iodide of mercury added until no more precipitate ensued. This solution was filtered and the filter, with the precipitate, dissolved with fifteen per cent. solution of potash and water and again precipitated with hydrochloric acid and iodide of mercury. This precipitate was again dissolved in potash solution and water and

the solution again treated with hydrochloric acid and iodide of mercury. All the filtrates were then put together and precipitated with two volumes of 96 per cent. alcohol. The glycogen now separated in flakes and fell to the bottom. This solution was again filtered and the glycogen on the filter washed with alcohol and ether, and then dried.

The muscles of one half of the body after fine division were treated in the same manner. In some cases the liver and muscles were combined and treated by the above method.

Senator and Richter have calculated that a normal rabbit, with its heat economy remaining the same and of a weight of two kilograms, needs 60 calories per kilogram or 120 calories to maintain its temperature. If the normal temperature of the rabbit is 39° C. and the air temperature 19° C., then to keep the temperature normal 120 calories will be necessary, an elevation of temperature of 39° C. less 19° C. equals 20° C. For a rise of one degree centigrade in the rabbit there would be needed six calories (120/20 = 6 calories), to elevate the temperature of the rabbit 2° C., 12 calories. One gram of glycogen by combustion yields 4.1 calories, so that three grams of glycogen would have to be oxidized to raise the temperature two degrees centigrade. The presence in the rabbit of .01 gram of glycogen would not affect the conclusion that a rise of two degrees Fahrenheit in the rabbit cannot be ascribed to the glycogen. The following experiments show the rise of temperature in animals deprived of glycogen:

Experiment 4.—Gray female rabbit was given cabbage diet for five days; no food for four days except water.

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7:00 P. M.	Adrenalin 15 mgr. by intra-muscular injection.	
10:00 A. M.	Hypodermic injection 1 c.c. strych. sulph. (.01 per cent.).	
10:15	Same injection.	
10:30	" "	
10:45	" "	
11:00	" "	
11:15	" "	Convulsions.
11:30	" "	
11:45	" "	
12:00	" "	

12:30 P. M. Same injection.
1:00 " "
2:00 " "
3:00 Injection of .5 c.c. strychnine sulphate solution.
4:00 Same injection.
5:00 " "
6:00 " "
7:00 " "

Convulsions continued until 9 P. M.

10:00 P. M. 15 mgr. adrenalin intra-muscular injection.

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7:00 A. M. 15 mgr. adrenalin intra-muscular injection.

Time.	Temperature.	
3:00 P. M.	100.5° F.	.01 gram naphthylamin hypodermically.
3:10	100.6	
3:20	100.8	.01 gram naphthylamin hypodermically.
3:30	101.0	
3:40	101.2	
3:50	101.4	
4:00	101.6	
4:10	101.8	
4:20	102.1	
4:30	102.4	
4:40	102.6	
4:50	102.7	
5:00	102.8	
5:10	102.9	
5:20	103.0	
5:30	103.0	+ 2.5° F.

Liver, weight	46.0 grams.	Precipitate and filter	1.42 grams.
		Filter	1.41
		Glycogen in liver	.01
Muscles (leg, arm and side), weight	73.0 grams.	Precipitate and filter	1.39 grams.
		Filter	1.39
			.00

No glycogen was found in the muscles.

Experiment 5.—Black female rabbit was given cabbage diet five days; no food for four days except water.

7:00 A. M. Adrenalin 15 mgr. intra-muscularly.
1:00 P. M. Injection of 1 c.c. strych. sulph. sol. (.01 per cent.).

1:15	Same injection.	
1:30	" "	
1:45	" "	Twitchings.
2:00	" "	
2:15	" "	
2:30	" "	
2:45	" "	Spontaneous convulsions until 11:00 P. M.
3:00	" "	
3:30	" "	
4:00	" "	
4:30	" "	
5:30	Injection of 0.5 c.c. strych. sulph. sol.	
6:30	Same injection.	
7:30	" "	
8:30	" "	
11:00	Adrenalin 15 mgr. intra-muscularly.	
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7:00 A. M.	" "	"
12:00	" "	"

Time.	Temperature.	
4:00 P. M.	102.4° F.	.01 gram naphthylamin hypodermically.
4:10	102.5	
4:20	102.6	.01 gram naphthylamin hypodermically.
4:30	102.8	
4:40	103.0	
4:50	103.2	
5:00	103.5	
5:10	103.7	
5:20	103.9	
5:30	104.1	
5:40	104.2	
5:50	104.3	
6:00	104.4	
6:10	104.5	
6:20	104.5	+ 2.1° F.

Liver, weight	43.0 grams.	Precipitate and filter	1.31 grams.
		Filter	1.30
		Liver glycogen	.01
Muscles (leg, arm and side), weight	92.0 grams.	Precipitate and filter	1.27 grams.
		Filter	1.27
			.00

No glycogen was found in the muscles.

Experiment 6.—Brown rabbit was given cabbage diet for five days; no food for four days except water.

7:00 A. M.	Adrenalin 15 mgr. hypodermically.	
10:00	Hypodermic injection of 1 c.c. strych. sulph. solution.	
10:15	Same injection.	
10:30	" "	
10:45	" "	Twitchings.
11:00	" "	
11:15	" "	
11:30	" "	
11:45	" "	
12:00	" "	
12:30 P. M.	" "	
1:00	" "	Spontaneous convulsions continued up to 8:00 P. M.
1:30	" "	
2:30	Injection of 5 c.c. strych. sulph. sol.	
3:00	Same injection.	
3:30	" "	
4:30	" "	
5:30	" "	
8:00	Adrenalin 10 gtt.	

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8:00 A. M. " 15 "

Time.	Temperature.	
1:00 P. M.	102.0° F.	.01 gram naphthylamin hypodermically.
1:10	102.1	
1:20	102.2	.01 gram naphthylamin hypodermically.
1:30	102.4	
1:40	102.6	
1:50	102.8	
2:00	103.0	
2:10	103.2	
2:20	103.3	
2:30	103.5	
2:40	103.6	
2:50	103.8	
3:00	103.9	
3:10	104.0	
3:20	104.1	
3:30	104.1	
3:40	104.1	+ 2.1° F.

Liver, weight	46.0 grams.	Precipitate and filter	1.35 grams.
Muscles (leg, arm and side), weight	97.5 grams.	Filter	1.34
		Glycogen	.01
	143.5		

Experiment 7.—Black rabbit was given cabbage diet for five days; no food for four days except water.

7:00 A. M.	Adrenalin 15 mgr.	
12:00	Hypodermically 1 c.c. strych. sulph. sol. (.01 per cent.).	
12:15 P. M.	Same injection.	
12:30	" "	
12:45	" "	Twitchings.
1:00	" "	
1:15	" "	
1:30	" "	
1:45	" "	Spontaneous convulsions to 9:00 P. M.
2:00	" "	
2:30	" "	
3:00	" "	
5:00	Injection of .5 c.c. strych. sulph. sol.	
6:00	Same injection.	
7:00	" "	
8:00	" "	
9:00	" "	
11:00	Adrenalin 10 mgr. hypodermically.	

7/10/'07.

7:00 A. M. " 15 " "

Time.	Temperature.	
2:25 P. M.	102.8° F.	.01 gram naphthylamin hypodermically.
2:35	103.0	
2:45	103.2	.01 gram naphthylamin hypodermically.
2:55	103.6	
3:05	104.0	
3:15	104.2	
3:25	104.4	
3:35	104.5	
3:45	104.7	
3:55	104.8	
4:05	105.0	
4:15	105.1	
4:25	105.1	
4:35	105.1	+ 2.3° F.

Liver, weight	56.0 grams.	Precipitate and filter	1.33 grams.
Muscles (leg, arm and side), weight	98.5 grams.	Filter	1.33
	154.5		.00

We performed twenty experiments. We did not find it an easy matter to free the animals completely of glycogen; but we had

some completely freed of it. We have given some examples of our results. They showed that beta-tetra-hydro-naphthylamin will produce fever in a glycogen-free animal. The fever here must be due to a using up of the proteid. The metabolism of the proteid is set into activity by the stimulation of the thermogenic centers in the corpus striatum and the tuber cinereum, for the removal of these centers prevents the naphthylamin from causing a rise of temperature.

That puncture will not cause any rise of temperature in a rabbit free of glycogen is probably due to a weak stimulation of the thermogenic centers. Naphthylamin is a much more powerful stimulant and is like the poisons of infectious fevers. Albumoses and peptones are also probably too weak as stimulants to the thermogenic centers in a glycogen-free rabbit. Here the naphthylamin stimulates the nerve centers, which cannot act on glycogen, but acts upon the proteid initiating changes in it. These facts do not support the views of Krehl and Rolly that puncture of the brain acts only on glycogen, while the infectious fevers produce a toxic metabolism of proteid.

Nearly all observers agree that in fever there is an increased proteid metabolism, but no increased fat metabolism except such as may result from inanition in the individual. There is every reason to believe that with both puncture of the thermogenic centers and with the infectious fevers, fever is produced by an action on the thermogenic centers. As Aronsohn has contended, there is no toxic destruction of proteid except through the trophic nerves of the thermogenic centers. The intra-cellular ferments also have a share in the metabolic changes of fever.

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