THE INFLUENCE OF HIGH PROTEIN DIET ON THE KIDNEYS.

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The literature contains conflicting reports concerning the effect of excessive protein intake on the kidneys of laboratory animals and man.

Newburgh (1) fed rabbits egg white. It was fed alone to one group, alternated with common stock diet in another group, and mixed with other food in a third group. The time of feeding varied from a few days to 7 months. Casts and albumin appeared in the urine and by serological tests the albumin in the urine was shown to be different from egg albumin. Examination of the kidneys revealed casts in the tubules and varying degrees of tubule damage.

He also fed rabbits 15 to 30 gm. of casein daily, mixed with other articles of diet. Kidney damage was found in rabbits fed 3 weeks, 10 weeks, and 4 months, but one ate the diet for 11 months at which time it had albuminuria but no kidney injury was found by microscopic examination.

Another group of rabbits was fed soy beans and water. The controls were killed at the end of 7 months and had no gross or microscopic evidence of kidney damage. Of the ones fed soy beans, five were killed at the end of 2 months. Four of these were negative, but one had degeneration of tubular epithelium and casts in the lumina. The remaining fifteen were fed 4½ to 12 months longer and eight died. All of these had acute and chronic changes in the tubules, and in five of these no other cause of death than nephritis was found. The remaining seven were killed and all had kidney damage, but it was slight in one animal. The primary effect was on the tubular epithelium and was accompanied by an overgrowth of connective tissue. There was gain in weight. Blood urea determinations on the controls averaged 31 mg. per 100 cc., while those fed soy beans had blood urea of 100 mg. or more per 100 cc. of blood.

Newburgh and Clarkson (2) also found kidney damage in rabbits fed meat. One group of animals ate a diet containing 35 per cent protein and in 6 weeks all had albumin and casts in the urine. They lived from 4 to 7 months. The kidneys were large, the tubules dilated and degenerated. A second group ate a similar diet

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containing 25 per cent protein. Early lesions in these animals were swelling and desquamation of the tubular epithelium. Those living from 24 to 59 weeks had dilatation of the tubules with atrophy and degeneration of the epithelium. The glomeruli were normal and there was no connective tissue increase. Albumin and casts were found in the urine. Nineteen were used as controls, one of which had dilated tubules and scars in the kidney were frequently found.

Similar results are reported by Polvogt, McCollum, and Simmonds (3) who avoided some criticism applicable to Newburgh's work by using rats, because they are omnivorous, and composing a diet containing enough fat, carbohydrate, and accessory food substances for normal growth and reproduction. They varied the protein content by shifting the proportions of the ingredients. The diet consisted of wheat, maize, casein, liver, beans, peas, sodium chloride, calcium carbonate, and butter fat or cod liver oil. The protein content was 31 per cent, 40.9 per cent, 40.6 per cent, and 41.3 per cent in four different arrangements of the above articles. The control diet contained 18 per cent protein. The time of feeding lasted from 129 to 489 days and included five generations. The average blood urea for the controls was 17.6 mg. and that for the others 23.5 mg. per 100 cc. of blood. The kidneys of all except the control group were large, congested, had casts in the tubules, hyaline material in the capsular spaces, and degeneration of the tubular epithelium. There was gain in weight, good growth, and activity of all animals.

Osborne, Mendel, Park, and Darrow (4) also fed rats a high protein diet, but report different results. The articles of diet are not enumerated but the protein content is given as 75 per cent. Weight of these animals increased from 60 to 260 gm. The only kidney change found at the end of the experiment was hypertrophy.

Putnam and Gamble (5) while working on another problem fed rats casein, starch, butter fat, and salt, a diet consisting of 75 per cent protein, and at the end of 2, 3, and 5 months found no retrogressive kidney lesions but there was hypertrophy.

Howe (6) studied the diet of monkeys and found that they do not tolerate over 8 per cent protein. To a group of twenty he fed diets of 18 to 25 per cent protein with enough fat, carbohydrate, and vitamine for their needs. Postmortem examination of these animals included microscopic study and no nephritic changes were found.

Squier and Newburgh (7) studied the effect of high protein diet on five patients with symptoms and signs of beginning chronic nephritis consisting of headache, dizziness, disturbances of vision, high blood pressure, and low phenolsulfonephthalein output. One case, only, had albuminuria. Blood urea nitrogen ranged from 9.8 to 19.1 mg. per 100 cc. of blood. The protein intake was raised from 33 gm. to from 100 to 175 gm. daily, after which red blood cells appeared in the urine of four patients, albumin appeared in three and increased in the one that already had it. Blood urea nitrogen rose to from 15.4 to 28.9 mg. per 100 cc. in three instances, but in one it fell from 15.8 before to 14 mg. while the high protein diet was being taken. Blood pressure was not influenced.

They also studied the effect of feeding two meals of 1½ pounds each of beef steak in a day to each of four normal young men. Red blood cells were found in the urine of every individual and these were taken as evidence of renal irritation.

Procedure.

With these reports as a basis for work the following procedure was planned and carried out.

Young, adult, albino rats were divided into six groups of six each and fed diets containing fat, carbohydrate, protein, salt, and accessory food substances. The ingredients were changed in proportion for each group so as to vary the amount of protein. Obviously, the fat and carbohydrate will also vary in proportion if natural food is used. In one group soy beans furnished practically all of the protein. The food analysis was calculated from tables given in Laboratory handbook for dietetics by Rose. The diet sheets are given below.

	Group No.					
	I	II	III	IV	V	VI
	per cent in gm.	*per cent in gm.*	*per cent in gm.*	*per cent in gm.*	*per cent in gm.*	*per cent in gm.*
Wheat	2.0	30.0	27.0	27.0	—	20.0
Casein	—	1.0	5.0	15.0	—	35.0
Maize	—	—	30.0	30.0	—	—
Orange juice.*	17.0 (cc.)	—	—	—	—	—
Corn starch	70.0	46.0	—	—	19.5	27.0
Dried peas	2.0	10.0	20.0	10.0	—	5.0
Soy beans	1.0	5.0	10.0	10.0	75.0	5.0
Sodium chloride	1.0	1.0	1.0	1.0	1.0	1.0
Calcium carbonate	1.5	1.5	1.5	1.5	1.5	1.5
Butter	5.5	5.5	5.5	5.5	3.0	5.5
Analysis:						
Protein	1.36	9.56	20.17	29.89	28.76	40.13
Carbohydrate	67.80	69.78	55.65	49.90	37.50	42.70
Fat	4.89	6.06	7.42	7.32	13.60	5.82

* Fed separately.

At the beginning of the experiment the left kidney was removed from one rat in each of the above groups save Group I. In this way the load of the remaining kidney was doubled. The food was given *ad libitum*. After 6 months of feeding blood urea nitrogen determinations were made, all remaining animals killed, and complete postmortems performed. Group III was the control.

A seventh group consisted of sixteen pied rats which were fed cooked lean beef

and whole milk. The stock room diet was given to three additional ones for controls. Blood uric acid determinations were made at the beginning and end of the feeding time which was 9 weeks. Then the animals were killed and examined.

RESULTS.

The results can be readily written and much more easily read if put in tabular form as below.

Rat No.	Weight.	Blood urea nitrogen.	Weight of kidneys.			Diameter of tuft.	Diameter of tubule.*	Anteroposterior diameter of kidney.
			Right.	Left.	Body.			
Group I.								
	gm.	*mg. per 100 cc.*	*gm.*	*gm.*	*per cent*	*μ*	*μ*	*mm.*
36†	95.0	—	0.65	0.57	1.28	—	—	—
37	96.0	0.42	0.51	0.47	1.02	78.0	34.2	6.0
38†	87.0	—	0.56	0.57	1.29	—	—	—
39†	71.0	—	0.49	0.52	1.42	—	—	—
40†	72.0	—	0.48	0.45	1.29	—	—	—
47†	87.0	—	0.52	0.50	1.17	—	—	—
Average.....	84.6	0.42	0.53	0.51	1.24	78.0	34.2	6.0
Group II.								
61†	144	—	0.65	0.66	0.90	—	—	—
62†	150	—	0.66	0.62	0.83	—	—	—
65	154	4.83	0.80	0.79	1.03	73.1	35.4	6.0
68†	135	—	0.64	0.61	0.92	—	—	—
69	164	0.42	0.70	0.77	0.89	82.5	33.0	6.0
Average.....	149	2.62	0.69	0.67	0.91	77.8	34.2	6.0
34‡	151	0.84	0.79	—	0.52	94.2	43.5	7.2
Group III.								
70	154	2.80	0.78	0.80	1.02	102.6	40.5	7.5
71	148	4.41	0.70	0.68	0.93	80.1	36.9	7.0
72	164	4.41	0.62	0.60	0.74	95.1	35.7	6.5
73	118	—	0.54	0.50	0.88	103.8	34.2	6.0
74†	115	—	0.53	0.50	0.90	—	—	—
Average.....	140	3.87	0.63	0.61	0.89	95.4	36.8	6.7
75‡	209	1.51	1.13	—	0.54	104.4	42.3	8.0

* Each entry is an average of ten measurements with an ocular micrometer.

† Animal died before end of feeding time.

‡ Animal on which nephrectomy was performed.

Rat No.	Weight.	Blood urea nitrogen.	Weight of kidneys.			Diameter of tuft.	Diameter of tubule.*	Anteroposterior diameter of kidney.
			Right.	Left.	Body.			
Group IV.								
	gm.	*mg. per 100 cc.*	*gm.*	*gm.*	*per cent*	*μ*	*μ*	*mm.*
76	200	3.22	1.20	1.15	1.17	97.5	38.7	7.5
77	261	4.41	1.15	1.10	0.86	107.4	43.2	8.0
78	178	4.06	0.85	0.85	0.95	89.2	36.9	7.0
79	229	3.22	1.10	1.06	0.94	98.1	40.8	8.0
80	165	3.64	0.78	0.75	0.92	89.7	38.4	7.0
Average.....	206	3.71	1.01	0.98	0.97	96.4	39.6	7.5
81‡	204	3.22	1.50	—	0.73	106.2	43.2	9.0
Group V.								
53	210	9.08	0.80	0.85	0.78	90.9	36.6	7.0
54	174	3.64	0.64	0.65	0.74	109.5	34.2	6.5
55	162	4.06	0.79	0.75	0.95	86.1	35.7	7.5
57	142	5.25	0.66	0.61	0.89	89.7	31.8	6.5
59	166	4.76	0.80	0.78	0.95	91.5	33.9	6.8
Average.....	171	5.36	0.74	0.73	0.86	93.5	34.4	6.8
60‡	142	6.86	0.91	—	0.64	103.5	36.0	7.2
Group VI.								
82	140	4.83	0.80	0.85	1.17	107.4	33.9	7.0
83	178	4.83	0.95	0.90	1.03	97.2	39.6	7.5
84	184	8.47	0.84	0.85	0.91	105.2	44.4	7.5
85†	119	—	0.52	0.51	0.86	—	—	—
86	144	5.25	0.84	0.78	1.12	97.5	37.8	7.5
Average.....	153	5.84	0.79	0.78	1.02	101.8	38.9	7.4
87‡	188	8.47	1.10	—	0.58	105.9	40.8	8.0

Complete postmortem examinations were made in every instance and no gross evidence of nephritis was found in any. Microscopic study was made of all kidneys of the animals that lived to the end of the feeding time but no evidence of kidney damage was found in any instance.

Group VII.

Rat No.	Before feeding.		After feeding.	
	Weight.	Blood uric acid.	Weight.	Blood uric acid.
	gm.	*mg. per 100 cc.*	*gm.*	*mg. per 100 cc.*
1	300	3.5	315	3.4
2	250	2.9	250	4.2
3	290	3.0	300	6.8
4	250	3.2	195	3.8
5	300	3.8	310	—
6	185	3.8	245	4.7
7	285	4.1	295	3.0
8	225	3.3	240	3.5
9	230	3.4	225	4.3
10	275	3.4	300	6.0
11	310	3.9	305	3.4
12	260	4.0	Died.	—
13	190	3.8	225	3.7
14	200	4.0	205	2.9
15	210	3.3	245	3.3
16	215	3.0	235	3.2
Average.....	248	3.5	259	4.0
Controls.				
17	190	2.4	210	4.4
18	175	1.7	215	4.7
19	180	2.6	200	2.9
Average.....	181	2.2	208	4.0

No evidence of kidney damage was found by gross and microscopic study.

DISCUSSION.

Omnivorous animals were used and the source of protein was both animal and vegetable.

The animals in Group I were all markedly emaciated. The weight of the kidneys in this group is smallest but the per cent of kidney weight to body weight is largest, indicating that the estimation of kidney hypertrophy by calculating the per cent of kidney weight to body weight is in error because there is no standard of the state of body nourishment.

The average weight of the kidneys in the control group is less than

the figure given by Donaldson (8) but the animals eating from 28.76 to 40.13 per cent protein had kidneys larger than his figure, indicating that there was definite hypertrophy. Additional evidence of hypertrophy is found in the actual measurements of the capillary tufts, convoluted tubules, and anteroposterior diameters of the kidneys. This is greatest in the animals eating high protein in every case of the averages for the group. The nephrectomized animals that ate high protein diet had no kidney changes save hypertrophy and this amounted to an increase in weight of an average of 0.54 gm. or 85 per cent of the average weight of the right kidneys of the controls. Even on a diet of 40.13 per cent protein the limit of hypertrophy has not been reached as is shown by the results in the animals with one kidney.

So far at least, there is no proof of any damage to the kidneys of men who go from parts of the world where mixed diet is eaten to the far north and live entirely on meat. Stefansson (9) estimates that he has lived for a total of 9 years on an exclusive meat diet, the longest single period being 9 successive months. Lieb (10) has recently reviewed Stefansson's reports and writes, "Stefansson affirms that his observations on the health and longevity of the Eskimo led him to the conclusion that the high protein diet has no deleterious effect on their circulation or kidneys."

The work here reported contains no evidence for kidney damage resulting from high protein diet but the erroneous conclusion, that patients with nephritis may eat any amount of protein, must not be drawn. It is rational to relieve the diseased kidney of as much work as possible.

SUMMARY.

Seven groups of rats were fed on diets containing protein varying in amount from 1.36 to 40.13 per cent derived mainly from grain, casein, meat, and milk with carbohydrate, fat, and vitamines. From a number of animals one kidney was removed to double the load on the remaining one. The time of feeding was from 9 weeks to 6 months. Blood uric acid, blood urea nitrogen determinations, and microscopic examinations of the kidneys revealed no evidence of kidney damage. There was evidence of kidney hypertrophy consisting of increased

weight of the kidney, large diameters of the capillary tufts, convoluted tubules, and kidneys in the animals receiving high protein diet. The nephrectomized animals that ate high protein had no kidney changes save hypertrophy and this amounted to an increase in weight of an average of 0.54 gm. or 85 per cent of the average weight of the right kidneys of the controls.

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