DIETARY PROTEIN IN HEMORRHAGIC BRIGHT'S DISEASE

I. Effects upon the Course of the Disease with Special Reference to Hematuria and Renal Function[1]

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The question of the possibility of injury to the kidneys by the proteins of the diet has received the attention of a number of investigators. Recently Newburgh and coworkers have published some observations which throw new light on the problem. In 1919 Newburgh (14) reported a series of experiments in which renal injury was observed in rabbits to which high protein diets were given. In 1928 a further report (15) was made of experiments in which white rats were given 75 per cent of their diet in the form of proteins, either as liver, or as beef muscle, or as casein. Renal injury was noted in all groups after varying lengths of time. In the group receiving liver, the kidneys at autopsy were enlarged, granular and characterized by both glomerular and tubular lesions and fibrosis. These changes were well marked at the end of "less than a year" of the liver diet. In the case of casein the renal injury was least marked, being confined to the tubules, and required the longest time for its production, while the lesions occurring in the group receiving beef muscle were intermediate between the two extremes both in degree and in the rapidity of their production. In a more recent report Newburgh (16) expressed the belief that the difference in results obtained in previous work was due to the nephrotoxic effects of products of nuclear material and not to the proteins *per se*, since feeding of sodium nucleate produced hematuria. He was able to produce kidney injury with less than 75 per cent of liver in 80 per cent of the animals.

Other workers have reported the production of renal lesions in animals by the feeding of high protein diets. These include Osborne, Mendel, Park and Winternitz (17), and Polvogt, McCollum and Simmonds (18). On the other hand Drummond, Crowden, and Hill (5), Jackson and Riggs (7), and Addis, MacKay and MacKay (3) failed to find renal injury in similar experiments. MacLean, Smith and Urquhart (12) were able to produce renal injury in rabbits by means of high protein diets only when green leaves and vegetables were omitted from the diet.

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In 1921 Squier and Newburgh (20) reported that albuminuria was increased when large amounts of protein were given to patients with nephritis, and that red blood corpuscles appeared in the urine of normal men under similar circumstances. On the other hand Addis (1) counted the formed elements in the urinary sediments of a number of normal adults before and after a single ingestion of one and one-half pounds of meat. No increase was observed.

Two Arctic explorers were kept under observation by McClellan and DuBois (11) for one year while subsisting on a protein and fat diet. The protein intake ranged from 100–140 grams daily. No evidence of renal damage was discovered by either laboratory or clinical observations.

Pospischill and Weiss (19) kept one-half of a series of 2373 cases of scarlet fever on a diet of milk, while the other half received the usual diet containing meat. The incidence of Bright's disease was the same in both groups. The general condition of those patients who received the meat was better. Jochmann (8) came to similar conclusions in observing a series of 1000 cases of scarlet fever.

Recently one of us (W. S. M.) (10) has reviewed the many aspects from which the metabolism of protein in nephritis must be considered. The question of the "wear and tear" quota, the requirements of growth, the "toxic destruction" of protein, and the possiblities of limiting protein catabolism by high caloric diets, were discussed in their bearing upon the diet of the patient with nephritis, with special reference to nephrotic syndromes, true uremia and renal acidosis.

METHODS

In the present paper are reported the observations made on four patients with hemorrhagic Bright's disease, who received at different times both high and low protein diets. In all four patients the acute stages were observed in the hospital. The experimental observations recorded here were carried out in the early chronic active stage in three patients, and in the latent stage in one. The diagnosis of hemorrhagic Bright's disease was based upon the clinical findings supported by quantitative counts of the formed elements in the urinary sediments, made by the technique of Addis (2). Two of the patients were observed in the special metabolism ward, which has been described by one of us (4). The other two remained on general medical wards, where they received weighed diets prepared in the special diet kitchen of the hospital. All four patients were intelligent and cooperated in every way in maintaining the accuracy of excreta collections and in consuming their diets completely.

The general plan was to begin with a fore-period in which moderately low protein was given, followed by moderately high protein diets, and again by lower protein. The major contrasts are between levels of 40,

75 and of 150 grams of protein. Urinary sediment counts were made at least twice a week, more frequently when the urine was of high specific gravity and proper acidity. Counts were not done when the urine specimens were not sufficiently acid and of low density. Urea clearance tests were done according to the method of Möller, McIntosh, and Van Slyke (13), between the hours of 7 and 10 A. M., before the patient had risen and while he was still fasting. Urea determinations were made by the gasometric method of Van Slyke (21). The urinary protein was estimated daily by the method of Kingsbury, Clark, Williams and Post (9). The total nitrogen of the urine and stools was determined by the usual Kjeldahl procedure. The stools corresponding to each period were separated by means of carmine. Chemical analyses were done on blood specimens obtained before breakfast according to the following methods: non-protein nitrogen, Folin and Wu (6); serum proteins, Wu and Ling (22).

Patients were weighed daily, before breakfast. Urine and stool specimens were stored in a refrigerator as soon as they were obtained.

CASE REPORTS

Case 1. J. B., number 40617, a boy of 15 years was admitted November 5, 1930. Three weeks before this date a tooth was extracted because of an abscess. Three days later he had a "sore throat" accompanied by mucopurulent nasal discharge. One week before admission he began to have general malaise, headache, vertigo, nausea, vomiting, pain in the lumbar regions, edema of the face and legs, oliguria and hematuria. No previous attack of this nature had been observed. For five or more years he had suffered from repeated attacks of upper respiratory infection characterized by mucopurulent nasal discharge, chronic cough productive of mucopurulent sputum in the morning only, and occasional attacks of sore throat. There was no history of scarlet fever.

On examination the temperature, pulse and respirations were found to be normal. The skin was pale, but the mucous membranes were of good color. There was slight, but definite, edema of the face and lower extremities. The eye grounds were normal. The nasal septum was deviated to the left and there was slight, not very definite tenderness over the antra. The tonsils were enlarged with exudate in the crypts. The posterior chain of cervical lymph nodes was palpably enlarged. The examination of the lungs was essentially negative. On percussion the left border of cardiac dullness was found to be 10 cm. from the midsternum. The systolic blood pressure was 170 mm. Hg, diastolic 90 mm. Hg. The liver edge was felt just below the costal margin.

Laboratory findings. The urine was grossly bloody. It contained a considerable amount of albumin, and many hyaline, granular, and cellular casts. The blood count was as follows: hemoglobin 75 per cent (11.25 grams per 100 cc.), red corpuscles 4,100,000, leucocytes 15,800. Chemical analysis of blood gave the following results: nonprotein nitrogen, 45 mgm. per 100 cc.; serum albumin, 4.28 grams per 100 cc.; serum globulin, 1.84 grams per 100 cc. The phenolsulfonphthalein excretion was 20 per cent in 2 hours. The Wassermann and Kahn reactions of the blood were negative. A blood culture

remained sterile. Roentgen examinations of the sinuses revealed cloudiness of the ethmoids, and sphenoidal sinus, and of both maxillary sinuses. Those of the teeth were negative. The films of the chest revealed peribronchial feathering extending from both hilus regions, clear apices, and thickening of the pleura at the left base. The transverse diameter of the heart was slightly increased.

The nose and throat consultant found no evidence of acute sinusitis. Ephedrine inhalant was used in the nose, and the respiratory symptoms rapidly improved. The patient was given a low-salt diet containing 30 to 50 grams of protein. Fluids were limited to 1200 cc. for the first six days. The edema disappeared. The systolic blood pressure decreased to 100–120 mm. Hg. On November 13th the standard urea clearance was about one-third of normal. On November 19th the leucocyte count was 9000. The phenolsulfonphthalein excretion on November 20th was 70 per cent in 2 hours. The urine, however, continued to contain the same amount of blood.

Tonsillectomy was performed on November 24, 1930. This was followed by a febrile period of one week. Thereafter, hematuria and albuminuria decreased. The patient was discharged to his home on December 24, 1930, to be re-admitted on January 5th for further observation in the metabolism ward for a period of nine weeks.

In Table 1 a summary of these observations is given covering the entire period from November 5, 1930 to May 13, 1931. To conserve space data of daily observation have been summarized by periods, which were usually 7 days. Blood chemical data, weight, and blood pressure were recorded for the first day of each period. Only the maximum and minimum figures for the urinary sediment counts during each period are given. The urinary protein values are recorded as an average of the daily amounts. The day to day variations are recorded graphically in Figures 1 and 2.

Comment. Referring to Table 1 observations are recorded for a period of more than 6 months. A fore-period of 9 weeks on low protein intake (30 to 50 grams) is followed by nine periods in the metabolism ward where the protein intake was first increased to 75 grams for two weeks, and then to 150 grams for six weeks, and thereafter again reduced to 75 grams for a period of ten weeks.

In Table 2 is presented an analysis of the sources of the dietary protein. The total calories were maintained at the general level of 2500 calories. Carbohydrate and fat were used in nearly equal amounts. The percentage of calories derived from protein varied from 12 per cent (75 grams) to 24 per cent (150 grams). In all but three periods (I, II and IX) the major portion of the protein was derived from beef muscle, supplemented by that of milk and egg and small amounts from vegetable sources. In periods VII and VIII liver was substituted for beef protein.

From Table 1 it will be seen that a positive nitrogen balance was obtained in all periods from I to VIII. In period IX a slight loss occurred due to the lag in reduction of urinary nitrogen when the food nitrogen was suddenly reduced. In the periods of nitrogen retention the level of nonprotein nitrogen and urea of the blood increased. This increase of urea was more striking than that of total nonprotein nitrogen. These levels

TABLE 1

*Case 1, J. B.**

Date	Period	Diet protein daily	Nitrogen exchange						Blood					Urinary red cells per 12 hours	Urea clearance		Blood pressure	Weight
			Intake	Output			Balance		Non-protein nitrogen	Urea nitrogen	Serum		Hemoglobin		C_s	C_m		
				Urine	Feces	Total	Period	Per diem			Albumin	Globulin						
1930		*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*grams per 100 cc.*	*grams per 100 cc.*	*per cent*	*millions*	*cc. per minute*	*cc. per minute*	*mm. Hg*	*kgm.*
November 5		30–50							45		4.3	1.8	75	Gross			170/90	56.5
November 13									37	20			70		19		120/70	52.0
December 4										11					40	47		50.2
December 20														250				51.6
1931																		
January 7–13	I	75	83.8	61.2	6.0	67.2	+16.6	+2.3	26	10	5.4	2.5		122–235	45	57	120/60	51.3
January 14–20	II	75	83.6	73.0	4.3	77.3	+ 6.3	+0.9	32	11	5.4	2.5	86	165–310	67	77	110/55	51.3
January 21–27	III	150	169	127.5	5.6	133.1	+35.9	+5.1	26	9	5.3	2.4		165–284	71		110/60	51.8
January 28 to February 3	IV	150	168.5	135.2	4.7	139.9	+28.6	+4.1	40	19	6.1	2.5		125–500	75	70	110/60	52.4
February 4–10	V	150	168.5	133.7	4.9	138.6	+29.9	+4.3	38	21	4.6	2.0		140–260	75		110/60	52.1
February 11–17	VI	150	167.4	138.2	7.8	146.0	+21.4	+3.0	40	16	5.0	2.2		105–126	73	88	110/55	52.8
February 18–24	VII	150	167.6	137.7	6.1	143.8	+23.8	+3.4	43	18	4.7	2.2		80–140		79	105/55	52.7
February 25 to March 3	VIII	150	167.8	139.2	5.2	144.4	+23.4	+3.3	43	19	4.1	2.4		110–135	74	86	105/60	53.0
March 4–7	IX	75	48.0	49.5	2.9	52.4	− 4.4	−1.1	39	17	4.6	2.5	90	90		86	110/60	53.2
March 8–15		75							34	15				60–75	65		110/60	52.9
March 16–31		75							36	16	4.3	2.2		18–32				54.3
April 1–15		75							29	14	4.4	2.0		24–61	51	74		54.4
April 16–30		75							28	7				10–38		71		55.5
May 1–14		75							30	11				12–18	56	70	115/60	58.2

* Blood chemistry values, weight and blood pressure are for first day of period. Sediment counts are extreme values obtained during each period. Urea clearance values are the average for all determinations of each period.

$C_s = \frac{U\sqrt{V}}{B}$ = "standard" clearance. $C_m = \frac{UV}{B}$ = "maximum" clearance, i.e. when V exceeds 2 cc. per minute.

of blood urea must be considered in relation to the level of fluid intake which is not shown in the chart. In periods I and II the average daily total water intake was 2600 cc. In periods III and IV it was increased to 2900 cc., and thereafter to 3300 cc. daily, which resulted in a slight decrease in urea values.

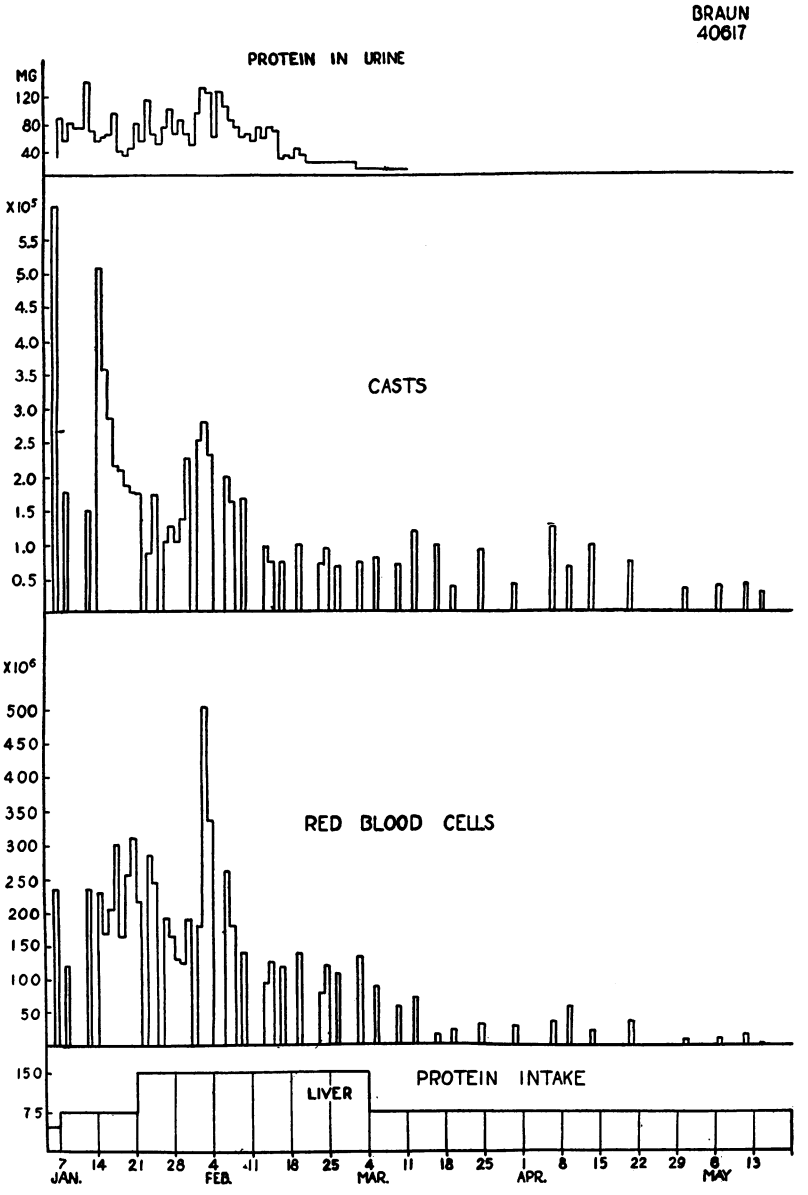

FIG. 1. CASE 1. J. B. CHRONIC HEMORRHAGIC NEPHRITIS

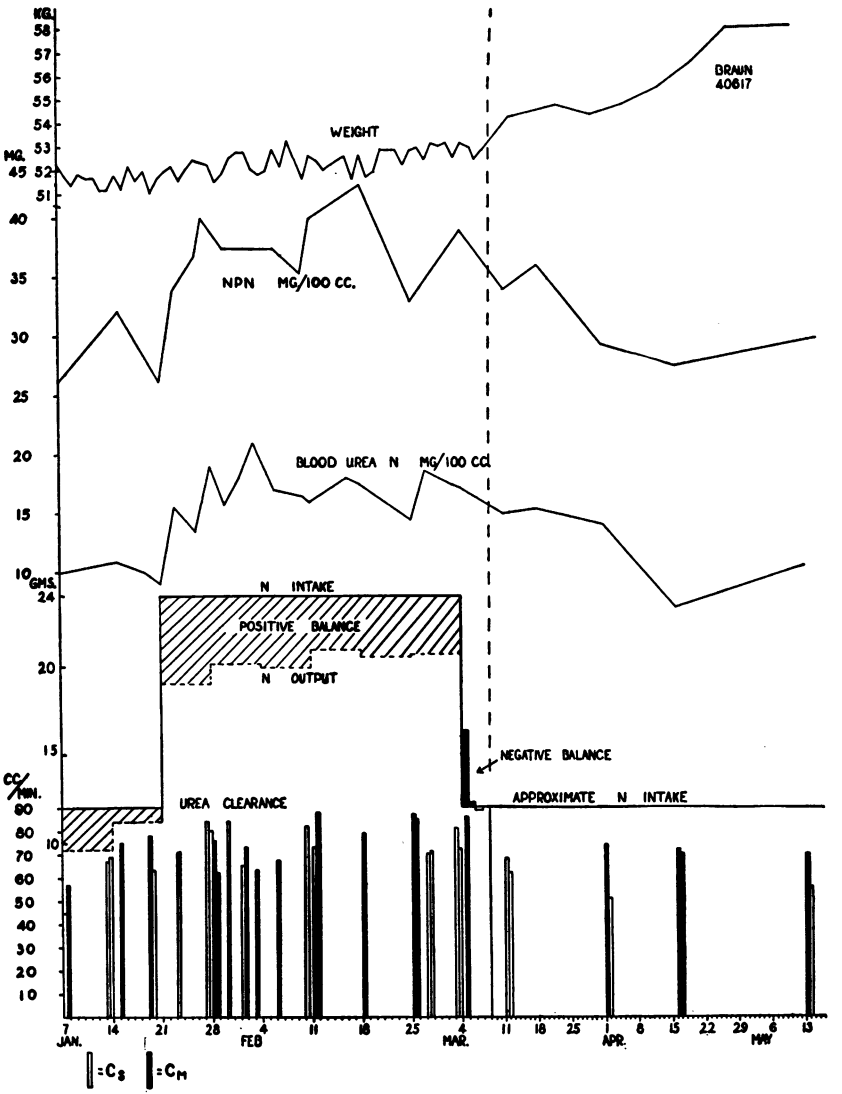

FIG. 2. CASE 1. J. B. DATA COLLATERAL TO FIG. 1

C_s is the "standard," C_m the "maximum" clearance of blood urea.

The serum proteins fluctuated somewhat without any direct relation to the protein intake. The serum albumin remained within nearly normal limits. The serum globulin was slightly low throughout.

The hemoglobin rose from 70 to 90 per cent during the observation.

The urinary sediment counts revealed a steadily decreasing hematuria in spite of the increase in dietary protein. There was a transient increase in period IV probably due to a slight cold which developed at that time.

TABLE 2

*Analysis of sources of protein in diet of Case 1, J. B.**

Period	Calories per day	Carbohydrate	Fat	Total protein		Muscle daily	Liver daily	Egg daily	Milk daily	Vegetable daily
				Daily	Per cent of total calories					
		grams	*grams*	*grams*		*grams*	*grams*	*grams*	*grams*	*grams*
I, 7 days	2515	155	169	75	12.2	20		18.1	18.5	18.4
II, 7 days	2515	157	168	75	12.2	19		16.3	20.7	19.0
III, 7 days	2550	178	129	150	24.1	55		34.6	40.8	19.6
IV, 7 days	2560	177	131	150	24.0	54.3		35.8	40.6	19.3
V, 7 days	2540	168	133	150	24.2	62.0		32.5	36.1	19.4
VI, 7 days	2525	174	129	150	24.4	55.6		35.8	39.3	19.3
VII, 7 days	2635	175	140	150	23.3		61.2	32.4	37.9	18.5
VIII, 7 days	2630	172	141	150	23.4		61.2	31.8	38.6	18.4
IX 4 days	2500	161	165	75	12.3	18.4		21	18.1	17.5

* Figures represent daily average for each period.

Even in periods VII and VIII in which liver was given the hematuria did not increase. Casts fluctuated considerably in number, but were greatly decreased in the later periods. Both casts and protein of the urine increased in periods III and IV when the patient had a cold. They appeared to vary independently of the dietary protein and were greatly decreased in the later periods of observation.

Renal function, as measured by the urea clearance tests, increased considerably during the periods in which the higher protein diets were given, and showed a slight decrease when the protein intake was reduced. The blood pressure, after the first week, remained within normal limits throughout the entire period of observation.

The weight increased slowly, apparently because of the deposition of fat and protein, as there was no evidence of edema.

On March 18th the antra were punctured and considerable foul smelling pus was obtained. After repeated irrigations this disappeared. The diminished hematuria after this date may have been due to the relief of the sinusitis, instead of the reduction in dietary protein.

The data in this case reveal a steady improvement during the early chronic active stage of hemorrhagic Bright's disease on a regime in which 75 to 150 grams of protein were given. This improvement was marked by decreasing hematuria and proteinuria and increasing renal function, with the maintenance of normal blood pressure. The anemia improved greatly during this period of liberal protein in the diet.

Case 2. P. V., number 41641, a white man, 22 years old, was admitted on December 9, 1930. He had always been in good health until the present illness. He had rare attacks of sore throat. There was no history of scarlet fever. One month before admission he had a slight sore throat, cough, general

malaise and fever. Ten days before admission there appeared generalized edema, headache, vomiting and epistaxis.

On examination temperature, pulse, and respirations were normal. There was edema of the face, over the sacrum and lower extremities. The cervical lymph nodes were enlarged and tender. The eye grounds were normal. There was some discharge in the right nostril but no sign of sinusitis was discovered either by x-ray, transillumination, or puncture of the antrum. The ears were normal. The tonsils were not large but showed evidence of chronic infection. The examination of the heart and lungs revealed no abnormalities. The systolic blood pressure was 160 mm. Hg, diastolic 100 mm. Hg.

Laboratory findings. Hemoglobin 76 per cent (11.4 grams per 100 cc.), red corpuscles 4,630,000, leucocytes 10,400. The Wassermann and Kahn reactions of the blood were negative. The urine showed marked albuminuria, and the sediment contained many red corpuscles, hyaline, granular and cellular casts.

The nonprotein nitrogen of the blood was 75 mgm. per 100 cc.

Roentgen examination of the chest revealed slight enlargement of the heart.

Six days after admission the patient developed bilateral otalgia and the temperature rose to 38.5° C. Large blebs appeared on both drums. Bilateral myringotomy was done with the escape of serosanguineous fluid. The ears continued to discharge for some time. Hematuria persisted, and at times the urine was visibly blood tinged. There was a progressive anemia until on December 26, 1930 the hemoglobin was 60 per cent (9.0 grams per 100 cc.), red blood cells 2,800,000, leucocytes 16,000. The ears gradually improved, but hematuria continued, and the blood hemoglobin decreased further to 45 per cent (6.75 grams per 100 cc.), on January 26, 1931. On February 3rd he was given a transfusion. On February 12th a tonsillectomy was performed. Thereafter clinical improvement was rapid and hematuria decreased.

Upon entrance the patient was given a salt-poor diet containing 35 to 40 grams of protein daily. Edema decreased rapidly during the first few days and thereafter slowly. A month later demonstrable edema had entirely disappeared and did not reappear thereafter.

On January 29th, fifty days after admission, the protein of the diet was increased to approximately 50 grams. Beginning February 28th he was kept on a weighed diet containing varying amounts of protein as indicated in Table 4. On March 8th he was transferred to the metabolism division and remained there until discharge. He was in bed until May 5th after which he was allowed up for gradually increasing periods. On May 25th he was discharged home on a diet containing about 75 grams of protein. We believe that he received approximately this amount daily. During this interval he visited the hospital weekly for observations. On June 21st he was re-admitted to the metabolism division and immediately given a diet containing 150 grams of protein for a period of 12 days. He was discharged on July 2nd and has been under observation in the Out-Patient Department since that time.

As in Case 1 the fluid intake had to be quite small on some days in order that Addis sediment counts might be done. The average daily total calculated water intake while the patient was on 40 to 75 grams of protein was from 2700 cc. to 2900 cc. During the first week on 150 grams of protein it was about 3400 cc. daily, thereafter, because of increase in atmospheric temperature it was raised to 4000 cc. daily.

Laboratory observations on this patient are summarized in Table 3 and Figures 3 and 4.

TABLE 3

*Case 2, P. V.**

Date	Period	Diet protein daily	Nitrogen exchange					Blood					Urinary red cells per 12 hours	Urea clearance		Blood pressure	Weight
			Intake	Output			Balance for period	Non-protein nitrogen	Urea nitrogen	Serum proteins		Hemoglobin		C_s	C_m		
				Urine	Stools	Total				Albumin	Globulin						
1930		*grams*	*grams*	*grams*	*grams*	*grams*	*grams*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*grams per 100 cc.*	*grams per 100 cc.*	*per cent*	*millions*	*cc. per minutes*	*cc. per minutes*	*mm. Hg*	*kgm.*
December 10								75		3.3	2.2	76	++++			160/100	85.4
December 12		35–50											607			145/110	83.4
1931																	
February 19								50		4.5	3.0	53					65.4
February 25													295	26			65.4
February 28 to March 8	I	75	108	84.2				34	23	4.6	2.4	57	240–270	24		120/60	66.4
March 9–15	II	75	84	64.1	5.8	69.9	+14.1	33	19	4.7	2.2	61	240–250			100/60	65.6
March 16–22	III	40	45	44.5	6.7	51.2	− 6.4	35	19	4.4	2.5	70	180–300	29		105/65	65.9
March 23–29	IV	40	45	37.2	4.7	41.9	+ 2.9	24	12	4.5	1.8		158–200	24		105/60	65.4
March 30 to April 5	V	75	84	55.1	6.5	61.6	+22.4	28	13	4.7	2.0		110–167	27		90/50	65.8
April 6–12	VI	75	84	58.2	5.8	64.	+20.0	31	16	4.8	2.2		115–220	23		100/50	66.5
April 13–19	VII	150	168	107.0	7.3	114.3	+53.7	34	16	4.7	2.3	80	180–200	26	41	100/60	67.2
April 20–26	VIII	150	168	123.2	9.6	132.8	+35.2	42	24	4.7	2.8		152–163	39	42	105/70	69.0
April 27 to May 3	IX	150	168	124.1	9.4	133.5	+34.5	49	23	4.6	2.4	78	178–200	42		110/70	70.1
May 4–10	X	150	168	130.5	10.7	141.2	+26.8	44	30	4.0	2.4		225	35		120/75	70.8
May 11–17	XI	150	168	126.7	7.6	134.3	+33.7	43	23	4.4	2.0	78	174–212	47	48	110/70	71.7
May 18–24	XII	40	45	46.0	10.4	56.4	−11.6	41	20	4.4	2.2		73–113	26	50	120/70	72.7
May 25		75						28	9	4.5	1.8	80	77	20	27	110/65	72.3
June 22 to 26	XIII	150	122	79.8				35	18	4.7	2.3	82	26–45	55			71.1
June 27 to July 1	XIV	150	120	87.4	6.3	93.7	+26.3						24–45				70.6
July 2								46	22	4.6	3.6		62	57			70.6

* Blood chemical, weight, and blood pressure values are for first day of period. Sediment counts are extreme values obtained during each period. Urea clearances all done on first day of period except periods XI and XII. C_s is the "standard" urea clearance, C_m the "maximum" clearance.

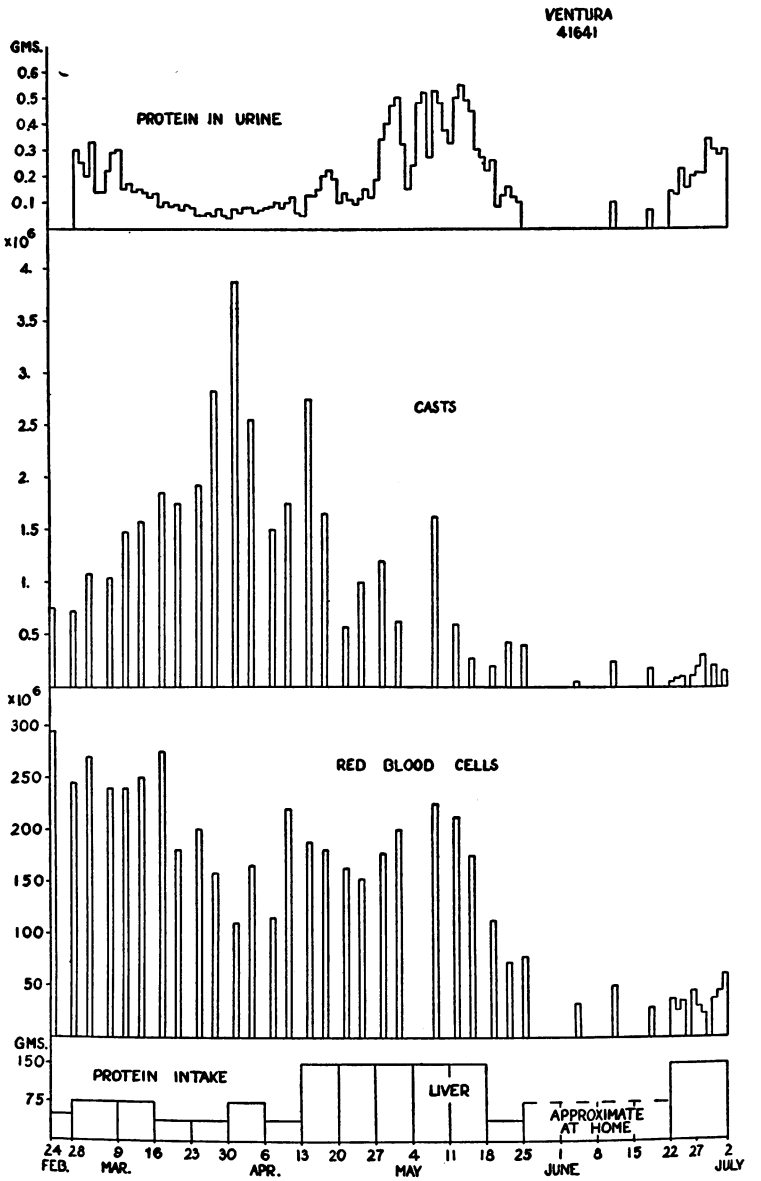

FIG. 3. CASE 2. P. V. CHRONIC HEMORRHAGIC NEPHRITIS

Comment. The observations made on Case 2 extend over a period of 6 months and 22 days. These are summarized in Table 3. During a fore-period of 77 days the protein of the diet was about 35 to 50 grams. During 12 weekly periods he was observed in the metabolism ward, where the protein intake was varied from 40 to 150 grams per diem.

In period IV the patient came into nitrogen balance during the second week on 40 grams of protein. All periods in which 75 or 150 grams were given showed a positive nitrogen balance. The total caloric intake in all periods varied from 3000 to 3800 calories per diem, the increase being necessary to satisfy the patient's hunger. Carbohydrate and fat were given in nearly equal amounts. The percentage of total calories derived from protein varied from 5 to 18 per cent. Considerable amounts of this protein were derived from beef muscle, but relatively more came from egg and milk than in Case 1. See Table 4.

During periods IX and X beef muscle was replaced by liver.

The total nonprotein nitrogen of the blood rose slightly above normal

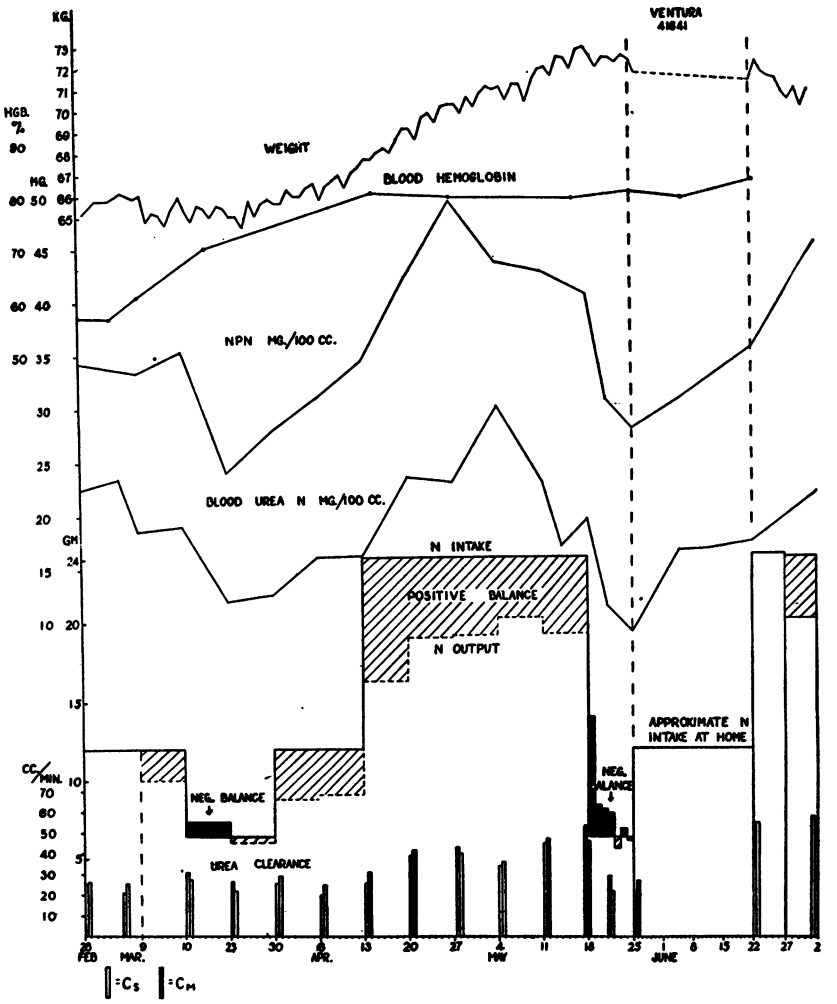

FIG. 4. CASE 2. P. V. DATA COLLATERAL TO THAT OF FIG. 3

TABLE 4

Analysis of sources of protein in diet of Case 2, P. V.

Period	Calories per day	Carbohydrate	Fat	Total protein		Muscle daily	Liver daily	Egg daily	Milk daily	Vegetable daily
				Daily	Per cent of total calories					
		grams	*grams*	*grams*		*grams*	*grams*	*grams*	*grams*	*grams*
I, 9 days	3000			75		25.5		10.4	14.5	24.6
II, 7 days	3017	184	210	75	10.2	23.7		18.1	15.6	17.6
III, 7 days	3180	204	234	40	5.1	9.5		10.8	5.7	14.0
IV, 7 days	3238	203	241	40	5.1	9.3		10.8	5.9	15.0
V, 7 days	3143	179	226	75	9.8	20.4		18.0	15.7	20.9
VI, 7 days	3213	179	234	75	9.6	20.3		15.6	17.5	21.6
VII, 7 days	3850	229	247	150	16.0	60.2		24.1	37.8	27.9
VIII, 7 days	3788	224	242	150	16.2	60.0		25.8	36.7	27.5
IX, 7 days	3457	210	213	150	17.8	10.0	57.5	29.3	26.9	26.3
X, 7 days	3510	211	218	150	17.5	16.6	57.0	27.6	23.2	25.6
XI, 7 days	3743	218	240	150	16.4	60.0		26.0	37.2	26.8
XII, 7 days	3688	204	243	40	4.5	9.4		10.8	6.1	13.7
XIII, 5 days	3780	219	243	152	16.5	56.5		28.4	37.2	27.9
XIV, 5 days	3837	230	245	150	16.0	58.5		25.2	39.4	26.9

in periods VIII to XI, but decreased when more fluids were given. The fluctuations in blood urea followed roughly the fluctuations in protein intake.

The serum proteins changed but little. During the fore-period serum albumin was below normal. As the edema cleared it rose to about 4.5 per cent and remained at that level independently of the level of protein ingestion. The globulin remained rather constantly at a slightly low level throughout.

The hemoglobin which had fallen to 57 per cent at the beginning of period I, rose to about 80 per cent during the next four months of liberal protein intake.

The urinary sediment counts revealed a marked decrease in hematuria during the fore-period. From period I on this tendency to decrease was slower but steady and no essential difference was found between periods in which 40 grams of protein were given and those in which 150 grams were taken.

The urinary protein showed some tendency in this case to increase or decrease as the dietary protein increased or decreased.

The urea clearance tests showed a steady tendency to increase. In this case as in the preceding one the standard clearance values were higher in the high protein periods. From beginning to end the urea clearance was more than doubled.

After the fore-period the blood pressure remained entirely within normal limits throughout and showed no tendency to vary in relation to the level of protein intake.

Weight was lost during the fore-period when edema disappeared. During the subsequent periods there was a steady gain in weight due to the deposition of protein and fat.

In summary of Case 2 it may be said that no deleterious effects upon the kidneys were observed during periods of liberal protein intake at levels of 75 to 150 grams per diem. All measurable factors such as hematuria and renal function showed improvement. The slight increases in proteinuria may be disregarded in view of the great improvement in other factors.

Case 3. R. W., number 54426. A 25 year old truck driver was admitted on November 26th, 1931. Previous to the present illness he had always been in good health except for recurrent sore throats. There was no history of scarlet fever or acute rheumatic fever. Two weeks before admission he had a severe sore throat which lasted several days. Four days before admission he developed edema of the face and extremities, oliguria, nausea, vomiting, and weakness. Twelve hours before admission he became stuporous and remained so until being brought to the hospital. Physical examination showed a well developed, semi-comatose man. The temperature was 37.9° C., pulse rate 76, respirations were of the Cheyne-Stokes type. There was edema of the face, extremities, and sacrum. The ocular fundi were thought to show slight edema of the discs but the vessels were considered to be normal. The heart was slightly enlarged to the left. There was a loud systolic murmur at the apex. The blood pressure was 185 systolic and 100 diastolic. The neck was stiff and there was a positive Kernig sign; otherwise neurological examination was negative.

Laboratory findings. The urine was grossly blood tinged. Blood hemoglobin was 80 per cent (12 grams per 100 cc.), red blood cells 4,100,000, leucocytes 20,000. The nonprotein nitrogen of the blood was 60 mgm. per 100 cc. The Wassermann reaction was negative in blood and spinal fluid. Cultures of blood and spinal fluid yielded no growth.

Course in hospital. During the first few days the patient received glucose solution intravenously and subcutaneously. At first the edema remained stationary and then began to decrease slowly. A lumbar puncture on November 29th showed an initial pressure of 420 mm. of water. The spinal fluid contained 14,000 erythrocytes per cu. mm. On a second lumbar puncture on the following day initial pressure was 300 mm. of water. The spinal fluid was xanthochromic and contained 1,000 erythrocytes per cu. mm. During the first days of December the stupor cleared gradually, and the blood pressure fell to normal by December 9th. A motor aphasia and weakness of the upper part of face, arm and leg on the right were observed. Tendon reflexes were increased on the right. There were no sensory changes. There was incontinence of urine and feces. During the middle of December he improved slowly. The edema disappeared and did not return. By December 24th the hemiparesis had cleared entirely and there were no peripheral neurological signs. From that time on improvement was rapid. Slight dysarthria persisted until discharge.

Further findings during the period of improvement were as follows: On December 28th roentgenographs of the chest revealed no abnormalities of heart or lungs except that the aortic knuckle was rather prominent considering the age of the patient. Examinations of sinuses and teeth were negative. The phenolsulfonphthalein excretion was 45 per cent in two hours on December 24th.

TABLE 5

Case 3. Acute hemorrhagic Bright's disease

Date	Diet protein daily	12 hour urinary sediment count		Urine protein daily	Urea clearance		Blood					Blood pressure	Weight
		Red cells	Casts		C_s	C_m	Nonprotein nitrogen	Urea nitrogen	Serum		Hemoglobin		
									Albumin	Globulin			
	grams	*millions*	*thousands*	*grams*	*cc. per minute*	*cc. per minute*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*grams per 100 cc.*	*grams per 100 cc.*	*per cent*	*mm. Hg*	*kgm.*
1931													
November 26	20–40	++++		++++			60	33	3.1	1.6	80	185/110	66.2
December 9		++++	+	+++			33	17	3.6	2.6		120/70	54.6
26	30	210	185									120/70	55.6
28						44					92		
1932													
January 1	30	300	160	2.0								120/70	57.2
4	30			0.9		44	27	8	4.1	2.5			
5	30	310	260	1.1							90		58.0
8	30	410	330	1.5									
11	220	120	180	lost	43	53	26	7	4.2	2.5		115/80	59.4
12	100	260	250	1.6							93		
17	100			1.8			35	15	4.0	2.2		110/70	61.2
19	100	177	110	1.5								120/80	62.0
22	100	375	280	1.0		55		14					
24	100			0.9			39	18	4.6	2.3			62.0
26	100	184	335	1.1		66					90		62.8
29	40	290	384	0.4	40	56							62.4
30	40			0.4			25	12	4.6	2.9			
February 3	40	270	250										62.8
4					46	53		12				120/80	

The diagnosis was acute hemorrhagic nephritis, with hypertensive encephalopathy and minimal true uremia. The nonprotein nitrogen, which was 60 mgm. per cent on admission, decreased to normal in two days.

Detailed observations of this patient are recorded in Table 5 and Figure 5. During the fore-period from November 26 to December 26, 1931 quantitative measurement of diet and excreta was impossible. As the edema subsided

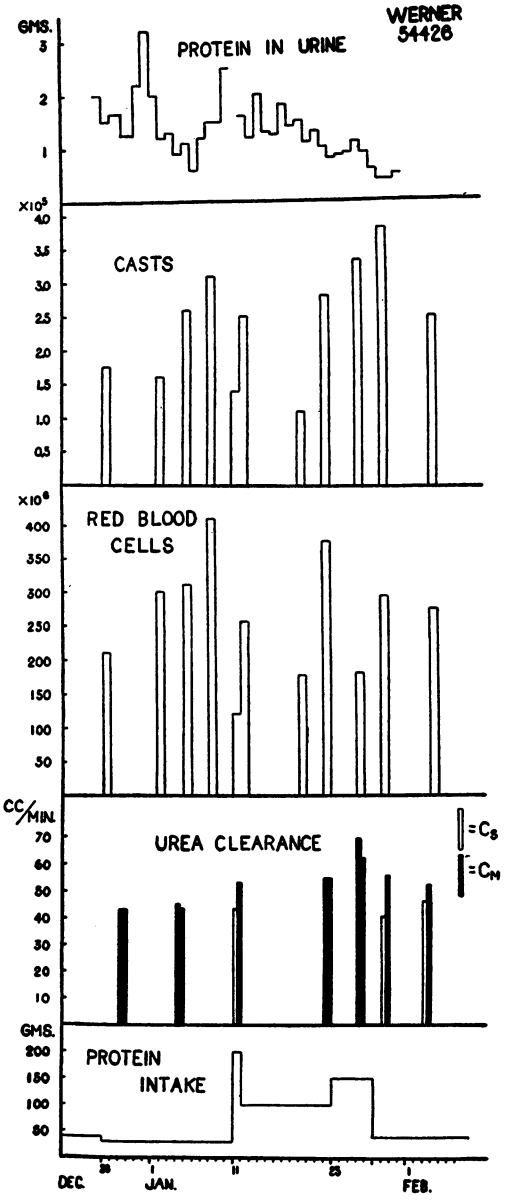

FIG. 5. CASE 3. CHRONIC HEMORRHAGIC NEPHRITIS

the weight decreased from 66 to 55 kgm. Albuminuria and hematuria persisted. The blood hemoglobin rose from 80 to 92 per cent. Both serum albumin and globulin were initially low. During the period of improvement both increased. The diet during the fore-period contained from 20 to 40 grams protein per diem.

From December 26, 1931 to January 10, 1932 the protein intake was 30 grams per diem. Hematuria, estimated by the Addis sediment count, varied from 210–410 millions of erythrocytes per 12 hours; proteinuria from 0.6 to 3.2 grams per diem. The serum albumin continued slowly to rise. The maximum urea clearance increased from 44 to 53 cc. per minute.

From January 12th to 23rd the protein intake was 100 grams per diem. Hematuria fluctuated through the same range as in the preceding period, as did the cast count and proteinuria. The nonprotein nitrogen remained within normal limits, but the blood urea increased somewhat. Serum proteins did not change significantly. Urea clearance remained stationary. Blood pressure fluctuated within normal limits.

From January 23rd to 28th the patient received 150 grams of protein without increasing hematuria. Proteinuria continued to decrease. Serum albumin increased slightly. The urea of the blood rose slightly without an increase in nonprotein nitrogen. The maximum urea clearance increased somewhat.

From January 28th to February 4th, 1932, the protein intake was again reduced to 40 grams per diem. Hematuria continued unchanged. Proteinuria continued to decrease. Blood urea fell as did the urea clearance. The serum proteins maintained their previous level. Blood pressure was unchanged.

During all these periods there was a slow steady gain in weight which was not due to edema.

The conclusion drawn from the observations in this case is that no unfavorable effect was produced upon the process of recovery in an attack of acute hemorrhagic Bright's disease.

Case 4. E. B., number 18898. A 21 year old man was admitted the first time on September 16, 1929. His past history was essentially negative. He had not had scarlet fever or acute rheumatic fever. For several years he had had occasional sore throats, but during the late winter and early spring of 1929 these had become quite frequent. In July he had a severe tonsillitis. About a week later he began to gain weight rapidly, and noticed generalized edema, blurring of vision, and abdominal tenderness. He entered a hospital in a neighboring town on July 18th and was there eight days. He was kept on a low salt, low protein diet and lost most of the edema. Thereafter he was under the care of a physician at home and was admitted to the surgical service of this hospital for tonsillectomy.

Physical examination on admission: The temperature, pulse, and respirations were normal. The skin and mucous membranes were of good color. There was no demonstrable edema. There was a moderately large, tender lymph node on the anterior right side of the neck. The eye grounds were normal. The tonsils were small, scarred, inflamed, and imbedded. The examination of the heart and lungs was negative. The blood pressure was 108 systolic and 70 diastolic. The urine was cloudy but not grossly bloody, albuminuria was moderate. The sediment contained many red cells, but no casts were seen. Tonsillectomy was done the day after admission.

On the following day he was transferred to the Medical Service. On this

day gross hematuria appeared and albuminuria increased markedly. Blood hemoglobin was 92 per cent, red blood cells 5,100,000, leucocytes 14,400. Blood nonprotein nitrogen was 30 mgm. per 100 cc. The Wassermann reaction was negative. Stereoroentgenographs of sinuses showed no evidence of infection. Roentgenographs of teeth revealed evidence of an abscess at the base of the lower left second bicuspid.

The patient was given a salt poor diet containing 60 grams of protein. Hematuria decreased very slowly at first. On October 21st the bicuspid tooth was extracted. An abscess was found at its apex and *streptococcus viridans*, *streptococcus hemolyticus*, and *micrococcus crassus* were discovered by culture of the apical granuloma.

During the following month (November) hematuria, as indicated by Addis sediment counts, decreased. The protein of the diet was increased to 80 grams and he was discharged on December 12th, 1929. He was in Texas from January until July 1930, at which time he returned to Rochester. He has been followed closely and sediment counts and urea clearance tests have been done periodically. Both of these tests indicate improvement. The routine urine examinations for more than a year past have been negative, but the sediment counts show that red cells are still present in numbers slightly greater than normal.

On December 1, 1929, after he had been on a protein intake of 80 grams daily, he was given a large beefsteak at the noon meal, making his total protein intake for the day 160 grams. Urinary sediment counts on the morning before the large protein meal and the morning after showed no evidence of an increase in hematuria.

Beginning November 9, 1930 he was under observation while on a weighed diet. The protein content of the diet and the laboratory findings for this period are summarized in Figure 6.

During a 10 day period in which the protein intake was increased to 200 grams per diem the number of red corpuscles in the urinary sediment fluctuated within limits which were no greater than during preceding periods in which the protein intake had been maintained at the lower level of 60 to 90 grams per diem.

The urea nitrogen of the blood rose during the periods of higher protein intake. This is partly due to the fact that water ingestion was limited on the days preceding the urinary sediment counts.

The blood urea clearance during the period of high protein remained at the high level which existed in the preceding periods. In the subsequent periods when protein ingestion had been reduced to 60–90 grams per diem, lower values for urea clearance were obtained.

SUMMARY

The four subjects of these experiments were all suffering from hemorrhagic Bright's disease. It is believed that this represented a *diffuse* glomerulonephritis in each case, since all exhibited a latent period between the onset of infection and the onset of nephritis, all exhibited impairment of function at some stage, and all had edema.

The dietary experiments were carried out in the early chronic active stages of Cases 1, 2, and 3, and in the latent stage of Case 4

In cases such as these the two most important objective criteria which

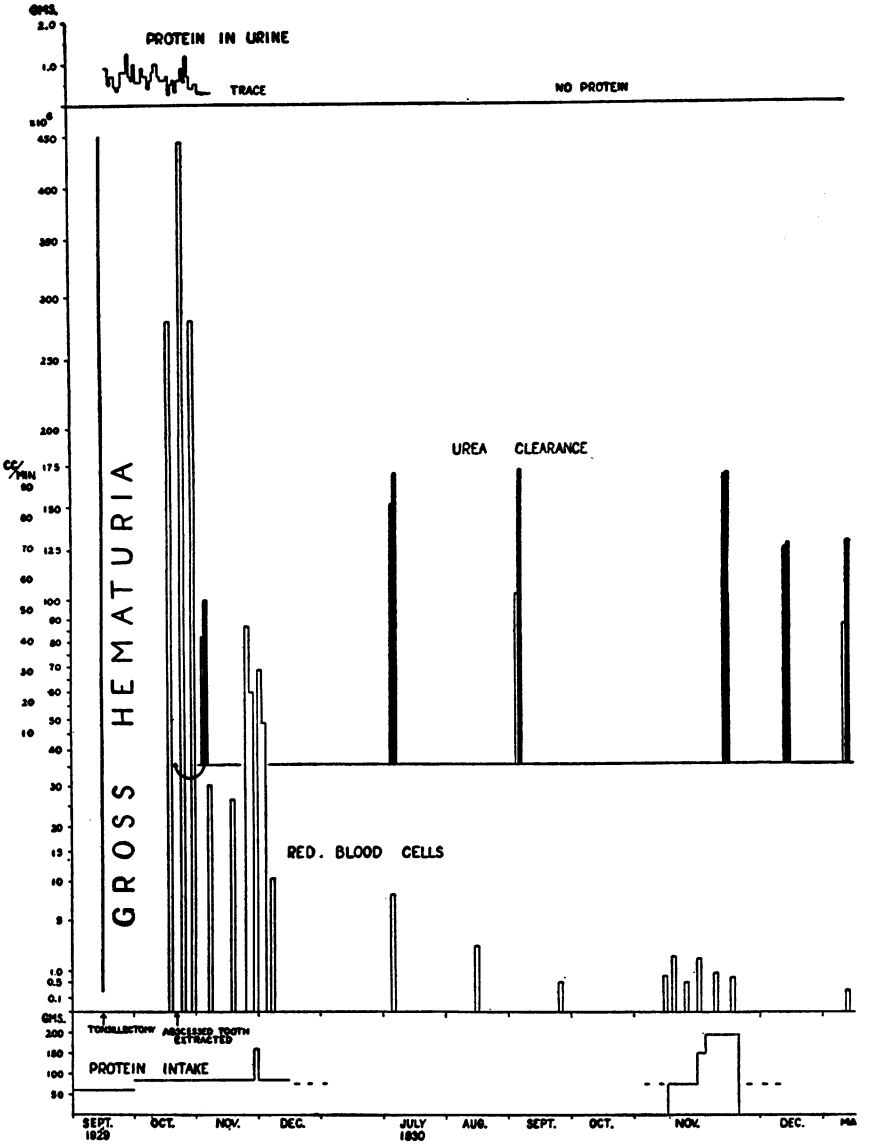

FIG. 6. CASE 4. E. B. CHRONIC HEMORRHAGIC NEPHRITIS, IN LATENT STAGE AT TIME OF EXPERIMENT NOVEMBER 1930

may be applied to the observation of the course of the disease are the erythrocyte counts in the urinary sediment and the estimation of renal function by the blood urea clearance tests. The observations of Addis and of Van Slyke have shown that hematuria is the best index of the intensity of the process of disease in the glomeruli, and that the blood urea clearance is the best index of the degree of impairment of renal function.

The possession of a means of evaluating both the intensity and quantity factors in glomerulonephritis makes it possible to study experimentally the factors which modify the course of the disease favorably or adversely.

Hematuria. In the cases which have been presented there is evidence that increasing the protein of the diet from the low level of 40 grams to levels of 75, 150, or even 200 grams, resulted in no significant increases in hematuria. Transient increases in hematuria occurring while the more liberal protein diets were given can be explained in each case by temporary exacerbations of chronic infections. In two of the patients the higher levels were maintained for 5 to 6 weeks at a time, a period long enough to permit deleterious effects to become obvious. It is also clear that the substitution of liver for beef muscle in equivalent amounts for periods as long as two weeks did not increase hematuria.

Renal function, as measured by urea clearance, was usually higher during the periods in which more liberal protein intake was given. This may represent the continuance of improvement during the period of the liberal protein ration, and possibly the stimulation of increased functional activity in response to increased demand. In any case there is no evidence of a decrease in functional capacity resulting from a liberal protein allowance.

Azotemia was sometimes slightly increased during the periods of higher protein intake. This is due to the fact that water ingestion was maintained at too low a level in order to make possible accurate urinary sediment counts. Toxic symptoms from this cause were never apparent.

The *urinary protein* increased during the higher protein periods in Cases 1 and 2 but not in Cases 3 and 4. The increases were not large, nor were they associated with any other signs of deleterious action.

Visible *edema* was absent during the experimental observations on higher protein diets. It was present in the fore-periods or in previous observations in all cases. The fluctuations in serum proteins were not large, and in no case could they be directly related to the level of protein intake. In Cases 1, 2 and 3 the serum albumin increased as the edema decreased during the fore-periods while moderately low protein diets were being given.

Blood pressure was not increased during the higher protein periods as contrasted with the lower. Hypertension was not great in any case, and when it occurred was a transient initial phenomenon of the acute attack.

In every case in which anemia was present improvement in the blood counts occurred.

These experiments are not comparable to those which Newburgh carried out on animals, either in point of duration or as regards the percentage of the total diet consisting of protein. It is not possible to keep human subjects on diets furnishing as great a portion of the energy from protein as Newburgh employed. In our experiments the maximum level was 25 per cent of the total energy of the diet.

The diets with which we have experimented contained more than the usual amount of protein taken spontaneously by the average American. The protein content is greatly in excess of the amount commonly prescribed by physicians in cases of nephritis. It was principally derived from animal sources (Tables 2 and 4).

CONCLUSIONS

Four patients with chronic hemorrhagic Bright's disease were observed during periods at different levels of protein intake, ranging from about 40 to 200 grams per diem. No deleterious effects upon the course of the disease were observed during periods of liberal protein intake.

(1) Hematuria, as a measure of intensity of glomerular injury, was not increased.

(2) Functional capacity, as measured by blood urea clearance, continued to increase.

(3) Slight increases in proteinuria which occurred in two cases during the higher protein diets are believed to be without deleterious significance.

(4) Slight increases in azotemia occurred, which were accentuated by the restriction of water intake necessary in making sediment counts.

(5) Serum proteins fluctuated independently of the level of protein intake and of nitrogen balance.

(6) Blood pressure was not increased by the more liberal protein allowance.

(7) General clinical improvement occurred in all cases. Weight increased (not due to edema), anemia improved, and patients returned to their normal state of strength and vitality.

BIBLIOGRAPHY

1. Addis, T., J. Clin. Invest., 1926, ii, 417. The Effect of Some Physiological Variables on the Number of Casts, Red Blood Cells, and White Blood Cells and Epithelial Cells in the Urine of Normal Individuals.
2. Addis, T., J. Am. Med. Assoc., 1925, lxxxv, 163. A Clinical Classification of Bright's Disease.
3. Addis, T., MacKay, E. M., and MacKay, L. L., J. Biol. Chem., 1926, lxxi, 139. The Effect on the Kidney of the Long Continued Administration of Diets Containing an Excess of Certain Food Elements. I. Excess of Protein and Cystine.
4. Bassett, S. H., Elden, C. A., and McCann, W. S., J. Nutrition, 1931, iv, 235. The Mineral Exchanges of Man. I. Organization of Metabolism Ward and Analytical Methods.
5. Drummond, J. C., Crowden, G. P., and Hill, E. L. G., J. Physiol., 1922, lvi, 413. Nutrition on High Protein Dietaries.
6. Folin, O., and Wu. H., J. Biol. Chem., 1919, xxxviii, 81. A System of Blood Analysis.
7. Jackson, H., Jr., and Riggs, M. D., J. Biol. Chem., 1926, lxvii, 101. The Effect of High Protein Diets on the Kidneys of Rats.
8. Jochmann, G., Lehrbuch der Infektionskrankheiten für Ärzte und Studierende. Springer, Berlin, 1914, p. 704.

9. Kingsbury, F. B., Clark, C. P. Williams, M. S., and Post, A. L., J. Lab. and Clin. Med., 1926, xi, 981. The Rapid Determination of Albumin in Urine.
10. McCann, W. S., Ann. Int. Med., 1931, v, 579. The Many Sided Question of Protein in Nephritis.
11. McClellan, W. S., and DuBois, E. F., J. Biol. Chem., 1930, lxxxvii, 651. Clinical Calorimetry. XLV. Prolonged Meat Diets with a Study of Kidney Function and Ketosis.
12. MacLean, H., Smith, J. F., and Urquhart, A. L., Brit. J. Exper. Path., 1926, vii, 360. The Effect of High Protein Diet on Renal Function.
13. Möller, E., McIntosh, J. F., and VanSlyke, D. D., J. Clin. Invest., 1928, vi, 427. Studies of Urea Excretion. II. Relationship between Urine Volume and the Rate of Urea Excretion by Normal Adults.
14. Newburgh, L. H., Arch. Int. Med., 1919, xxiv, 359. The Production of Bright's Disease by Feeding High Protein Diets.
15. Newburgh, L. H., and Curtis, A. C., Arch. Int. Med., 1928, xlii, 801. Production of Renal Injury on the White Rat by the Protein of the Diet. Dependence of the Injury on the Duration of Feeding and on the Amount and Kind of Protein.
16. Newburgh, L. H., and Johnston, M. W., J. Clin. Invest., 1931, x, 153. High Nitrogen Diets and Renal Injury. The Dependence of the Injury upon the Nature of the Nitrogenous Substance.
17. Osborne, T. B., Mendel, L. B., Park, E. A., and Winternitz, M. C., J. Biol. Chem., 1927, lxxi, 317. Physiological Effects of Diets Unusually Rich in Protein or Inorganic Salts.
18. Polvogt, L. M., McCollum, E. V., and Simmonds, N., Bull. Johns Hopkins Hosp., 1923, xxxiv, 168. The Production of Kidney Lesions in Rats by Diets Defective only in that they Contained Excessive Amounts of Proteins.
19. Pospischill, D., and Weiss, F., Ueber Scharlach. Karger, Berlin, 1911, p. 137.
20. Squier, T. L., and Newburgh, L. H., Arch. Int. Med., 1921, xxviii, 1. Renal Irritation in Man from High Protein Diet.
21. Van Slyke, D. D., J. Biol. Chem., 1927, lxxiii, 695. Determination of Urea by Gasometric Measurement of the Carbon Dioxide Formed by the Action of Urease.
22. Wu, H., and Ling, S. M., Chinese J. Physiol., 1927, i, 161. Colorimetric Determination of Proteins in Plasma, Cerebrospinal Fluid, and Urine.