THE EFFECT OF HIGH PROTEIN DIETS ON EXPERIMENTAL RENAL HYPERTENSION*

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Although the belief is widely held that a high protein diet is deleterious to the hypertensive patient, a careful survey of the literature discloses that this is not a generally substantiated point of view. Some clinicians (1–4) in particular Newburgh (5), have insisted that the withdrawal of protein from the diet of patients with hypertension results in the reduction of their blood pressure and the elimination of the concomitant symptoms. Others have maintained that the amount of protein in the diet generally has little or no relation to the blood pressure (6, 7). It has even been suggested that a continued low protein diet may be pathogenic (8, 9).

The relationships between renal excretory insufficiency and diet have been studied experimentally by numerous investigators (10), but the recent development of a satisfactory method for the experimental production of persistent renal hypertension (11) has made possible studies on the relationship between the factors of diet, renal excretory insufficiency and hypertension of renal origin in animals (12, 13).

Although the processes which result in relative renal excretory insufficiency and those factors which lead to hypertension are frequently seen together, we have shown that they are fundamentally distinct (14, 15). Nevertheless there still remains the possibility that an augmented load on the kidney might cause an increased amount of work and thus lead to a relative renal ischemia and the induction of those processes which lead to hypertension. We have therefore undertaken a study of the effect of high and low protein diets upon dogs with: (*a*) normotension and unimpaired renal function; (*b*) normotension and embarrassed renal function due to temporary complete occlusion of the renal arteries; (*c*) normotension and relative renal excretory insufficiency due to chronic partial occlusion of the renal arteries; (*d*) moderate hypertension with slight evidence of renal excretory insufficiency; (*e*) severe hypertension with frank renal excretory insufficiency.

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TABLE I

Summary of Pertinent Data on Effects of Diet Changes

Dog	Diet	Days on diet	Blood N.P.N.	Blood pressure			
				Ave.	Max.	Min.	Last
			mg. %	*mm. Hg*	*mm. Hg*	*mm. Hg*	*mm. Hg*
V-43,* normal; pregnant; no renal impairment; normotensive	Standard	5		145/75	150/80	140/70	140/70
	Bread and milk	24		160/85	175/95	120/60	155/90
	Meat	30		165/90	180/100	160/75	150/100
	Standard	37	27	150/75	150/80	140/70	140/70
	Meat and salt	10		130/80	135/85	120/75	125/85
	Standard	3		125/80			120/75
Y-1,† uninephrectomy; contralateral temporary renal artery occlusion for 2 hrs.; moderate renal failure; normotensive	Standard	53		170/100	190/115	150/85	190/110
	Bread and milk	30	47	180/100	200/120	170/95	160/105
	Meat	27	98	170/100	175/100	165/85	165/85
			88				
	Bread and milk	16	56	195/105	210/110	175/90	175/90
			38				
Y-80,§ temporary renal artery occlusion for 2 hrs.; moderate renal failure; normotensive	Standard	25	54	155/85	170/100	150/70	160/95
	Bread and milk	25	96	150/75	165/80	130/70	150/75
			58				
	Meat	30	124	165/80	155/100	150/75	175/75
			96				
			59				
	Bread and milk	18	41	160/80	175/95	150/70	150/70
			46				
W-67,‖ uninephrectomy with contralateral partial renal artery occlusion; kidney function partially impaired; normotensive	Standard	17	39	180/90	170/90	175/85	175/75
	Bread and milk	15	31	140/75	155/90	125/50	155/70
	Meat and salt	11	56	155/80	185/100	100/50	165/100
	Bread and milk	11	39	150/80	160/90	140/75	160/85
	Meat	9	64	160/90	165/95	150/80	160/85
	Bread and milk	7	30	165/75	175/75	150/75	175/75
W-87, bilateral partial renal artery occlusion; kidney function partially impaired; normotension	Standard	13	31	155/85	175/95	150/70	150/75
	Bread and milk	18		145/75	160/100	130/70	160/90
	Meat and salt	10	47	170/80	170/85	120/75	120/75
	Bread and milk	12	38	160/85	170/100	125/75	125/85
	Meat	17	55	145/95	175/100	125/75	150/95
	Bread and milk	2	35	145/75	160/75	130/75	130/75
U-45, uninephrectomy; contralateral kidney explanted; partially impaired renal function due to trauma to explanted kidney; normotension	Standard	20	45	170/80	165/85	190/75	150/80
	Bread and milk	7		165/90	160/100	150/70	170/85
	Meat and salt	12	70	165/90	175/100	155/75	165/85
	Bread and milk	9	36	165/90	175/85	145/90	170/90
	Meat	9	52	175/95	175/100	170/85	175/100
	Bread and milk	3	49	185/100	190/100	180/100	190/100
W-77, bilateral partial renal artery occlusion; moderate impairment of renal function, normotensive	Standard	12	38	140/75	160/85	125/75	125/70
	Bread and milk	17	45	140/70	150/75	125/65	150/75
	Meat and salt	11	66	150/80	165/85	125/75	125/75
	Bread and milk	12	38	145/80	145/85	140/75	150/75
	Meat	15	92	170/100	170/100	175/95	175/95
	Bread and milk	16		155/75	165/75	150/75	150/75
	Standard	33		140/80	120/85	130/70	130/70
	Bread and milk	61	37	145/80	170/100	140/65	175/85
			41				
	Meat	32	84	150/85	175/100	140/75	165/90
	Bread and milk	17	46	160/90	180/100	150/75	175/100
	Standard	24		150/80	175/85	125/70	160/85
	Bread and milk	25	45	160/85	175/110	150/70	150/70
	Meat	21	72	150/80	155/90	150/70	145/70
			63				
	Bread and milk	16	35	150/75	150/90	125/70	125/70
			36				
	Standard	1					175/95

TABLE I—*Concluded*

Dog	Diet	Days on diet	Blood N.P.N.	Blood pressure			
				Ave.	Max.	Min.	Last
			mg.	*mm. Hg*	*mm. Hg*	*mm. Hg*	*mm. Hg*
Y-9, bilateral partial renal arterial occlusion. Kidney function unimpaired; renal hypertensive	Standard	43	32	160/95	175/100	150/80	165/90
	Bread and milk	60	34	160/95	195/120	140/75	140/75
	Meat	38	38	165/100	140/125	140/80	120/105
	Bread and milk	12	30	175/110	175/120	175/100	175/120
	Standard	5		175/105	175/105	175/105	175/105
X-29, uninephrectomy with contralateral partial renal artery occlusion; kidney function partially impaired; renal hypertensive	Standard	21	44	180/100	230/130	140/85	140/85
	Bread and milk	5		170/110	250/150	155/100	165/105
	Meat and salt	11	54	160/100	185/125	145/80	175/110
	Bread and milk	9	55	130/95	165/105	140/80	155/90
	Meat	9	70	165/100	185/115	135/80	185/115
	Bread and milk	4	42	165/85	170/85	100/75	170/85
X-53, bilateral partial renal arterial occlusion. Kidney function slightly impaired; renal hypertensive	Standard	16		200/105	200/110	200/105	200/110
	Bread and milk	69	35	170/110	250/150	155/100	165/105
			41				
	Meat	32	34	175/110	195/125	160/95	175/100
	Bread and milk	18	46	180/110	185/115	170/100	170/100
	Standard	5		175/105	175/105	175/100	175/105
U-39, bilateral partial renal artery occlusion; renal function unimpaired; renal hypertension	Bread and milk	28	36	195/115	230/135	185/100	225/130
	Meat	32		190/115	210/125	190/105	185/110
	Standard	31		195/115	200/125	180/100	200/110
X-55, bilateral partial renal arterial occlusion. Kidney function unimpaired; renal hypertensive	Standard	21		195/110	205/125	195/95	195/95
	Bread and milk	61	27	190/120	220/130	170/100	170/105
			37				
	Meat	32		200/125	225/150	175/105	225/130
	Bread and milk	15	27	200/120	200/125	205/115	205/115
X-64, bilateral partial renal artery occlusion; kidney function partially impaired; renal hypertensive	Standard	18	37	200/120	200/120	205/115	190/120
	Bread and milk	48	38	190/110	200/125	175/75	180/100
	Meat	33	43	185/110	200/125	170/95	185/110
	Bread and milk	7		200/115	200/125	195/100	200/110
X-92,** bilateral partial renal artery occlusion; moderately severe renal insufficiency; renal hypertension	Standard	8		225/140	250/150	235/130	250/150
	Bread and milk	64	40	210/125	230/150	200/100	200/100
			44				
	Meat	19	62	250+/160	280/185	200+/135	250/135
	Bread and milk	35	102	265/145	275/170	235/125	235/125
			40				
	Meat	9	86	190/155	245/155	180/150	180/150
	Bread and milk	8	82	245/155	230/175	230/125	250/145
			44				
	Standard	23	55	240/145	250/160	230/125	250/150
	Bread and milk	52	36	225/140	200+/165	200/125	200/125
	Meat	24		230+/150	225+/160	230+/130	230+/130
	Bread and milk	18	49	235/140	250/150	250/125	250/150
			41				
			38				
	Standard	2		215/135			225/150

* V-43, pregnant (near term) while on meat and salt.

‡ Y-1, refuses meat when N.P.N. is 98 mg. per cent and on meat regime N.P.N. falls to 56 mg. per cent.

§ Y-80, as in Y-1, refuses meat when N.P.N. is 124 mg. per cent and N.P.N. then gradually falls to 96 and finally 59 mg. per cent on meat regime.

‖ W-67, while on meat alone is in estrus.

** X-92, on first regime of meat N.P.N. goes to 62 mg. per cent and dog has uremic symptoms. The N.P.N. on the first day of bread and milk is 102 mg. per cent. On the second meat regime, the N.P.N. rose acutely to 86 mg. per cent; the dog was very sick with advanced uremic symptoms and diet was changed to bread and milk. On the third regime of meat the N.P.N. does not rise sharply; the dog now refuses meat during peroids of azotemia.

In order to give the high and low protein diets an adequate period to influence the blood pressure and non-protein nitrogen of the blood the experimental animals were maintained on each diet for varying periods up to 2 months before the dietary regime was altered.

Methods

Blood pressures were determined at least triweekly on trained unanesthetized dogs by direct arterial puncture with the Hamilton manometer (16). The method of training and the range of normal blood pressures have previously been described (17). Particular attention was given to the diastolic pressure since this is the more reliable index of the state of peripheral resistance. Blood non-protein nitrogen was determined according to the method used at this hospital (18).[1]

Hypertension was induced by partial occlusion under nembutal anesthesia of the renal arteries with either Goldblatt clamps or linen ligatures (11, 19). Dogs were considered hypertensive when the diastolic blood pressure was maintained at a minimum of 40 to 50 mm. Hg above the control level. The possibility that some of the more severely hypertensive animals were already maximally responding to the hypertensive stimulus was obviated by using several animals with a mild form of hypertension, *i.e.*, with a diastolic blood pressure of 20 to 30 mm. Hg above the control level.

Renal excretory insufficiency without hypertension was induced by complete occlusion of the renal arteries for a period of about 2 hours. After release of the occlusion relative renal excretory insufficiency ensued (20). Chronic relative renal excretory insufficiency was considered to be present when the blood non-protein nitrogen was consistently above the normal level of 25 to 35 mg. per cent, or could be significantly raised above that level by an increased protein intake.

The standard diet used for feeding our normal and hypertensive animals consists of scraps of vegetables, meat, bread, and milk returned from the hospital commissary. Representative samples indicate that approximatey 35 to 40 gm. of protein are in such a daily ration for each dog. The low protein diet consisted of powdered milk and white bread and contained about 15 gm. of protein per dog per day. The high protein diet consisted of 800 gm. of ground beef chuck containing 160 gm. of protein per dog per day. In six experiments 10 gm. of sodium chloride were added to the daily meat ration for each dog.

RESULTS

The essential data are summarized in Table I and illustrative experiments are shown in Figs. 1–3.

(*a*) The effect of the low and high protein diets was tested on a normotensive unoperated pregnant dog (V-43). The several dietary changes had no effect on the blood pressure even when repeated with sodium chloride added to the meat.

[1] We are indebted to Dr. D. J. Cohn of the Department of Chemistry for these determinations.

(*b*) The substitution of the low protein diet for the standard diet, and the later substitution of the high protein diet had no effect on the blood pressure of two dogs (Y-1, Y-80) with normal blood pressure and relative renal excretory insufficiency. As expected, the blood non-protein nitrogen rose during the high protein phase of the dietary regime. (This is illustrated for Y-80 in Fig. 1.)

(*c*) In three dogs with normotension and relative renal excretory insufficiency due to partial renal arterial occlusion (W-67, W-87, U-45) six experi-

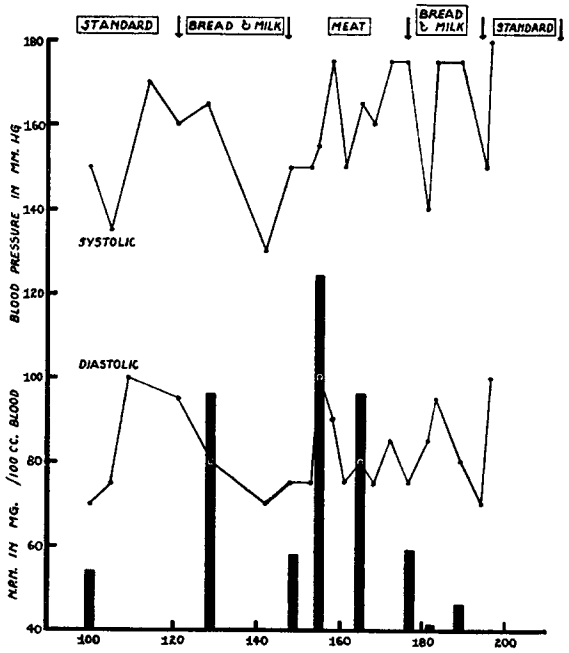

FIG. 1

ments were carried out. In the first series of these, sodium chloride was added to the meat diet. In the second phase the meat was fed alone. In all instances a rise in non-protein nitrogen occurred without a change in the blood pressure. In a fourth dog (W-77) an elevation in systolic and diastolic pressures was seen while on the meat regime after the animal had failed to show a rise in pressure on the meat and salt regime. The blood pressure rose from an average of 145/80 to an average of 170/100 during the high protein diet. This interesting response led us to twice repeat the dietary sequence; in neither of subsequent dietary regimes did the animal respond with an increased blood pressure, yet in each instance the blood non-protein nitrogen was increased during the period of high meat intake (Fig. 2).

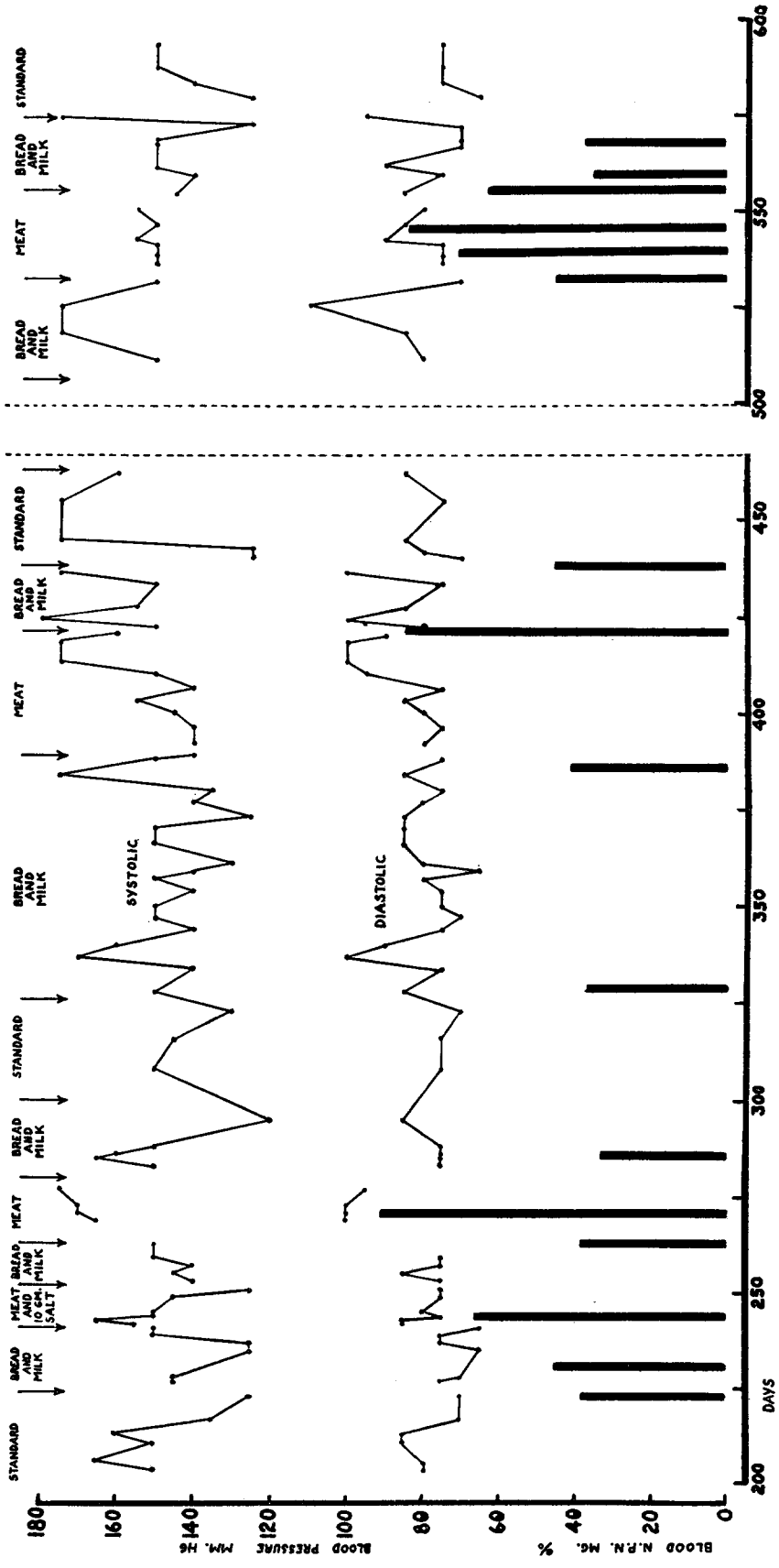
STANDARD
BREAD AND MILK
MEAT AND 10 GM. SALT
BREAD AND MILK
MEAT
BREAD AND MILK
STANDARD
BREAD AND MILK
SYSTOLIC
MEAT
BREAD AND MILK
STANDARD
DIASTOLIC
BLOOD PRESSURE MM. HG
BLOOD N.P.N. MG. %
DAYS
180
160
140
120
100
80
60
40
20
0
200
250
300
350
400
450
500
550
600

FIG. 2

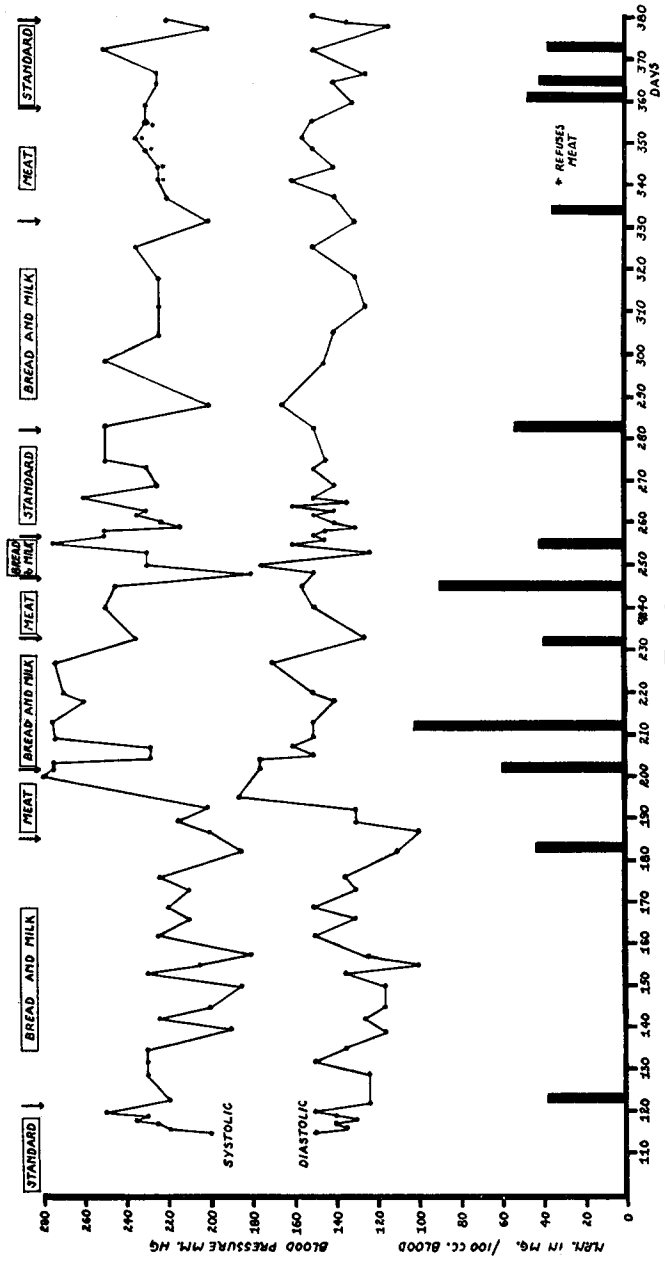
STANDARD
BREAD AND MILK
MEAT
BREAD AND MILK
MEAT
BREAD & MILK
STANDARD
BREAD AND MILK
MEAT
STANDARD
SYSTOLIC
DIASTOLIC
BLOOD PRESSURE MM. HG
NPN. IN MG. /100 CC. BLOOD
* REFUSES MEAT
DAYS

FIG. 3

(*d*) Three dogs (Y-9, X-29, X-53) with mild hypertension and relative renal excretory insufficiency due to partial occlusion of the renal arteries were subjected to the dietary sequence. The non-protein nitrogenous substances of the blood increased during the high protein phase of the diet and returned to the basal level again when the dogs were placed on the standard diet. One of these dogs (X-29) was also subjected to a diet of meat with added sodium chloride; this procedure had no effect on the blood pressure.

(*e*) Four dogs with severe hypertension and relative renal excretory insufficiency (U-39, X-55, X-64, X-92) were subjected to the succession of high and low protein diets with no significant changes in blood pressure except in one case (X-92). In this animal the first high protein diet was accompanied by an acute rise in blood pressure and non-protein nitrogen as well as symptoms and signs usually associated with malignant hypertension such as anorexia, diarrhea, vomiting, loss of weight, muscular twitching, and corneal infections. In order to ascertain whether these hypertensive and uremic manifestations were causally related to the high protein diet or whether they were coincidental, this animal was twice subjected to a repetition of the diets. In the repeated experiments on this dog the blood pressure began to rise acutely when fed on a high protein diet. When the associated uremic symptoms discussed above manifested themselves along with a concomitant rise in non-protein nitrogen the blood pressure began to fall toward the previous hypertensive level (Fig. 3). The 24 hour urinary concentration test gave a specific gravity of 1.037 and 3 plus albumen was present.

DISCUSSION

In order to judge the significance of our experimental results it is necessary to analyze the interrelationships which may exist between relative renal excretory insufficiency and renal ischemia.

In the normal animal under homeostatic conditions the amount of the excretory work performed by the kidneys is determined by the excretory load placed upon them. The load placed upon each nephron is a function of the concentration and type of metabolic products in the blood stream. The amount of excretory work the kidney can accomplish is limited by its oxygen supply since otherwise a progressively increasing oxygen debt would be incurred and this would of course have an upper limit.

When the blood flow to the kidney is limited, as in nephrosclerosis or partial occlusion of the main renal arteries, an increased load on the kidney may result in relative renal excretory insufficiency or an increase in renal excretory activity sufficient to compensate for the added burden.

The steps involved under these two circumstances can be briefly summarized. With the presence of a decreased rate of blood flow through the kidneys, the blood non-protein nitrogen content as well as other renal excretory products

may rise and thus cause an increased load on the kidney. If the work done by the kidney increases to meet this load but the blood flow cannot increase sufficiently to supply the kidney with an adequate amount of oxygen, pressor products of renal intermediate metabolism can be released into the blood stream in sufficient concentration to cause a generalized increase in the systemic peripheral resistance. An elevated blood pressure will follow. This in turn will cause an increase in the pressure head driving blood through the kidney, thereby leading to an augmentation of the rate of blood flow and of the filtration pressure in the glomeruli. This process would tend to reduce the level of the non-protein nitrogenous products and other renal excretory substances in the blood to a mininum. In this way a mechanism may be postulated whereby renal excretory insufficiency may set up the conditions for renal ischemia.

Should the increased load fail to rouse the nephrons to sufficient effort, little change in the metabolic processes of the kidney would occur. The blood flow might remain adequate for the effort. Hence no increase of renal intermediate metabolites would occur and renal hypertension would not ensue. Despite the unchanged blood pressure the rising concentration of the non-protein nitrogenous products of the blood would cause by simple physical means an increased elimination of these products through all the excretory organs of the body. In such a manner, a purely physical equilibrium may be achieved and allow the existence of an individual for a period of time in an advanced state of azotemia without hypertension.

Compensation for an inadequate renal function may in time also be aided by the process of renal cellular hypertrophy and hyperplasia. The increase in non-protein nitrogenous products in the blood has been reported (10) to cause an increase in the volume of the renal parenchyma by a proliferation of the cellular elements without any change in the number of nephrons.

Obviously, the various processes described above may occur in different degrees and combinations.

The experimental results cited in this report corroborate previous work in this laboratory which emphasizes that renal excretory insufficiency and renal ischemia are separate and distinct processes (14). In addition we suggest a mechanism by which these often concomitant processes may be interrelated.

In only two of our ten dogs (W-77 and X-92) that showed signs of renal excretory insufficiency did the arterial pressure rise during the high protein diet. In the other eight animals compensation for the increased inadequacy of renal function took place either by physical means or by hypertrophy and hyperplasia.

Since both the systolic and diastolic blood pressure of normotensive and hypertensive dogs may show spontaneous fluctuations even under the controlled conditions which were maintained in these experiments, it is necessary

that minor changes in blood pressure be disregarded. It is possible that the amount of change in blood pressure which various workers consider significant may be responsible for some of the discrepancies in the literature (12, 13).

Our results suggest that the elimination for therapeutic purposes of large amounts of protein from the diet of patients with hypertension and little or no renal damage is not generally indicated. Even in patients with hypertension and moderate or greater renal damage, elimination of protein from the diet is probably of little value in the treatment of the elevated blood pressure, although it may be of value in the treatment of the concomitant azotemia.

SUMMARY

The effect of high and low protein diets were studied on fourteen dogs in twenty-four different experiments. In only two of these animals, both with moderate renal excretory failure, was a reversible rise in blood pressure elicited by a high protein diet.

The possible mechanisms involved in meeting an increased excretory load are discussed.

We are indebted to Mr. R. Asher and Miss L. Friedberg for their assistance in these experiments.

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