DIET AND TISSUE GROWTH.

V. The Effect of Dietary Protein on the Remaining Kidney of Adult White Rats Following a Unilateral Nephrectomy.

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Plates 4 and 5.

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INTRODUCTION.

The recent literature contains an increasing number of accounts of investigations on the effect of the ingestion of excessive amounts of protein on the kidneys of experimental animals. There is general agreement on the observation of a physiologic enlargement but conflicting results are reported concerning the part played by protein in the production of pathologic renal lesions.

The character of the physiologic enlargement has been the subject of prolonged dispute. The literature on this question has been summarized by Arataki (1926, *a*) who reported from his own studies on rats that there is no increase in the number of glomerular unit systems but that the enlargement consists in an increase in the size of both the glomeruli and tubules, an hypertrophy, together with an actual cellular increase of the interstitial tissue, an hyperplasia. He believes in addition that there is an hyperplasia of the constituent cells of the glomeruli and tubules. Furthermore he observed that the enlargement is incomplete after 80 days, and stated that in some instances it may approximate 100 per cent.

Although there is no increase in the number of glomeruli in the rat, in response to feeding excessive amounts of protein, the formation of these structures continues throughout the first 100 days of life according to Arataki (1926, *b*). He stated further that the total number of glomeruli at birth is about 10,000, and at the age of 25 days about 25,000, and that by the 100th day the maximum of 30,000 has been attained. This level is maintained to the age of 350 days but by the 500th day it has fallen to 22,000.

In a study of the compensatory enlargement of the opposite kidney after ligation of one ureter in white rats Hinman (1923) has stated that the histologic

changes of compensatory renal hypertrophy may be divided into three stages: first, initial congestion; second, active mitosis and growth, and third, the final equilibrium of hypertrophy. He mentioned further that the increase in the size of the intact kidney is complete after an average of 20 to 30 days; the average total increase is 20 per cent of the normal and doubling of the renal tissue is never observed. The question of diet is not discussed in either of the above papers.

Smith and Moise (1927) have reported an extensive series of experiments on the relation of the protein constituent of the diet to the rate and degree of compensatory enlargement of the remaining kidney after unilateral nephrectomy in adult white rats. These authors have observed that on the "standard" diet containing a moderate concentration of protein (18 per cent, Table I) there is a rapid increase (24 per cent) in the compensatory enlargement of the remaining kidney within the

TABLE I.

Composition of Experimental Diets.

	"Standard food"		"High protein" food	
	Part of diet	Part of total calories	Part of diet	Part of total calories
	per cent	*per cent*	*per cent*	*per cent*
Protein (casein)[1]	18	14	85	76
Carbohydrate (raw cornstarch)	51	39		
Fat lard	22	47	7	24
Fat cod liver oil	5		4	
Salt mixture[2]	4	4	4	
700 mg. dried yeast daily given with each of the diets				

[1] A commercial product containing 13 per cent nitrogen.

[2] Osborne, T. B., and Mendel, L. B., *J. Biol. Chem.*, 1919, xxxvii, 557.

first 3 weeks. A similar series on a high protein diet (85 per cent casein) showed an extremely rapid gain to 63 per cent in 21 days. The curves of enlargement on the two diets continue approximately parallel and at 150 days the average enlargements are 48 and 121 per cent for the standard and high protein diets respectively. When adult white rats were fed diets containing increasing concentrations of protein, observations at a constant time interval (21 days) after unilateral nephrectomy showed that the increase in the size of the remaining kidney is directly proportional to the protein content of the food. The values vary from 24 per cent with the standard ration to 77 per cent with the high protein diet. All of the diets used are adequate for maintenance and growth. The large proportion of calories obtained from protein in some of the rations is the variable factor.

The material obtained from this investigation (Smith and Moise, 1927) affords a unique opportunity of studying the histologic changes in a large series of kidneys not only performing approximately double functional duty owing to the previous unilateral nephrectomy but also subjected to the additional burden of eliminating the metabolites of an extremely high protein diet (Table I). The purpose of the present communication is to report such structural changes and if possible to explain the discrepancy in the reports of other investigators.

In earlier studies of a somewhat similar nature (Newburgh, 1919), egg white, casein and soy beans were fed to three different groups of rabbits for periods of time varying from a few days to 7 months. Examination of the kidneys revealed evidence of acute and chronic renal disease, consisting chiefly of casts in tubules, varying degrees of injury to tubular epithelium and scarring of the cortex. There were no marked glomerular lesions. Newburgh and Clarkson (1923) observed marked dilatation of the tubules of the kidneys of rabbits fed diets containing lean beef amounting to 27 and 37 per cent of the ration for several months. There were no marked glomerular lesions. They called attention to the difference between the focal cortical scars occurring spontaneously in rabbits and the lesions observed in their experiments.

Evans and Risley (1925) described definite tubular and glomerular lesions in white rats fed a variety of substances containing between 27 and 75 per cent protein for periods from 6 to 15 months but the diets used in their studies were admittedly inadequate in salts and vitamines.

In all of the above mentioned experiments the diets were not only extreme but also inadequate and furthermore the early studies on rabbits (Newburgh, 1919) have been criticised because of the common occurrence of spontaneous lesions in this animal. Polvogt, McCollum and Simmonds (1923) made similar studies on white rats, with diets adequate for maintenance and growth and containing between 31 and 41 per cent protein. The time of feeding varied from a minimum of 129 to a maximum of 485 days. Congestion, degeneration of the tubular epithelium, casts and cellular detritus in the lumina of the tubules, hyaline material within the capsular space and adhesions between the glomerular tuft and Bowman's capsule were described in the kidneys of these animals.

Osborne, Mendel, Park and Winternitz (1927) observed tubular and glomerular lesions in the kidneys of eighteen white rats that had been fed high protein diets for long periods of time. These authors state that the lesions were focal in nature and were exceedingly slight in the entire group with the exception of seven animals, five of which were on a 40 per cent casein diet for 400 days or more. Exactly similar lesions were observed in five of the control animals maintained on Sherman's stock diets for over 500 days. The series also included eighteen rats on high protein diets (60 to 95 per cent) for periods varying from 200 to 360 days in which no renal lesions were observed. The average age of the animals on the high protein diet showing lesions was 348 days while those showing the lesions described as "severe" were over 400 days old.

On the other hand numerous investigators (Osborne, Mendel, Park and Darrow (1923), Osborne, Mendel, Park and Winternitz in a preliminary report (1925), Drummond, Crowden and Hill (1922), Reader and Drummond (1925), Miller (1925), Jackson and Riggs (1926), Anderson (1926), Addis, MacKay and MacKay (1926) and Kennedy (1926)) have reported that no pathologic structural changes were observed in the kidneys of intact animals (white rats, rabbits and cats) maintained on high protein diets for relatively prolonged periods. There is thus confusion in the literature on a point which is not only of academic interest but also of clinical importance.

EXPERIMENTAL.

Immediately following a right nephrectomy the animal was placed on the diet to be used and after a definite time interval the remaining kidney was removed for study. All of the kidneys were accurately weighed for determination of gross enlargement. Some were used for the determination of total solids while for the present study a large number were fixed in 10 per cent formalin, sectioned and stained with hemotoxylin and eosin.

The findings are based on the study of histologic sections from over 200 adult rats; namely, the left kidney from 92 animals on the "high protein" diet (85 per cent casein) and from a slightly smaller number of animals on the standard diet (18 per cent casein), for periods varying from 3 to 150 days after the control nephrectomy. The kidneys from another series of 60 animals on six diets varying in protein content from 30 per cent to 90 per cent casein for a period of 21 days following a right nephrectomy were also sectioned for histologic study. The animals were all somewhat under a year old (approximately 275 to 350 days) at the end of the experimental period.

In addition to the series of animals on the 18 per cent casein ration, the kidneys from groups of rats maintained on Sherman's diets "A" and "B" for periods between 350 and 565 days were examined.* As further controls the removed right kidney from many of the experimental animals was available.

Although there is no significant anatomic evidence of renal injury in the animals on the standard diet, the kidneys of the rats on the "high protein" diet show some interesting structural changes. In the early and middle periods, excluding the phenomenon of gross enlargement, the observed changes are relatively inconsequential. However, in the late periods, namely, after 90, 120 and 150 days the kidneys of the animals on the high protein ration show significant glomerular and tubular changes (Table II).

* The authors are greatly indebted to Professor E. A. Park of the Department of Pediatrics, Yale University, and Professor H. C. Sherman, Columbia University, for the material included in this group.

These changes represent actual lesions of the kidney and were observed in all animals on the high protein ration for 90 days or more. The lesions were not merely isolated focal changes but were conspicu-

TABLE II.

Data on Rats Fed High Protein Diet and Showing Renal Lesions.

Rat No.	Age completion experiment	Initial body weight	Final body weight	Right kidney weight	Left kidney weight	Remarks
Interval after nephrectomy—90 days						
		gm.	*gm.*	*gm.*	*gm.*	
594[1]	292	310	320	1.225	3.205	
597	292	292	262	1.202	2.517	
602	295	279	268	1.239	2.321	
603	295	298	300	1.173	2.774	
606	295	309	300	1.250	2.865	
608	295	300	293	1.196	2.538	
Average[2]...		288	271	1.171	2.389 Enlargement 113 per cent	
Interval after nephrectomy—120 days						
562	317	280	288	1.120	2.558	
580	317	282	262	1.132	2.244	
584	317	272	241	1.108	3.504	
590	322	293	285	1.287	2.529	
592	322	293	251	1.384	2.266	
Average[2]...		288	276	1.205	2.608 Enlargement 123 per cent	
Interval after nephrectomy—150 days						
564	346	293	290	1.086	2.429	
568	346	299	284	1.121	2.381	
569	346	266	262	0.978	2.097	
575	348	291	271	1.190	2.400	
576	348	289	290	1.111	2.435	
578[1]	348	284	214	1.106	1.912	
Average[2]...		287	277	1.126	2.419 Enlargement 121 per cent	

The kidneys of the animals listed in this table (all rats maintained for 90 days or longer on the 85 per cent protein diet with the exception of those utilized for the total solid determinations) show the renal changes described above

These lesions become progressively more numerous and more widespread in the 90, 120 and 150 day periods

The second group in the 150 day interval (age 271 days) showed less enlargement and slightly less evidence of renal damage than was observed in the first group

TABLE II—*Continued.*

Rat No.	Age completion experiment	Initial body weight	Final body weight	Right kidney weight	Left kidney weight	24 hr. urine protein 120–140 days	Casts
Interval after nephrectomy—150 days							
		gm.	*gm.*	*gm.*	*gm.*	*mg.*	
667	271	245	184	1.147	1.718	119	Present
668	271	263	285	1.184	2.185	49	"
669	271	270	282	1.406	2.276	45	"
670	271	277	320	1.130	2.359	63	"
671	271	273	280	1.145	2.471	18	Absent
672	271	282	318	1.144	2.448	45	Present
673	271	261	238	1.012	1.928	70	"
674	271	257	315	1.176	2.541	84	"
675	271	234	291	0.981	1.968	60	"
676	271	243	271	1.008	1.827	40	"
Average...		261	278	1.133	2.172 Enlargement 79 per cent		

[1] Eliminated from computations of enlargement on account of large abscess (Rat 594) and marked emaciation (Rat 578).

[2] The average values for body weight and kidney weight are based on data from rats used for computation of total solids in addition to those listed in this table. For method of calculating per cent of renal enlargement see Smith, A. H., and Moise, T. S., *J. Exp.* Med., 1927, xlv, 263.

ous and relatively widespread becoming progressively more marked in the 90, 120 and 150 day periods. The structures included in an injured area are frequently radial in form suggesting the involvement of individual glomerular unit systems.

The changes in the glomeruli consist in serum in the capsular spaces, proliferation of the epithelium of Bowman's capsule with and without adhesions between the tuft and capsule, fibrous thickening of Bowman's capsule, partial fibrosis of the glomerular tuft and in many instances infiltration of round cells in and around these areas (Figs. 1 to 4).

In the same periods, 90, 120 and 150 days, the tubules show a rather conspicuous desquamation of the lining epithelium with many fairly well preserved epithelial cells and amorphous material within the lumina.

There is a slight general tubular enlargement with a somewhat diffuse patchy distribution of areas of marked tubular dilatation. In these dilated tubules the epithelium may form a single relatively flat layer or may appear in many layers as projections into the tubules and in some instances practically fills the lumina. In may such tubules the lining epithelium consists of recently formed cells in which mitotic figures are seen as evidence of active epithelial proliferation. There are many focal groups of dilated tubules with absent or markedly flattened epithelial lining cells showing no evidence of cellular activity. In some dilated tubules hyaline casts are seen. There are other areas showing an increase in the interstitial tissue with a variable amount of round cell infiltration. There are no red blood cells in the tubules or the capsule spaces (Figs. 5 and 6).

These changes are chiefly late manifestations of the injury or irritation to which the kidney has been subjected. It seems probable that the irritation produces slight changes in the early periods but that the methods of study only demonstrate the later aspects of the process. The findings in a single animal on a 75 per cent casein diet for 21 days after a right nephrectomy suggest the correctness of this hypothesis. In the sections of the left kidney from this animal showing an enlargement of 96 per cent a few glomeruli are seen in which the tufts are large with widely separated cells. In some instances the tuft and capsule are in actual apposition or the space is bridged by strands of fibrin. These findings suggest fresh adhesions and are possible precursors of the fibrous adhesions observed in the late periods. Such apparently fresh adhesions are also seen in the sections of the kidneys 150 days after nephrectomy.

In addition to these actual lesions of the kidney there are other changes of a physiologic nature. In the normal rat's kidney a few glomeruli are seen in which the tubular epithelium extends into and partially lines the glomerular sac. This condition is observed more frequently in the high protein animals and may involve fully one-half of the circumference of Bowman's capsule. It seems probable that this is a compensatory phenomenon whereby the tubular epithelium, in response to a functional demand, partially replaces the normal lining of Bowman's capsule.

In the early periods in spite of the extraordinarily rapid renal en-

largement, there is no histologic evidence of cellular proliferation in the kidneys of the animals on the high protein régime. In the late periods the physiologic enlargement is apparent in the increase in the size of the individual constituent parts of the kidney. Although no actual measurements were made the tubules are considerably dilated in all rats subsisting on the high protein diets for 90 days or more after unilateral nephrectomy. In some animals this dilatation was very striking. The tubular epithelial cells and the glomerular tufts and sacs also appeared to be larger in the high protein animals after 90 days. In the animals on the high protein diet for shorter periods of time the enlargement of the constituent parts of the organ was less evident but can probably be demonstrated by actual measurements. There was no evidence of infection in the kidneys of any of the experimental animals.

The urinary albumin excretion was studied as a supplement to the histologic findings referred to above. It is known that intact rats on a mixed adequate diet constantly show small quantities of protein in the urine (see Nelson and McCay, 1924, and Jackson and Riggs, 1926) and the aim in the present investigation has been to make a comparative study of the albuminuria in the rats fed the high protein diet and those fed the control food. The urine was examined for casts at the same time as the protein determinations were made.

The rats used were males, 120 days old at the time of the initial nephrectomy, and the determinations were made at short intervals from 25 days to 143 days after the operation. Daily urine collections were made over a period of 4 days. The rat was removed from the metabolism cage for 1 hour in the morning and 1 hour in the afternoon for feeding in order to prevent the contamination of the urine samples by food spilled within the metabolism cage.

The rat excretes a very concentrated urine and it is possible that some of the sample was lost by its drying on the metal parts of the cage with which it came in contact. The results, while they may not represent an accurate 24 hour collection, are, however, comparable.

In most of the determinations the samples as collected were made up to 50 cc. with distilled water. To 10 cc. of the filtered diluted urine in a graduated centrifuge tube was added 3 cc. 10 per cent potassium ferrocyanide and 2 cc. 50 per cent acetic acid. After mixing and allowing to stand for 10 minutes it was centrifuged at 1600 R. P. M., for 10 minutes, the volume of precipitate was read off directly and calculated on the basis of the 24 hour excretion. The method was checked with nitrogen determinations on the heat coagulum of the urine and a curve plotted correlating the ferrocyanide precipitate with mg. of protein.

The data are summarized in Table III. In order to obtain a large enough number of observations to permit statistical treatment, the results were grouped into four periods depending on the time interval after the nephrectomy. Although this grouping is arbitrary, it is perfectly obvious that at any period chosen after 60 days, the animals on the protein-rich food excrete significantly larger quantities of albumin than the rats on the standard ration.

There is a tendency for the values for the latter group to decrease with time after nephrectomy while in the rats in the former group the

TABLE III.

Correlation of the Protein Excretion in Urine with Diet.

Period.....		I	II	III	IV
No. of rats	Standard diet	6	4	9	11
	High protein diet	7	4	10	13
No. of determinations	Standard diet	31	16	43	63
	High protein diet	30	17	67	53
Interval after nephrectomy, *days*	Standard diet	25,37,53	64,72	88,101,107 109,114	122,125, 143
	High protein diet	25,34,40, 53	61,68	88,98,101, 104,119	122,125, 140
Average value of 24 hr. urine protein, *mg.*	Standard diet	33	35	28	18
	High protein diet	31	56	63	63

Average value of 24 hour urine protein in six intact rats on standard ration was 32 mg.

albumin values increase to a level reached at about 90 days. As an additional control, six intact rats were fed the standard food and the albumin excretion measured. The value for the 24 hour elimination, namely 32 mg., is practically the same as those of the above mentioned animals in Period I.

Jackson and Riggs (1926) found a variation of 4 to 21 mg. daily in normal rats. Data for comparison are also available on eight animals nephrectomized at 200 days of age. In a time interval after the operation corresponding to Period II in the table, the average of

thirty-four determinations was 49 mg., a value which corresponds fairly well with the data on the younger rats.

Samples of urine for casts were obtained directly from the urethral orifice on a slide by causing the rat to breathe ether vapor.

In Periods III and IV, those intervals when structural damage was observed, 112 samples from 13 rats on the protein-rich diet, casts were observed in 33 cases on 12 animals while in 107 samples from 11 rats on the control food, only 3 instances of casts were seen in 2 animals. Three observations of casts were made in the former group of rats in Periods I and II while none were found in the latter group. The increased excretion of protein in the urine and the greater incidence of casts furnish striking corroborative evidence for renal injury in the remaining kidney of the animals on the high protein diet.

DISCUSSION.

The necessity for adequate control in the differentiation of spontaneous renal disease and changes attributed to any experimental procedure is quite obvious and accordingly it is advisable to mention the occurrence of spontaneous renal lesions in rats. In a study of wild rats, Ophüls and McCoy (1912) have noted the common occurrence of a characteristic type of nephritis. Reader and Drummond (1925) observe that focal renal lesions are not uncommon in white rats. In the present investigation the occurrence of such changes in normal animals has been recognized.

There is little doubt that the structural changes observed in the animals on the high protein diet are a result of the experimental procedure and are not purely a part of the spontaneous renal changes that occur in white rats. In the present experiments actual renal lesions, including a proliferation of the tubular and capsular epithelium, adhesions between and a partial fibrosis of the glomerular tuft and capsule, were observed in animals maintained for 90 days or more after a unilateral nephrectomy on a diet containing 85 per cent casein. The kidneys of the animals on the high protein ration also showed marked tubular dilatation, including a rather diffuse change with evidence of active regeneration of the epithelium as well as other areas apparently atrophic in nature, showing groups of dilated tubules with a flattening or absence of the epithelium and without evidence of regeneration.

These latter groups of dilated tubules may be secondary to an injured glomerulus.

The lesions observed in animals fed the high protein food are widespread in distribution in contrast to the relatively inconspicuous focal lesions observed in the control animals. Occasional scattered focal lesions are not infrequently observed in normal adult white rats more than a year old and accordingly in the interpretation of our data no significance has been attached to isolated focal areas, of tubular dilatation, and, less frequently, of glomerular adhesions and capsular thickening. They are apparently phenomena of senescence and were observed regardless of the composition of the diet and became progressively more common with age. In the kidneys of control animals maintained on a normal dietary régime for 120 and 271 days respectively no focal lesions were found. Observations were made on the kidneys of rats maintained on Sherman's diets "A" and "B" for 350, 361, 372, 414 and between 500 and 565 days. At 350 days these focal lesions were inconspicuous or entirely absent but became progressively more common with successive periods. After 500 days they were present in a high percentage of animals. It is interesting to note in this connection that Arataki has observed a normal decrease in the total number of glomeruli with advancing age and it is possible that the spontaneous focal lesions are secondary to the normal process of glomerular involution.

In the experimental animals maintained on the standard ration such changes were practically never seen while in the animals on the high protein régime the focal lesions were larger and more frequently observed than in normal rats.

In searching for an explanation of the disagreement between the results reported by other investigators the important factors, namely, the animal, the diet and the duration of the experiment, must be considered. Although these points have been satisfactorily controlled in most of the investigations a careful analysis of the results suggests that a due consideration has not been given to the factor of age. The greater part of the reported experiments were initiated on young animals during the period in which active formation of glomeruli (Arataki, 1926, *b*) is taking place and it seems logical to assume that an animal may have greater powers of adaptation during this early period.

The fact that most of the observations mentioned in the literature reporting no pathologic renal changes were initiated on young rats, favors the above suggestion that such animals are less susceptible to the injurious effect of the ingestion of high concentration of protein. There are, however, experiments reporting negative results with a small number of adult animals (Miller, 1925, and Jackson and Riggs, 1926). In general the positive reports of the production of renal lesions by feeding of excessive amounts of protein have one or both of two serious objections, namely, the choice of the experimental animal or the inadequate and ill balanced diets in regard to the important accessory food requirements. Both of these factors are controlled in the experiments reported by Polvogt, McCollum and Simmonds (1923) who mention the production of lesions by feeding high protein diets. In their experiments young animals were placed on the diet in question for periods ranging from 129 to 485 days. An analysis of their protocols shows that the lesion described in the shorter periods consists in the variable factors of congestion with cellular detritus and serum in the tubules while the really significant lesions, the glomerular adhesions, are described only in animals that have been on the high protein diet for 400 days or more. Similarly, in the experiments reported by Osborne, Mendel, Park and Winternitz (1927), all animals having "severe" lesions were more than 400 days old. These findings are confirmatory evidence of the truth of our suggestion that the kidneys of young animals during the formative stage may be less susceptible to the irritating factor in high protein diets than adult animals.

Although the exact mechanism whereby structural lesions develop in animals ingesting excessive amounts of protein is not clear, two probable factors are suggested: either the changes are associated with the increased burden upon the kidney or, what is more probable, they result from the elimination of some injurious product of protein metabolism.

In the present studies such factors may include the high acidity of the urine, the phosphates, the urea and possibly amino acids. Addis, MacKay and MacKay (1926) have shown that no anatomic lesions are produced in a normal white rat with two kidneys by feeding diets containing an excessive acid or phosphate content. Neither Hinman (1923), Osborne, Mendel, Park and Winternitz (1927) nor MacKay,

MacKay and Addis (1927) were able to demonstrate consistent renal enlargement when quantities of urea equivalent to the protein in diet were given. These observations suggest that increased work is not the only important factor but they do not eliminate the possibility that the persistent effect of unusually large quantities of urea may result in structural damage to the kidney under the conditions of the present experiments. On the other hand Newburgh and Marsh *et al.* (1925) have described renal lesions after the intravenous administration of certain amino acids (lysine, histidine, tyrosine, tryptophane and cystine). The proliferative character of the epithelial changes suggests the persistent action of a mild irritant producing no extensive necrosis but by continual or frequently repeated slight injuries finally resulting in the lesions described above. Further investigation is necessary to determine the specific factor involved in the production of the lesions under the experimental conditions outlined in the present study.

SUMMARY.

The effects of the ingestion of diets containing different concentrations of protein on the remaining kidney in adult white rats after a unilateral nephrectomy has been studied.

In the animals on the high protein diet (85 per cent casein), actual glomerular and tubular lesions were observed in the kidneys of animals maintained for 90, 120 and 150 days after nephrectomy.

In the animals on the standard ration, 18 per cent casein, no significant renal lesions were observed within the experimental period.

Spontaneous focal lesions in the kidneys of rats maintained on Sherman's diets "A" and "B" were inconspicuous at the age of 350 days but became progressively more frequent and were commonly observed after 500 days. The animals on the high protein and standard rations were all under 350 days old at the completion of the experiment.

It is suggested that the age factor is of importance in that young animals may have greater powers of adaptation in withstanding the injurious effect of high protein rations.

The animals on the high protein ration excreted definitely larger quantities of protein in the urine, and showed a higher incidence of casts in periods roughly corresponding to those in which anatomic lesions were observed than did the rats on the standard diet.

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EXPLANATION OF PLATES.

PLATE 4.

FIG. 1. Rat 584. High protein diet for 120 days following a right nephrectomy. There is a small fibrous adhesion between the tuft and Bowman's capsule. × about 305.

FIG. 2. Rat 564. High protein diet 150 days following a right nephrectomy. There is marked proliferation of the epithelium lining Bowman's capsule with small adhesions between the tuft and capsule. There is a focal accumulation of small round cells adjacent to the glomerulus. × about 305.

FIG. 3. Rat 562. High protein diet for 120 days following a right nephrectomy. There is a large fibrous adhesion between the tuft and capsule involving approximately one-half of the circumference of the glomerulus. × about 305.

PLATE 5.

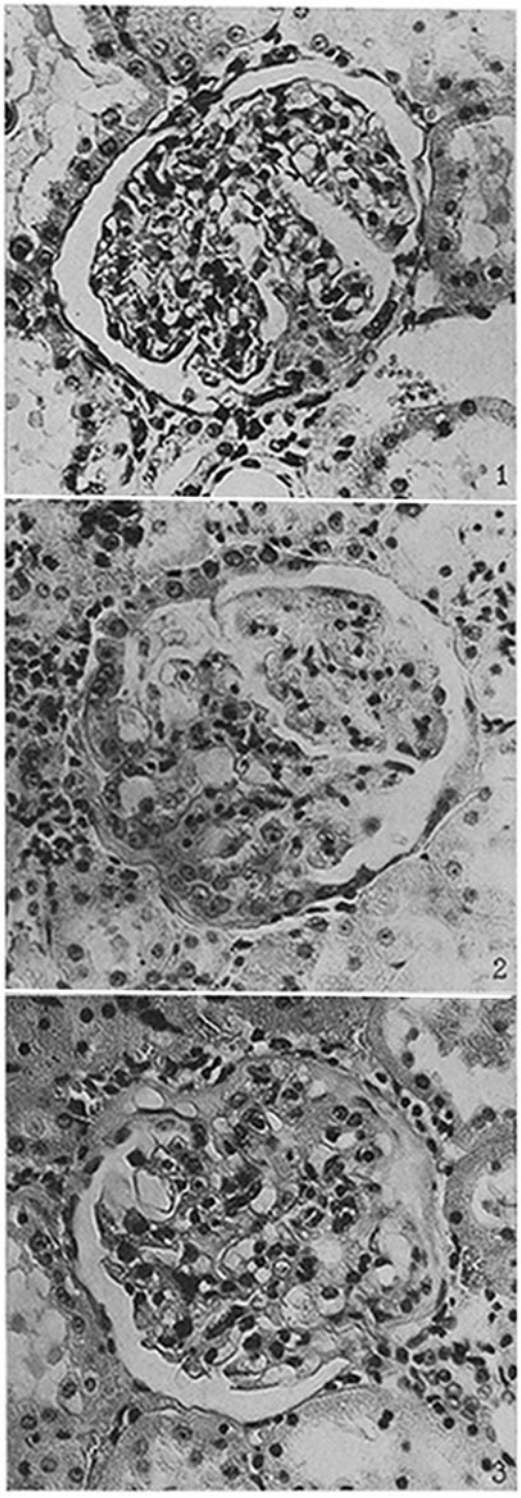
FIG. 4. Rat 674. High protein diet for 150 days following a right nephrectomy. There is a large fibrous adhesion between the tuft and capsule with fibrosis of approximately one-half of the tuft. × about 300.

FIG. 5. Rate 564. High protein diet for 150 days following a right nephrectomy. The figure shows two dilated tubules lined with newly formed epithelium. A mitotic figure is seen in the center of the figure. × about 360.

FIG. 6. *A*, Rat 667; *B*, Rat 674. High protein diet for 150 days following a right nephrectomy.

A—The tubules are moderately dilated. The lining epithelium is cubical with clear and vesicular nuclei. The tubules are widely separated due to an increase in the interstitial tissue. × about 300.

B—The tubules are markedly dilated. The lining epithelium is flat. There is no evidence of cellular activity. × about 300.



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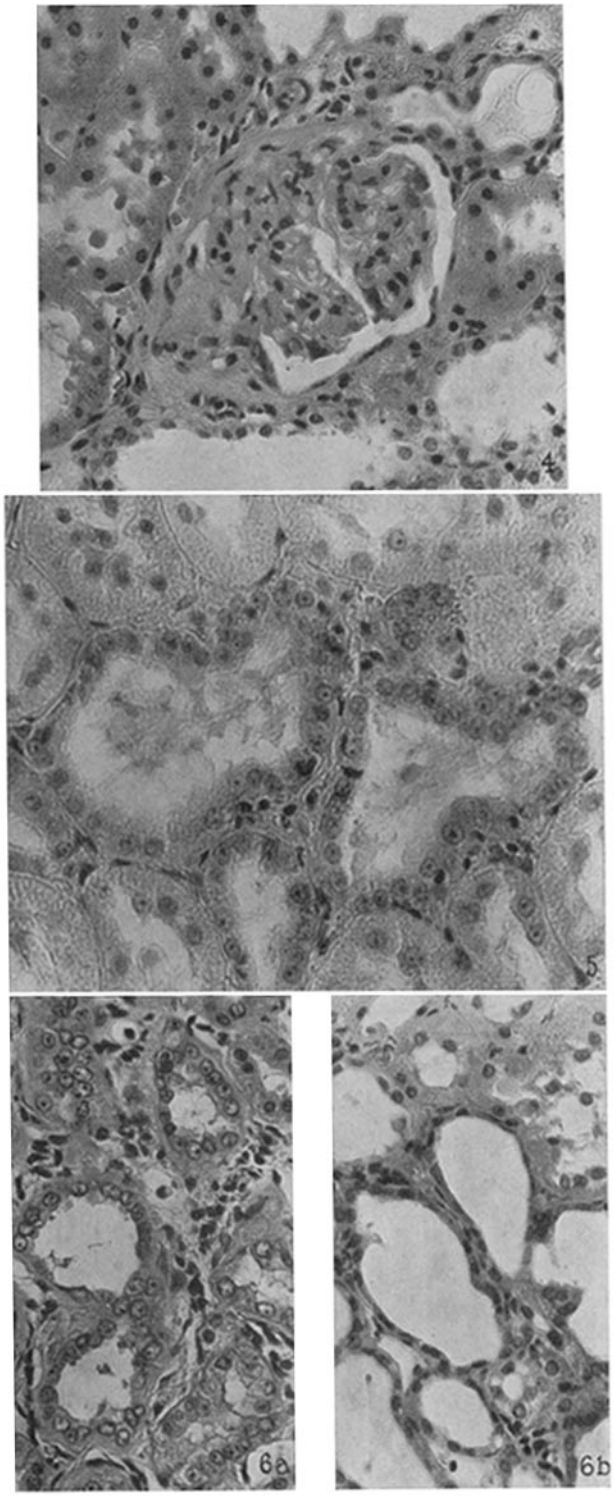

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