

THE MECHANISM BY WHICH EXPERIMENTAL NEPHRITIS IS
PRODUCED IN RABBITS INJECTED WITH
NEPHROTOXIC DUCK SERUM

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Glomerulonephritis develops in a rabbit injected with nephrotoxic duck serum, produced by the injection of rabbit kidney tissue into a duck. The disease has been studied by a number of investigators, including Masugi (1), Hemprich (2), Weiss (3), Ehrlich (4), Kay (5), Tsuji (6), and several others.

There has been little disagreement among investigators regarding the clinical and pathologic characteristics of the disease and their striking similarity to those observed in human glomerulonephritis. The injection of nephrotoxic duck serum into a rabbit is followed by an interval of several days during which the health of the animal remains unimpaired and the urine shows no abnormalities. This has been designated the incubation period. A sharp rise in blood pressure during this period has been described by Arnott, Kellar, and Matthew (7). Others have observed a small rise (1, 8), or no significant rise (5). Oliguria has been observed to occur immediately preceding the onset of albuminuria which marks the beginning of the active period of the disease (6, 9).

The first appearance of albumin in the urine is followed in a few hours by massive albuminuria, with casts, erythrocytes, and leukocytes in the urinary sediment. These abnormalities persist for weeks or months, depending upon the severity of the nephritis. The animal may continue to appear healthy, but in more severe cases it appears obviously ill and loses appetite. Blood urea retention is usually present in these animals which may later exhibit muscular twitchings and die in uremia. The volume of urinary output is depressed throughout the active period (6, 9). Ascites and edema of the extremities and genitalia have been observed. In our observations (5) an elevation of blood pressure during the active period of the disease was not an invariable manifestation, and when present it was small in degree. Moderate elevations were found by Masugi (1), and by Hámori and Korányi (8), whereas Arnott, Kellar, and Matthew (7) reported elevations of 20 to 40 mm. Hg.

Chronic nephritis following a single injection of nephrotoxic serum has been observed frequently in rats (1, 10, 11), but in rabbits it is a rare occurrence (Masugi (1), case VI; Tsuji (6), case XII). In the great majority of instances recovery ensues if the animal survives the first 20 days after injection. There is a gradual decrease in urinary abnormalities and other characteristics of the nephritis so that after 75 to 150 days no clinical evidence of the nephritis remains.

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The pathologic changes resulting from the injection of nephrotoxic serum into rabbits have been carefully studied and described in detail (1, 12, 2, 3, 4). Uniform and characteristic changes occur only in the kidneys. These changes are very similar to those observed in human glomerulonephritis. It is agreed that spasm of the arterioles, the mechanism believed by Volhard to occur in human glomerulonephritis, does not occur. The earliest change is a hyperemia of the glomerular capillaries, occurring during the period of incubation. This is followed by proliferation of the endothelial cells of the glomerular capillaries with resulting ischemia. These proliferative changes are usually clearly evident by the 6th to 8th day. Albuminous material containing fibrin, leukocytes, and erythrocytes is exuded into the capsular space. The loops of the glomerular tuft become distorted and adherent. About the 10th day the capsular epithelium begins to proliferate, frequently piling layer upon layer to obliterate the capsular space. Round cells, leukocytes, and connective tissue cells appear in varying numbers in and about the glomeruli. The afferent arterioles usually remain well filled with blood. Degenerative changes have occasionally been observed in their walls. The convoluted tubules are engorged with albuminous and cellular exudate, and casts are numerous in the collecting tubules. Hyaline or fatty degeneration of the tubule cells is rarely marked, but is often observed in mild degree. The degree of glomerular involvement and the number of glomeruli involved is variable, depending upon the severity of the nephritis. With a small dose of nephrotoxic serum most of the glomeruli may appear normal while others show the changes described—a focal nephritis. With a larger dose all glomeruli may be altered in greater or lesser degree, and with a very large dose, marked changes are seen in all the glomeruli—a diffuse glomerulonephritis. The pathologic process in the individual involved glomerulus appears identical whether few or many glomeruli are affected.

As recovery ensues, many of the involved glomeruli apparently return to normal. In others a portion of the tuft may appear normal and the rest distorted and ischemic. Crescentic adherence of the tuft to the capsule is frequently seen. In many glomeruli the tufts become atrophic and infiltrated with connective tissue—a whorl of cells in a bed of connective tissue and atrophic tubule remnants. In later stages, especially in animals which have survived a severe nephritis, many dilated collecting tubules with low cuboidal epithelium are seen.

A number of experiments dealing with the pathologic physiology of the disease have been reported. Ehrich and his colleagues (9) demonstrated that oliguria and diminished cyanol excretion which occurred in the active phase of the nephritis resulted chiefly from glomerular damage whereas tubular function, studied by azofuchsine I clearance tests, usually remained normal even when histologic changes in the glomeruli were maximal. Sarre (13) summarizes a large number of his studies of the circulation and metabolism of the experimentally nephritic kidney.

The mechanism by which the injection of nephrotoxic serum results in the development of nephritis had been the subject of considerable controversy. Debate had centered principally upon the rôle of allergy and hypersensitivity (1, 3, 12, 6, 4), upon the significance of the structure and function of the kidney in directing the attack to this organ (12, 13), and upon the cytotoxic specificity of the serum (1, 6, 12, 13). These controversial points

have in general been elaborations and variations of the basic concept as stated by Masugi: the antibody for kidney contained in the nephrotoxic serum reacts with the antigen inherent in the kidney to produce the nephritis—a concept which Masugi called reverse anaphylaxis.

In the course of an investigation of this form of nephritis in rabbits, studies were instituted to determine the relationships between the formation of antibodies to duck serum in the injected rabbit and the time of development of the nephritis. From these investigations evidence was found to suggest strongly a different concept of the mechanism from that stated originally by Masugi.

Preliminary Studies

Anti-rabbit-kidney duck serum was prepared by a modification of the method of Masugi (1). Eight to 24 injections of 5 to 15 cc. of a 10 per cent saline suspension of crushed, blood-free cortex of rabbit kidney were given intraperitoneally at 5 day intervals to each of 20 ducks. 5 cc. of a hemolytic streptococcus toxin, obtained by Berkefeld filtration of broth cultures, was added to the rabbit kidney suspension immediately preceding each injection to the duck. The streptococcus toxin presumably had the non-specific effect of stimulating the production of antibodies for rabbit kidney (15). The ducks were bled by partial decapitation and the sera obtained were immediately warmed to 56°C. for 25 minutes, and then frozen at -10°C. until ready for use. Precipitin titres of these sera against rabbit kidney antigen were determined by the usual methods. Some sera showed very little precipitation even in low dilutions, others formed a massive precipitate in the lower dilutions and traces of precipitation in dilutions as high as 1:64. The titre of lot X was especially high, and the *in vivo* potency of this serum was so great that nephritis invariably followed the injection of 1.0 cc. of this serum into a normal rabbit. As observed by others (1, 6) there was a rough correlation between precipitin titre and nephrotoxic potency *in vivo*.

Absorption of the nephrotoxic factor was effected by perfusion of nephrotoxic serum through rabbit kidneys. 15 cc. of a potent lot of serum was perfused at 37°C. four times through each of two blood-free, freshly killed rabbit kidneys. Each perfusion required about two minutes. Doses of 8 cc. and 5 cc., respectively, of perfused serum into two normal rabbits did not cause nephritis. Control rabbits injected with unperfused serum of the same lot consistently developed nephritis with doses of 3.5 to 5 cc.

A single strain of a mixed breed of young adult Dutch and American Blue rabbits was used. They were fed a diet consisting of cabbage, carrots, and mixed grains, and were placed in metabolism cages while under observation. Urine specimens were examined daily during the acute stages of the disease. Blood samples were obtained from the ear veins for determinations of blood non-protein nitrogen and leukocytes, and for the precipitin studies which will be described below.

In our earlier experiments varying doses of sera were given, usually in multiple daily doses. The clinical and pathologic features of the disease were studied and found to conform closely to those observed and described

by others. Elevations in blood pressure, however, were neither as frequently observed nor as marked in degree (5). The period of incubation varied from 4 to 9 days, but in the majority of instances the albuminuria appeared on the 6th to 8th day. This is in accordance with the observations of all other investigators who have worked with this form of nephritis.

This period of incubation attracted attention as an extremely interesting and important characteristic of the disease. It has been generally assumed, we believe, that the nephritic process begins at the time of injection and progresses gradually, though not definitely manifesting itself pathologically by swelling and proliferation of the glomerular tufts until about the 5th day, or clinically by the appearance of albuminuria a day or two later. In the analogous type of nephritis in the rat, clinical and pathologic changes are clearly evident within 12 to 48 hours (10, 11, 14). This striking dissimilarity has occasioned little or no discussion in the literature.

Thus it seemed essential to consider the probability that there exists a basic difference in the mechanisms of nephrotoxic nephritis in the rabbit and in the rat, and that in the former, nephritic changes actually do not commence until the 4th or 5th day. It was thought that if methods could be devised to alter significantly the duration of the period of incubation, valuable information might be gained, useful not only in interpretation of the incubation period, but in the interpretation of the entire mechanism of action of the nephrotoxic serum.

The problem was attacked from several angles. Experiments were first instituted to determine whether there existed any relationship in the injected rabbits between the formation of specific precipitins to the duck serum and the time of onset of the nephritis.

Methods

Serum was administered to from five to eight rabbits at a time. All animals which had previously received duck serum, whether normal or nephrotoxic, were desensitized to avoid anaphylaxis. This was done by giving normal duck serum (NDS) in eight increasing intravenous doses starting with 0.001 cc., doubling the dose with each injection, in a 2 day period. The following day nephrotoxic serum was given in hourly divided doses starting with 0.1 cc., doubling the dose with each injection until the desired amount of serum had been given. By this method no signs of anaphylaxis were observed in any of the rabbits. Although desensitization was necessary to avoid anaphylaxis only in those rabbits which had previously received duck serum, all of the animals were injected in an identical manner in order to maintain strict uniformity of method.

Samples of blood were obtained from each rabbit preceding the desensitization period, immediately after the injection of the nephrotoxic serum and on subsequent days thereafter. Each sample was tested by usual precipitin methods for antibody to duck serum by the addition of 0.2 cc. of a 1:30 dilution of normal duck serum to an equal volume of

1:1 to 1:16 dilutions of the sample. Likewise, the samples were tested for the presence of duck serum by the addition of 0.2 cc. of a 1:3 dilution of pooled anti-duck-serum rabbit serum to an equal volume of 1:1 to 1:1024 dilutions of the sample.

TABLE I
Normal Rabbits Injected with NTX Serum
Time Elapsing from Injection to Appearance of Antibody and Onset of Nephritis

Rabbit	Weight	Lot NTX serum	Dose		Date	Day of appearance	
			cc. per kg.	cc.		Antibody	Albumin
	<i>gm.</i>		<i>cc. per kg.</i>	<i>cc.</i>	<i>1939</i>		
4-5	1300	HL	2.0	2.6	June 26	3	7
4-6	1400		2.5	3.5	" 26	3	6
7-1	1600		2.5	3.9	July 10	3	6
7-2	1500		2.5	3.8	" 10	4	7
7-3	1500		2.5	3.8	" 10	4	6
1-01	1600	X	0.63	1.0	Mar. 30	3	6
					<i>1938</i>		
1-17	1900		0.53	1.0	Oct. 22	4	6
1-21	1900		0.53	1.0	" 22	4	7
1-22	1500		0.67	1.0	Nov. 10	3	7
1-23	1600		0.63	1.0	" 10	5	8
					<i>1939</i>		
4-01	1200	S	1.5	1.8	Sept. 29		7
4-02	1400		2.3	3.2	" 29		6
5-50	2300	F	2.5	5.7	Nov. 19	3	6
5-51	1200		2.5	3.0	" 19	4	6
5-52	1400		2.5	3.6	" 19	3	8
5-53	1300		2.5	3.3	" 19	4	7
5-20	1300	T	4.5	5.8	Dec. 14	3	8
5-21	950		4.5	4.2	" 14	3	5
					<i>1940</i>		
4-30	1600	M	2.0	3.3	Jan. 12		5
4-31	1750		5.0	8.8	" 12		8

Incubation Period and Precipitin Studies

Twenty normal rabbits were injected with six different lots of nephrotoxic serum. Albuminuria, indicating the clinical onset of the nephritis, appeared in from 5 to 8 days. Antibodies to duck serum were detected by precipitin methods in from 3 to 5 days.

The results are graphically illustrated in Fig. 1. The nephritis is seen to appear in from 2 to 4 days after the appearance of the precipitin, which

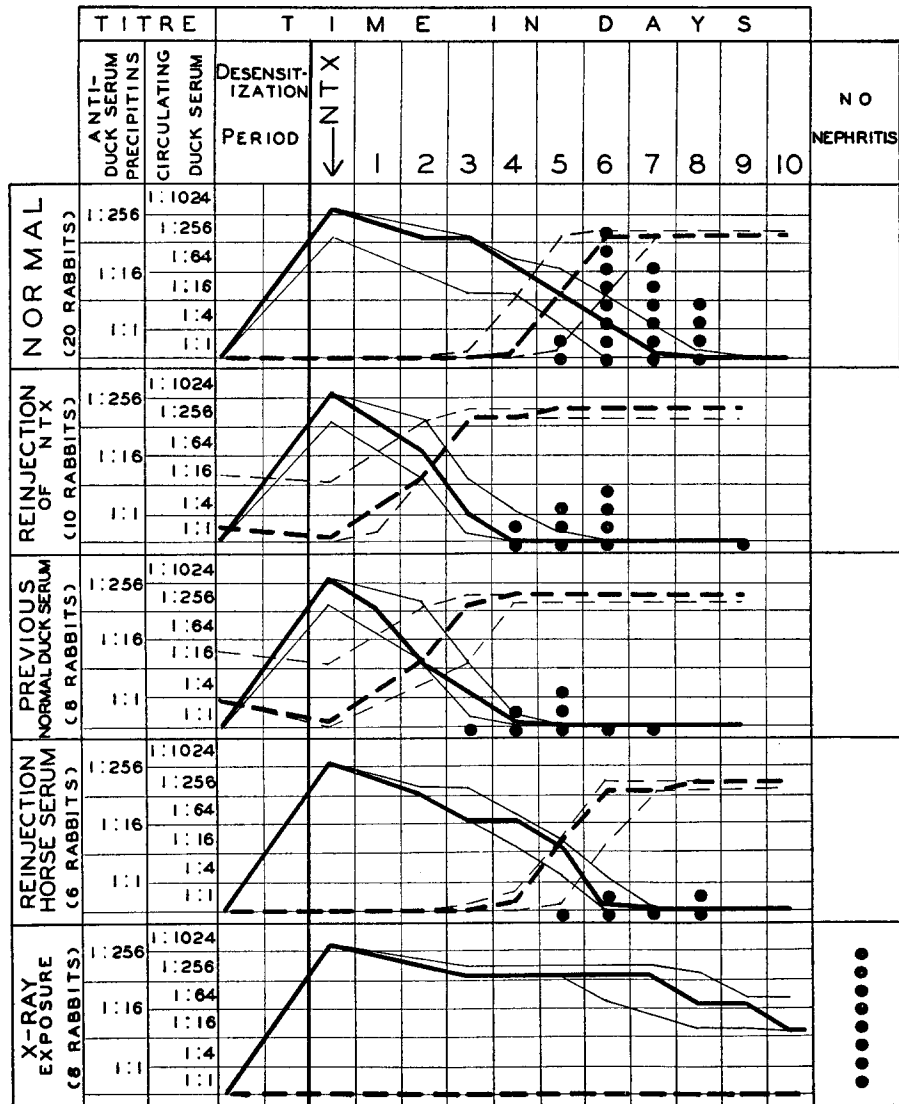


FIG. 1. Disappearance of circulating duck serum (solid lines), development of precipitins to duck serum (broken lines), and clinical onset of nephritis (each dot represents one rabbit), in rabbits injected with NTX serum.

Heavy lines indicate median values; light lines the maximum and minimum range.

is at about the time the maximum titre is obtained and the duck serum disappears from the blood of the rabbit.

In further experiments it was observed that rabbits which had recovered

from one attack of nephritis could be given a second attack by the reinjection of nephrotoxic serum.

Ten rabbits were injected with nephrotoxin. The nephritis was allowed to subside and the same dose of nephrotoxic serum was again injected. The second attack of nephritis was essentially the same as the first (5). Albuminuria appeared between the 4th and 6th days in nine of the ten animals. With but one exception this was an acceleration over the normal rabbit of from 1 to 2 days in the time of appearance of the nephritis. Refer-

TABLE II
*Original Injection and Subsequent Identical Reinjection of NTX
Comparison of Antibody Response and Onset of Nephritis*

Rabbit	NTX			Day of appearance		Interval days	NTX			Day of appearance		Difference days
	Lot	Dose		Anti-body	Albu-min		Lot	Dose		Anti-body	Albu-min	
		cc. per kg.	cc.					cc. per kg.	cc.			
1-17	X	0.52	1.0	4	6	104	X	0.45	1.0	<2	4	-2
1-21	X	0.54	1.0	4	7	42	X	0.5	1.0	<2	5	-2
4-01	S	1.5	1.8		7	99	S	0.83	1.8	<2	6	-1
4-02	S	2.2	3.2		6	99	S	1.6	3.2	<2	9	+3
5-50	F	2.5	5.7	3	6	149	F	2.9	5.7	<2	5	-1
5-51	F	2.5	3.0	4	6	149	F	1.6	3.0	<2	5?	-1
5-52	F	2.5	3.6	3	8	85	F	1.9	3.6	<2	6	-2
5-53	F	2.5	3.3	4	7	102	F	1.5	3.3	<2	6	-1
5-20	T	4.5	5.8	3	8	77	T	3.5	5.8	<2	6	-2
5-21	T	4.5	4.2	3	5	77	T	2.7	4.2	<2	4	-1

ring again to Fig. 1 it will be seen that precipitins to duck serum stimulated by the first injection were still present in varying titre. They were diminished during the period of desensitization but rapidly attained a high titre after the injection. As would be expected, with rapid formation of antibody the duck serum disappears very quickly. The acceleration of the nephritic response is suggestive if not clearly apparent.

It was then desired to know whether rabbits injected with normal duck serum prior to the injection of nephrotoxic serum would show a similar response.

Eight animals were injected with normal duck serum. After an interval, nephrotoxic serum was administered in the usual manner. There was

again a strong suggestion that the appearance of the nephritis was more rapid than in the control animals comparably injected.

As shown in Fig. 1, the antibody and duck serum curves are essentially the same as in animals reinjected with nephrotoxin.

TABLE III
Animals Injected with Normal Duck Serum Prior to Injection of NTX
Comparison of Antibody Response and Onset of Nephritis
Normal rabbits comparably injected (small figures)

Rabbit	Normal duck serum	Interval	Nephrotoxin			Day of appearance	
			Lot	Dose		Antibody	Albumin
				<i>cc. per kg.</i>	<i>cc.</i>		
		<i>days</i>					
9-0	Yes	42	X	0.59	1.0	<2	5
9-1	Yes	54	X	0.59	1.0	<2	4
9-2	Yes	54	X	0.63	1.0	<2	3
9-3	Yes	42	X	0.59	1.0	<2	4
1-01	No		X	0.62	1.0	3	6
1-17	No		X	0.53	1.0	4	6
1-21	No		X	0.56	1.0	4	7
1-22	No		X	0.66	1.0	3	7
1-23	No		X	0.62	1.0	5	8
6-51	Yes	68	F	1.7	3.0	<2	6
6-50	Yes	84	F	1.8	3.7	<2	5
5-50	No		F	2.5	5.7	3	6
5-51	No		F	2.5	3.0	4	6
5-52	No		F	2.5	3.6	3	8
5-53	No		F	2.5	3.3	4	7
6-20	Yes	43	T	3.0	5.0	<2	5
6-21	Yes	59	T	3.6	5.8	<2	7
5-20	No		T	4.0	5.8	3	8
5-21	No		T	4.0	4.2	3	5
Averages: Prior NDS.....							4.9
Controls.....							6.7

In the second and third groups we have seen an apparent correlation between the rapid appearance of a high precipitin titre for duck serum, and acceleration of the disappearance of circulating duck serum, and a shortening of the incubation period. From these experiments one can scarcely avoid the thought that there is some connection between the action of the nephrotoxic serum and the formation of antibody to duck serum in the rabbit.

An experiment was next devised to test the possibility that a non-specific antigen-antibody reaction would accelerate the onset of the nephritis. Six rabbits were desensitized and reinjected with horse serum. Simultaneously nephrotoxic duck serum was administered in the usual manner. The precipitin reactions and the nephritic responses in these rabbits, again shown in Fig. 1, were in no way significantly different from those observed in the normal rabbits. By analogy, therefore, the experiment suggests that the accelerated response observed in rabbits which had previously received duck serum, either normal or nephrotoxic, was not simply the result of a non-specific antigen-antibody reaction.

Having observed experiments in which an acceleration of the appearance of the nephritis was apparently correlated with an acceleration of antibody formation, a method was sought to inhibit or prevent antibody formation in order that further studies could be pursued. It was found that exactly this desired effect could be obtained by exposing the rabbits to x-ray. We were not familiar with the previous use of x-ray for the inhibition of antibody formation, although it has since been found that this method was employed for the purpose by Benjamin and Sluka (16) in 1908. They injected bovine serum into rabbits exposed to x-ray and found that precipitin formation was completely inhibited in most instances, and the bovine serum disappeared abnormally slowly from the circulating blood of the rabbit. Later experimenters reported inhibition of anaphylaxis in guinea pigs (17) and of bacterial agglutinins in rabbits (18) exposed to x-ray.

Each of seven rabbits was irradiated with a total of 480 r. delivered in a single 40 minute exposure of the entire animal. The following factors were employed: 200 kv. potential 20 ma., $\frac{1}{2}$ mm. Cu + 1 mm. Al filtration, 1 meter skin target distance. The eighth rabbit (9-50) received 1920 r.¹ Nephrotoxic serum was administered to each rabbit 3 days later. The animal (9-50) which had received the very large exposure to x-ray became weak and lost weight. The other rabbits appeared to remain perfectly well. Leukocyte counts dropped from the normal range of from 6000 to 12,000 per c.mm. to below 1000 in most of the animals, and below 2000 in all. The depression in the number of leukocytes persisted for several weeks. There was complete inhibition of antibody response, and nephritis did not develop in any of these rabbits. The disappearance of circulating duck serum was also greatly delayed. These results are graphically shown in Fig. 1. Control rabbits injected with nephrotoxic sera in the same dosages and

¹ Rabbits were treated with x-ray under the direction of Dr. George J. Farber, Associate in Radiology, The Johns Hopkins Hospital.

at the same times as the rabbits exposed to x-ray developed antibodies and nephritis in the usual manner.

Further experiments were carried out with four of the group of rabbits which had been exposed to x-ray and injected with nephrotoxic serum. After intervals of 33, 59, and 78 days, respectively, rabbits 9-22, 9-23, and

TABLE IV
Effect of X-Ray
Absence of Nephritis and Suppression of Antibody Formation
Rabbits exposed to 480 r. x-ray 3 days before NTX injection (large figures)
Normal rabbits simultaneously and identically injected (small figures)

Rabbit	Weight <i>gm.</i>	X-ray	NTX lot	Dose <i>cc. per kg.</i>	Antibody appears	Albumin appears
7-5	1500	Yes	HL	2.5	None (8 days)	None (8 days)
7-6	1600	Yes	HL	2.5	None (14 days)	None (14 days)
7-7	1250	Yes	HL	2.5	None (22 days)	None (22 days)
7-1	1600	No	HL	2.5	3	6
7-2	1500	No	HL	2.5	4	7
7-3	1500	No	HL	2.5	4	6
9-50	1350	Yes	F	2.5	None	None
5-50	2300	No	F	2.5	3	6
5-51	1200	No	F	2.5	4	6
5-52	1400	No	F	2.5	3	8
5-53	1300	No	F	2.5	4	7
9-22	1450	Yes	T	4.0	None	None
9-23	1500	Yes	T	4.0	None	None
9-24	1800	Yes	T	4.0	None	None
5-20	1300	No	T	4.0	3	8
5-21	950	No	T	4.0	3	5
9-31	1600	Yes	M	5.0	None	None
4-30	1600	No	M	2.0		5
4-31	1750	No	M	5.0		8

9-24 were reinjected with doses of nephrotoxic serum adequate to produce nephritis in the normal animal. The precipitin studies showed a rapid appearance of antibody but in very low titre, and a persistence of circulating duck serum almost as marked as after the original injection. An exceedingly mild nephritis developed, barely detectable clinically and lasting only a few days. Rabbit 9-50 was reinjected after 76 days. As after the original injection, neither antibodies nor nephritis developed in this rabbit. The

leukocyte counts during the period of the second injection had risen to normal or almost normal levels in all of these rabbits.

These experiments give further strong support to the contention that antibody formation by the rabbit is essential for the development of the nephritis.

DISCUSSION

According to the concept of Masugi, the antibody for rabbit kidney of the nephrotoxic serum reacts with the antigen of the rabbit kidney to produce the nephritis; the antibody-forming mechanism of the injected rabbit plays no rôle. This concept does not explain the universally observed period of incubation between the injection of the serum and the development of the nephritis. It completely fails to explain the acceleration of the onset of nephritis in rabbits previously injected with duck serum, or the complete inhibition of nephritic response in rabbits exposed to x-ray, as shown in these experiments.

The interpretation of the results of these experiments is difficult. It has been shown that an acceleration of the development of nephritis is associated with an accelerated development of antibodies to duck serum, and that inhibition of nephritis is associated with suppression of the antibody response. Consider the hypothesis suggested in Fig. 2.

The proteins of nephrotoxic duck serum consist of normal serum proteins and, in addition, proteins which are antibodies for rabbit kidney. The presence of the latter would be surmised from the method employed to produce the serum; they have been demonstrated by *in vitro* precipitin studies and by the perfusion-absorption experiments. Of especial interest in this regard are the recent experiments of Sarre (13). He found that when one renal artery was obstructed for a 15 minute period after the injection of nephrotoxic serum, nephritis subsequently developed only in the opposite kidney. If both renal arteries were obstructed, nephritis developed in both kidneys in the usual manner. It seems evident, therefore, that nephrotoxic serum contains specific antibodies for rabbit kidney, and that following injection, they are rapidly absorbed by the kidneys from the circulation.

Antibodies to duck serum proteins are formed in the normal rabbit injected with nephrotoxic duck serum. These have been demonstrated by precipitin methods. They proceed to react with any duck serum proteins available. Their interaction with the circulating duck serum proteins causes the disappearance of the latter, as demonstrated by the precipitin studies. This antigen-antibody reaction appears to be of little or no sig-

nificance. It takes place in a normal rabbit injected with normal duck serum without causing any apparent injury to the health of the animal.

The important factor is that these antibodies to duck serum react with the anti-rabbit-kidney duck proteins, originally contained in the nephrotoxic duck serum, now combined in the kidney and acting in the rôle of antigens. "If we grant that antibodies are actually proteins, it follows that a molecule of antibody can function either as an antibody or as an

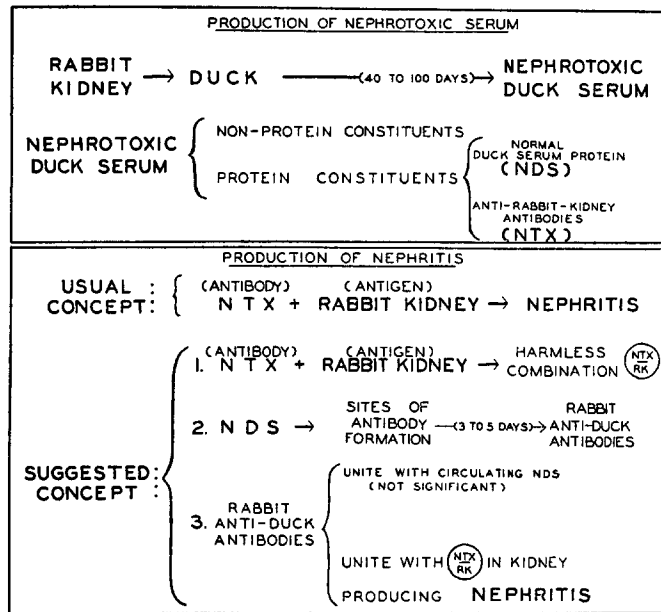


FIG. 2. Mechanism of experimental nephritis, produced in rabbits with nephrotoxic duck serum.

antigen" (19). The *in vitro* application of the principle has been demonstrated repeatedly (20, 21, 19). It is this antigen-antibody reaction which results in the development of the nephritis. Tissue responses to antigen-antibody reactions are discussed at length in several of the articles on nephrotoxic nephritis (14, 1, 2, 3, 6).

This tentative hypothesis appears to be in accordance with the results here obtained. It adequately explains the latent period as the time required for the formation of antibodies to duck serum. It explains the acceleration which occurs in animals previously injected with duck serum on the grounds that antibody formation is greatly accelerated, and it

explains the inhibition of nephritis in animals exposed to x-ray because antibodies to duck serum are not formed.

The foundations of this suggested concept are based upon well established principles, although considered as a whole the hypothesis is unique. Much further study will be necessary before it can be accepted as conclusive. Passive transfer and specific and non-specific desensitization experiments should prove especially interesting and significant. It is hoped that further investigation along lines suggested by these experiments may throw some light upon the complicated mechanisms involved in the development of human glomerulonephritis, and that the methods here employed may be usefully applied to immunologic experimentation in other fields.

SUMMARY

1. Glomerulonephritis was produced in rabbits by the injection of anti-rabbit-kidney duck serum.

2. The clinical and pathologic characteristics of the disease are discussed.

3. It was found possible by appropriate means either to accelerate the development of the nephritis or to prevent its appearance entirely.

4. An apparent correlation was found between the development of the nephritis and the formation of antibodies to duck serum by the injected rabbit.

5. The generally accepted concept of the mechanism of the disease does not appear to be in accordance with the facts here observed. A new hypothesis is presented.

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