THE BIPHASIC DEVELOPMENT OF MASUGI'S NEPHRITIS IN THE RABBIT

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At the turn of this century, SCHICK [27] and PIRQUET [19] concluded from clinical observations that nephritis after scarlet fever was an allergic reaction, and later the fundamental experiments of MASUGI [15, 16] shed light on essential mechanism of the pathologic process. It is still not known why it is just the kidney to which the antibodies are bound in human nephritis. The doctrine of autoallergic diseases represented some advance toward a better understanding of the elective localization of the antigen-antibody reaction. It has been suggested by many authors that nephritis is due to autoimmunization. On the other hand, others think that the physical and chemical structure of the antigen determines localization.

In spite of extensive investigations, the problem has not been completely elucidated. This was due mainly to the difficulty in proving the allergic character of human glomerulonephritis. Exposure, treatment by elimination or desensibilization in this case fail to decide the problem. The intradermal test as a proof of streptococcal allergy has been only occasionally employed. Passive transfer of allergy is not known to occur. Nevertheless, according to numerous authors the antigen-antibody reaction is the best explanation for the clinical picture and the course of human glomerulonephritis. The data supporting the allergic hypothesis may be summarized in brief as follows:

1. Glomerulonephritis is a secondary disease. The primary lesion is some kind of a streptococcal infection. The interval between the onset of the primary infection and the appearance of the clinical symptoms corresponds to the period required for the production of specific antibodies.

2. There is no proof that streptococci invade the kidney.

3. There is a discrepancy between the severity of the preceding infection and of nephritis.

4. The incidence of the disease decreases with age.

5. The disease is by far less frequent than are streptococcal infections.

6. Exacerbation of nephritis follows recurrence of streptococcal infection with a certain interval.

7. Serum complement decreases or disappears.

8. The presence of antibodies against streptococcal toxins in the blood.
9. The presence of anti-kidney autoantibodies.
10. The experimental production of allergic nephritis.

The above make it clear that the clinical data are merely suggestive and that the interpretation of the human disease has to be derived from animal experiments.

Among these the most important is the nephrotoxic nephritis of MASUGI, which resembles closely the clinical and pathological features of human nephritis following upper respiratory infection or scarlet fever, and furnished the basis for the allergic theory of human disease.

It now seems to be clear that MASUGI's nephritis has two types of clinical manifestation. If the antiserum acting on the kidney of a mammalian is of mammalian origin, the nephritic symptoms develop immediately after the injection (Type I) ; if the antiserum injected into a mammal has been produced by a bird, nephritis develops only after a latent period (Type II). This latter type resembles human postinfectious glomerulonephritis.

According to MASUGI [15, 16], the antigen is the kidney *in situ* and the antibodies are introduced "ready-made" with the nephrotoxic serum. This form of the antigen-antibody reaction has been called by MASUGI the reversed allergy of the kidney.

The antigen-antibody reaction takes place *in vivo* within a matter of a few minutes. SARRE and WIRTZ [24, 25] succeeded to block the development of experimental nephritis almost completely by clamping the renal arteries for 25 minutes. When the artery of only one kidney has been clamped, "unilateral glomerulonephritis" develops, indicating that the unclamped kidney has bound the antiserum completely within a few minutes. In harmony with this ROTHER [21] proved serologically that anti-rabbit-kidney antibodies disappear within 10 to 12 minutes from the circulating blood after the intravenous injection of nephrotoxic duck serum. It is therefore difficult to explain why after injecting anti-rabbit-kidney duck serum into rabbits, proteinuria appears only after 5 to 9 days. The first symptoms are violent. KORÁNYI and HÁMORI [14], who were among the first to reproduce and reinvestigate the phenomenon, pointed out that the characteristic interval and the violent onset correspond to an anaphylactic reaction and resemble serum sickness.

KAY [11, 12] tried to elucidate the cause of the latency. According to his results, nephrotoxic nephritis develops in two phases. In the first phase, immediately after the injection of the nephrotoxin, the specific immunoglobulin is bound to the kidney, the second phase coincides with the outbreak of nephritis. According to this new conception, the antibodies of the nephrotoxic duck serum form an innocuous combination with the rabbit kidney ; the outbreak of nephritis after a period of latency is due to antibody formation by the recipient rabbit against the foreign protein of the duck serum. When a

sufficient titre has been reached, these antibodies react with the circulating and kidney-bound duck protein. Albuminuria appears when the precipitin titre against the duck serum has reached a fairly high level. It has been confirmed by quantitative precipitation tests (ROTHER [21]) that the clinical onset of Masugi's nephritis coincides with the appearance of antibodies against the foreign serum proteins.

KAY has shown that whole body X-ray irradiation before the injection of nephrotoxin prevents in the rabbit the development of nephritis and the production of precipitins against duck serum. When, however, a few days after the injection of nephrotoxin the irradiated rabbits are injected with serum from rabbits immunized with normal duck serum, nephritis will develop. The favourable effect of X-rays appears to be due to inhibition of the production of antibodies eliciting the second phase. The favourable therapeutical results achieved in rabbits with Masugi's nephritis by the use of cortisone (SPÜHLER, ZOLLINGER and ENDERLIN [29]), ACTH (VOGT, WÜTHRICH and REUBI [31]), or hypophysis implantation (JULESZ, SZATMÁRI, HOLLÓ, ROMHÁNYI and SZUSZEKÁR [10]) have a similar explanation.

However, RATHE [20] has reported recently that rabbits pretreated with X-rays and nephrotoxin did not develop nephritis in response to the passive transfer of circulating antibodies (anti-duck-serum precipitins). RATHE, too, is inclined to accept the theory of biphasic development, but denies the participation of the normal serum proteins of nephrotoxic duck serum in the pathological process. Together with SPÜHLER [29], he believes, that immediately after the injection of nephrotoxic duck serum, the specific, anti-rabbit-kidney antibodies become fixed to their antigen, the kidney. The bound nephrotoxic factor combines with kidney proteins to form a new antigen. This complex gives rise to antibody formation, eliciting finally nephritis, as a manifestation of the anaphylactoid process.

In the present communication (a) experiments are reported on the second phase of MASUGI's nephritis, and (b) a re-evaluation of the first phase and (c) an analysis of the human disease are attempted.

Materials and methods

By a slightly modified technique of MASUGI's, extremely active anti-rabbit-kidney sera were produced in ducks. Technical details have been published elsewhere (TOMPA and KÁDAS [10]).

Adult rabbits of both sexes, weighing 2800 to 3800 g, kept in individual cages, and fed wheat and carrots, were used. Water was allowed ad libitum.

Body weight, urine and blood pressure were examined daily. Blood pressure was measured by the technique of GRANT and ROTSCHILD [5]. Nonprotein nitrogen, serum sodium, total serum protein, serum albumin and serum globulin were determined at intervals.

After sacrificing the animals, the kidneys were fixed in 10 per cent formaldehyde and 70 per cent alcohol, embedded in paraffine, stained with haematoxylin-eosin, or according to Mallory, and subjected to the test for alkaline phosphatase.

Table I

The effect of anaphylactic shock in rabbits sensitized with doses of nephrotoxic duck sera ineffective in themselves

Group	Rabbit No.	Sensitization	Reinjection	Urine after anaphylactic shock	
				Protein Esbach ‰	Sediment
1. Sensitization: 0,1 ml nephrotoxic duck serum ("4M") Reinjection: 1,0 ml nephrotoxic duck serum ("4M")	35	Dec. 25, 1954	Jan. 7, 1955	+++*	masses of erythrocytes
	38	Jan. 19, 1955	Febr. 1, 1955	5	40—50 erythrocytes, 2—3 hyalin casts
	39	Jan. 19, 1955	Febr. 1, 1955	2	30—40 erythrocytes, 4—5 hyalin casts
	42	Jan. 19, 1955	Jan. 24, 1955	12	5—10 erythrocytes, 4—5 hyalin casts, 1—2 granular casts
	47	Jan. 19, 1955	Jan. 25, 1955	2	20—30 erythrocytes, 2—3 hyalin casts
2. Sensitization: 0,1 ml nephrotoxic duck serum ("4M") Reinjection: 1,0 ml normal duck serum	48	Febr. 18, 1955	Febr. 24, 1955	2	10—20 erythrocytes, 2—3 hyalin casts
	156	Jun. 16, 1955	Jún. 23, 1955	6	20—30 erythrocytes, 4—5 hyalin casts
	157	Jun. 16, 1955	Jun. 22, 1955	2	5—10 erythrocytes, 1—2 hyalin casts
3. Sensitization: 0,1 ml normal duck serum Reinjection: 1,0 ml nephrotoxic duck serum ("4M")	46	Febr. 18, 1955	Febr. 24, 1955	0	0
	152	Jun. 18, 1955	Jun. 25, 1955	0	0
	153	Jun. 18, 1955	Jun. 24, 1955	0	0
4. Sensitization: 0,1 ml normal duck serum Reinjection: 1,0 ml normal duck serum	45	Febr. 18, 1955	Febr. 24, 1955	0	0
	155	Jun. 16, 1955	Jun. 22, 1955	0	0
	154	Jun. 20, 1955	Jun. 26, 1955	0	0

* +++: Intense precipitation by sulphosalicylic acid

The activity of the nephrotoxic sera (nephrotoxin) was assayed in preliminary tests, involving sera "4M" and "7M". First of all, we determined the certainly ineffective dose of nephrotoxin, which was found to be 0,1 ml. One ml produced mild, 2—3 ml severe glomerulonephritis.

In the experiment, rabbits were sensitized intravenously with an ineffective dose of nephrotoxin and after 5 to 13 days a non lethal anaphylactic shock was elicited by the intravenously administration of 1 ml nephrotoxic or normal duck serum.

One to 1½ minutes after reinjection the animals became restless, and developed severe dyspnoea for 4 to 5 minutes. Then for about half an hour they were inactive. Subsequently they again became active and apparently normal.

In the control experiments, rabbits sensitized with normal duck serum were used.

Finally, we elicited anaphylactic shock by injecting pig serum into rabbits sensitized with nephrotoxic duck serum + pig serum. The reaction was similar to that described above.

Results

Anaphylactic shock changed the course of MASUGI's nephritis if sensitization was produced by ineffective doses of nephrotoxic serum (Table I, group

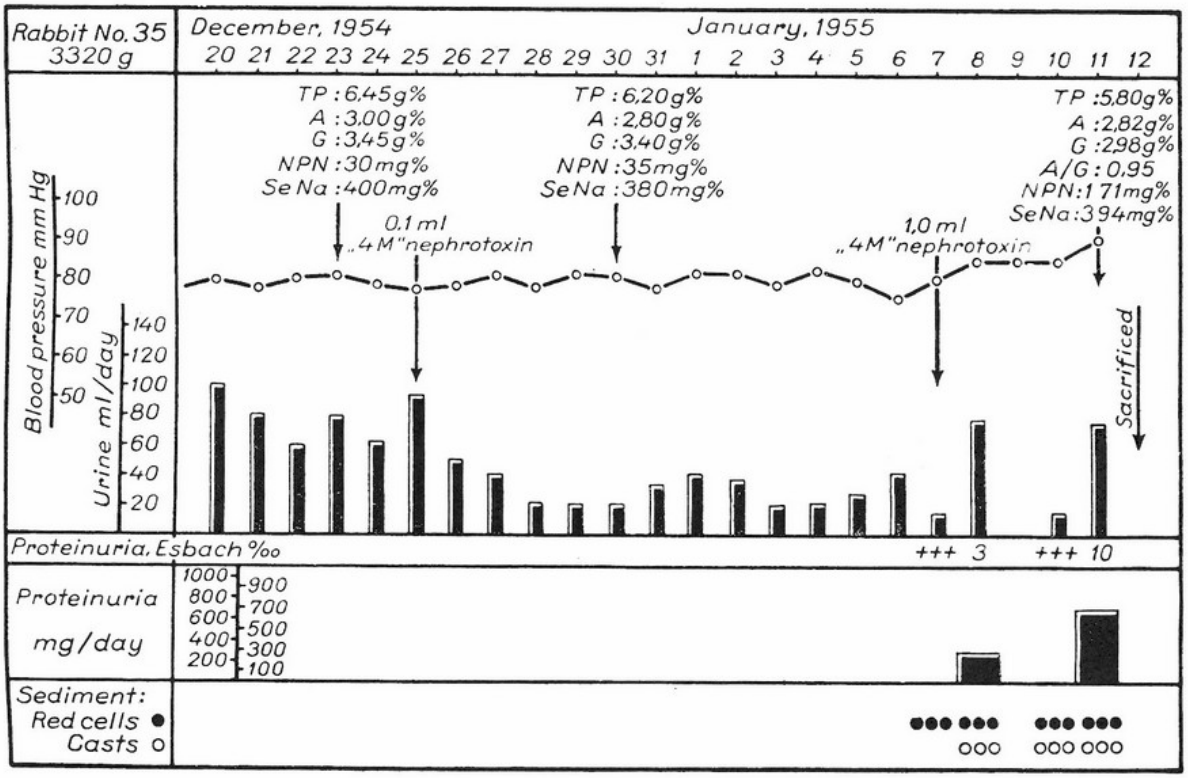

Fig. 1. Abbreviations: TP: total protein; A: serum albumin; G: serum globulin; NPN: nonprotein nitrogen; SeNa: serum sodium; +++: intense precipitation by sulphosalicylic acid

1 and 2), but failed to do so if the rabbits were sensitized with normal duck sera (Table I, group 3 and 4).

Fig. 1 demonstrates an experiment in which the rabbit had been sensitized with 0.1 ml nephrotoxic duck serum. Reinjection of 1,0 ml nephrotoxic

duck serum on the 13th day was followed immediately by severe proteinuria, i. e. without the interval otherwise characteristic for MASUGI's nephritis in rabbits. Simultaneously erythrocytes appeared in the sediment. Blood pressure began to increase and within a few days NPN rose to 171 mg per 100 ml, indicating diffuse glomerulonephritis. Thus, the anaphylactic shock had precipitated the onset of MASUGI's nephritis.

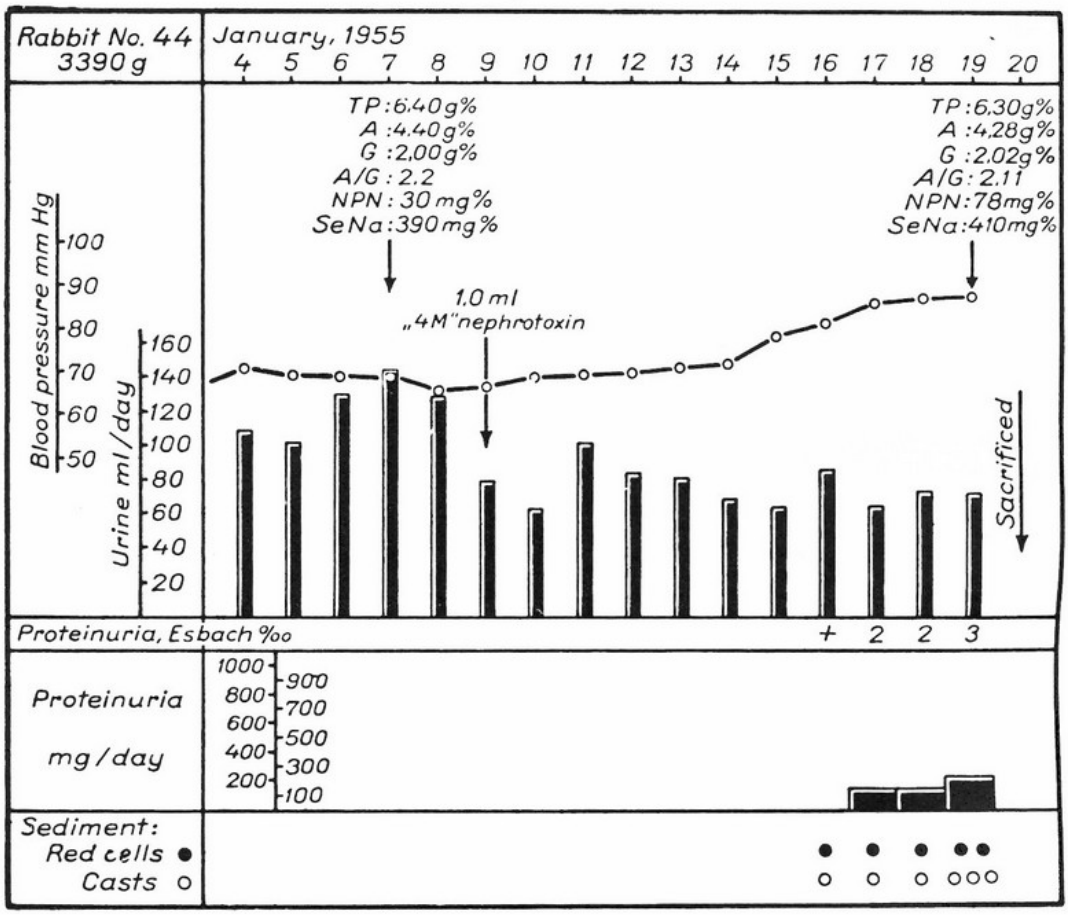

Fig. 2. Abbreviations: TP: total protein; A: serum albumin; G: serum globulin; NPN: nonprotein nitrogen; SeNa: serum sodium; +: traces of protein

Fig. 2 shows the effect of the injection of the same amount of the identical nephrotoxic serum without previous sensitization. In this proteinuria developed only after 7 days.

In the experiment shown in *Fig. 3*, the rabbit was sensitized also with an ineffective dose of nephrotoxin; reinjection took place on the fifth day and next day proteinuria, haematuria, hyalin and granulated casts appeared. Blood pressure increased within a few days from 70 to 93 mm Hg. Five days after reinjection NPN rose to 210 mg per 100 ml.

These experiments show if the rabbit is sensitized with an ineffective dose of nephrotoxin the kidney responds to reinjection as a "shock-organ". Even more convincing are experiments, in which instead of a nephrotoxic serum, normal duck serum was injected a few days after sensitization with an ineffective dose of a nephrotoxic serum, so that simple summation of the two doses of nephrotoxic serum can be excluded (Fig. 4). The animal had been

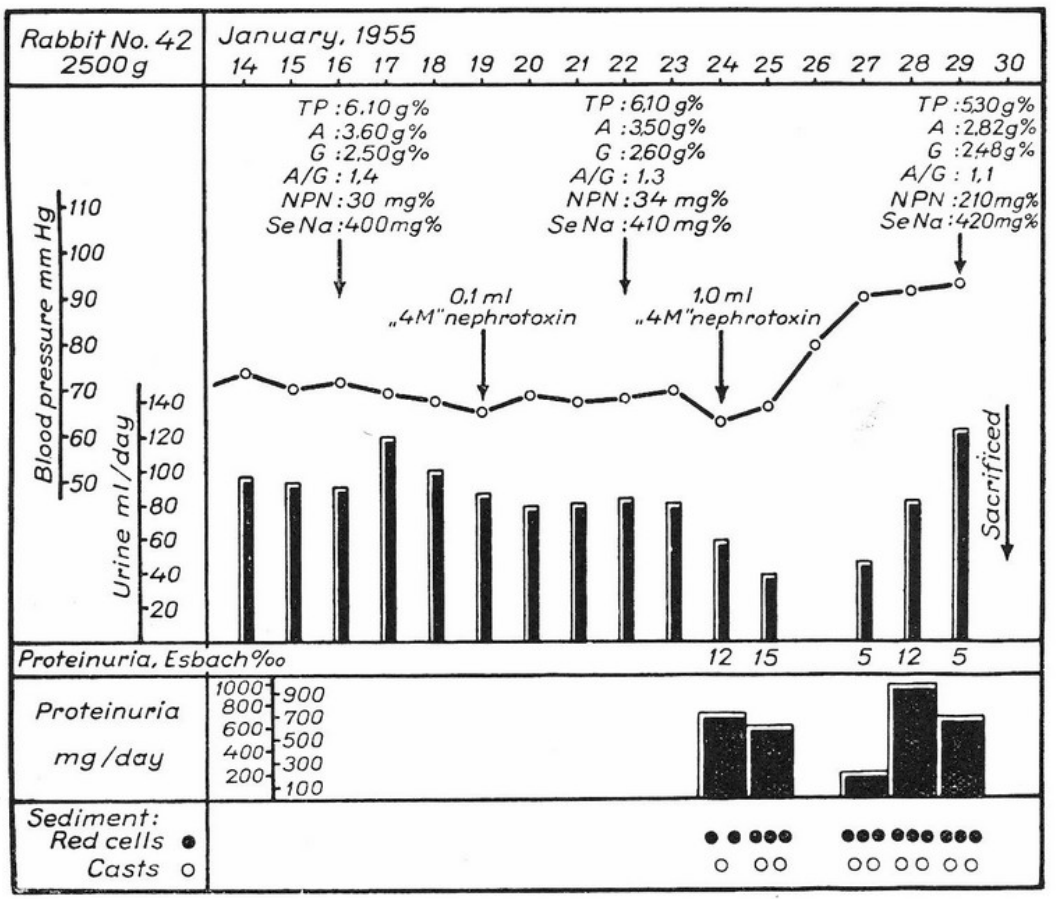

Fig. 3. Abbreviations: TP: total protein; A: serum albumin; G: serum globulin; NPN: nonprotein nitrogen; SeNa: serum sodium

sensitized with 0,1 ml of nephrotoxin and the anaphylactic shock was elicited with 1,0 ml normal duck serum. Reinjection was immediately followed by proteinuria and the appearance of erythrocytes and hyalin casts in the urinary sediment, and within a few days uraemia developed. On the fifth day after reinjection NPN was 120 mg per 100 ml. Thus, anaphylactic shock elicited by normal duck serum, was immediately followed by the onset of nephritis, although the animal received only an amount of nephrotoxin ineffective in itself.

The histological findings were characteristic for diffuse glomerulonephritis. Nearly all the glomeruli are enlarged by proliferative processes (Fig. 5).

The pathological process is obviously one of intracapillary proliferation. The glomerular changes manifest themselves in endothelial proliferation, ischaemia and thickening of the basal membrane, and in more advanced cases in extensive intraglomerular fibrosis (Fig. 6, 7, 8). The alkaline phosphatase activity of the tubules was normal in every case.

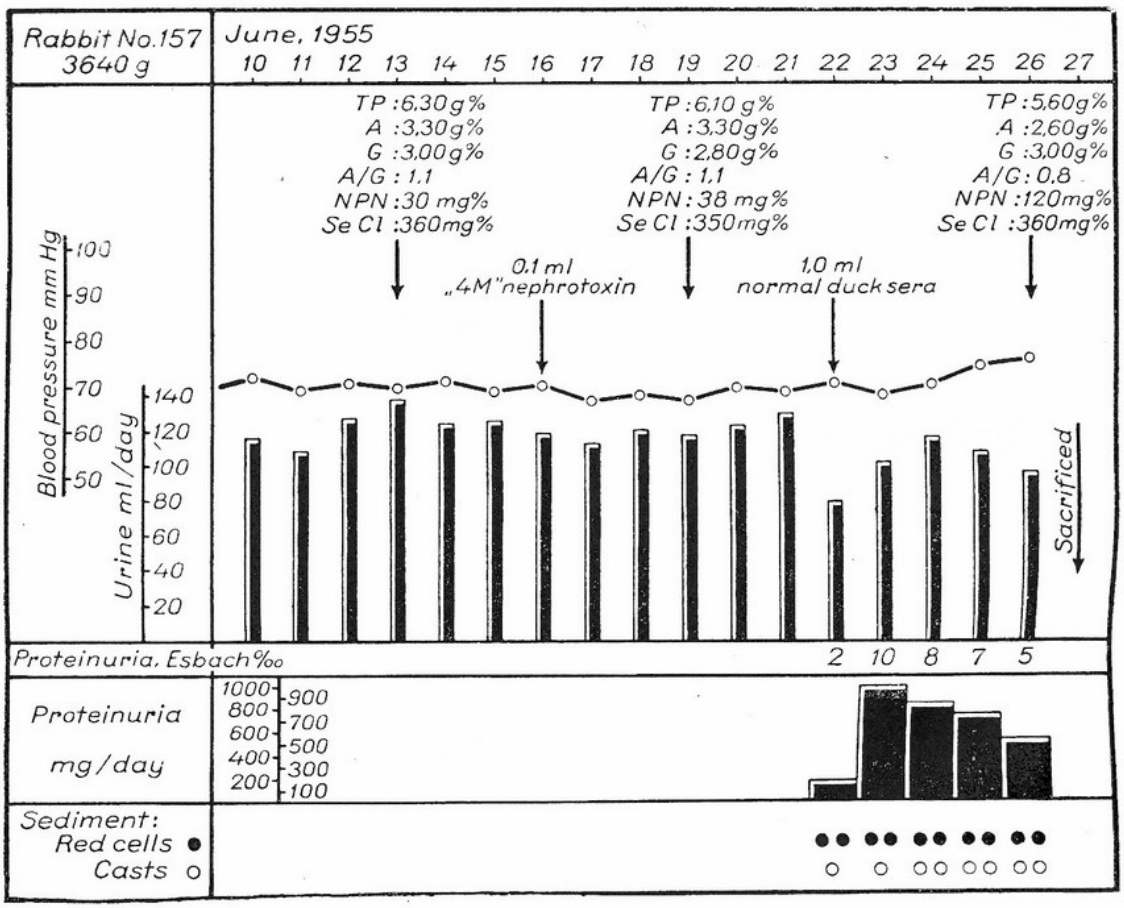

Fig. 4. Abbreviations: TP: total protein; A: serum albumin; G: serum globulin; NPN: nonprotein nitrogen; SeCl: serum chlorides

Sensitization with nephrotoxic duck serum, although ineffective in itself, is indispensable for eliciting a shock response from the kidney. Animals sensitized with normal duck serum do not develop proteinuria immediately even when reinjected with nephrotoxic duck serum (Fig. 9). Experiments involving sensitization with a small dose of nephrotoxic duck serum + pig serum and induction of shock with pig serum, failed also to cause proteinuria (Table II).

Control experiments with normal duck sera failed to produce proteinuria or any other symptoms of renal damage.

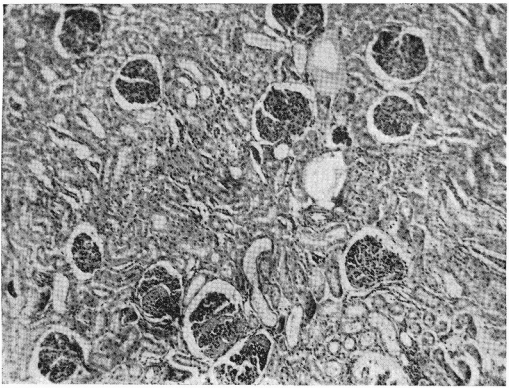

Fig. 5. Rabbit No. 157. Acute diffuse proliferative glomerulonephritis. (Haematoxylin-eosin)

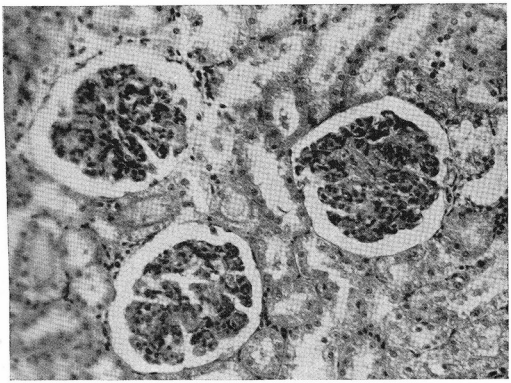

Fig. 6. Rabbit No. 157. Endothelial proliferation, thickening of basal membrane and glomerular ischaemia. (Haematoxylin-eosin)

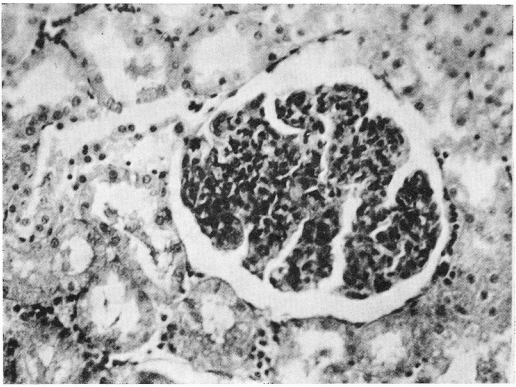

Fig. 7. Rabbit No. 157. Excessive endothelial proliferation. (Haematoxylin-eosin)

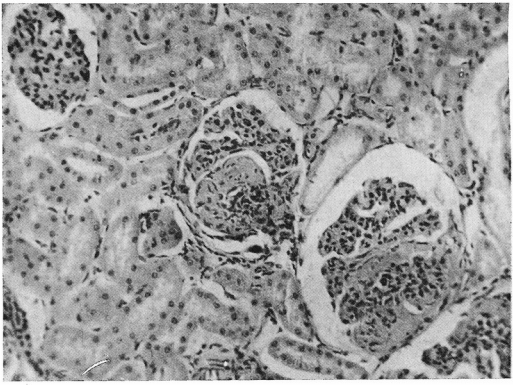

Fig. 8. Rabbit No. 157. Glomerular fibrosis. (Haematoxylin-eosin)

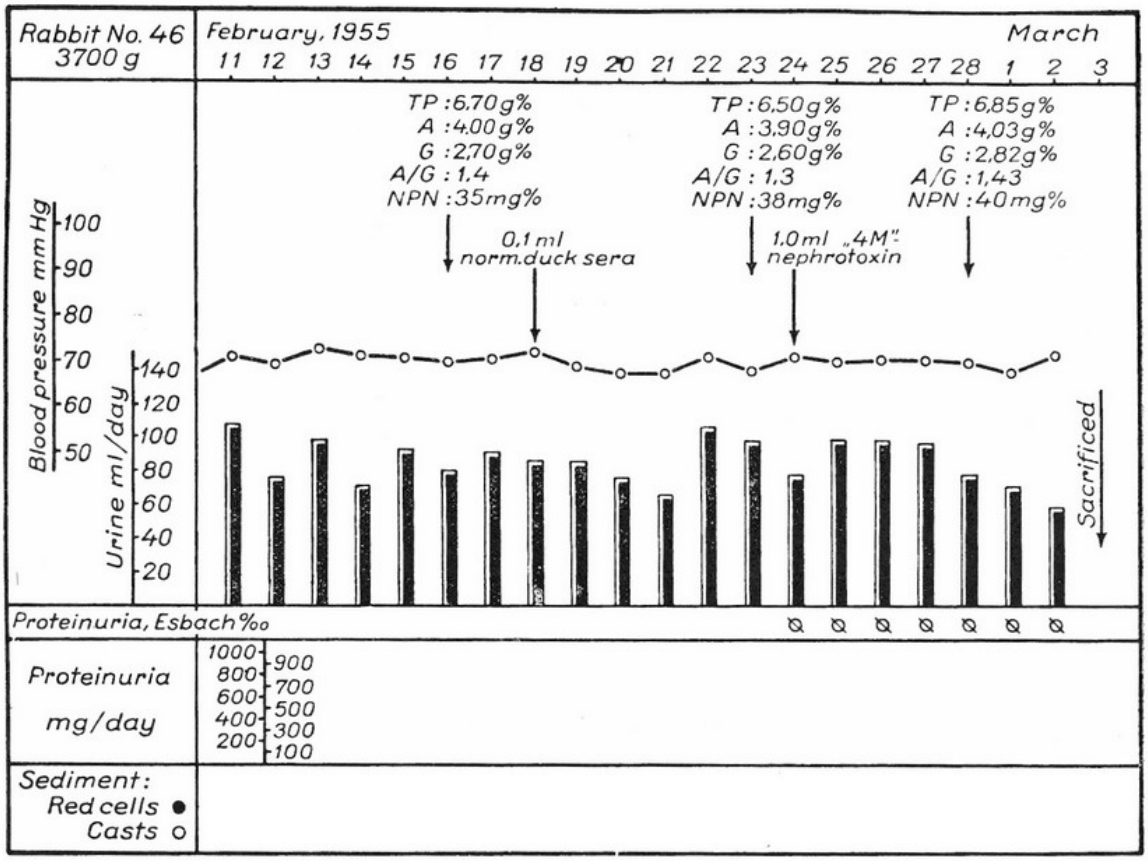

Fig. 9. Abbreviations: TP: total protein; A: serum albumin; G: serum globulin; NPN: nonprotein nitrogen

Discussion

A) *The mechanism of the second phase of Masugi's nephritis*

These experiments demonstrate that in rabbits, sensitized with doses of nephrotoxic duck serum ineffective in themselves, the kidneys respond to reinjection as a "shock-organ". The instantaneous appearance of renal symptoms shows that the anaphylactic process takes place mainly in the kidney. Anaphylactic shock produces very different anatomical and functional changes in different species, but the response is characteristic for any one species.

Guinea pigs are known to respond to anaphylaxis by bronchiolar spasm leading to asphyxia and convulsions. At autopsy, inflated, ballooned lungs mark the presence of extreme emphysema.

In the dog as a result of venous spasm the liver is extremely enlarged, blood pressure drops, and the animal "bleeds to death" into his own portal system.

In the rabbit the pulmonary arterioles are the site of the main reaction. Arteriolar constriction nearly blocks pulmonary circulation, the right ventricle

Table II

*The effect of reinjection of normal pig serum, or nephrotoxic duck serum, into rabbits sensitized with an ineffective dose of nephrotoxic duck serum + normal pig serum**

Rabbit No.		Urine after reinjection	
		Protein (sulphosalicyl reaction)	Sediment
1	Sensitization: 0,5 ml nephrotoxic duck serum ("7M") + 0,5 ml normal pig serum Reinjection: 1,5 ml normal pig serum	0	0
6	Sensitization: 0,5 ml nephrotoxic duck serum ("7M") + 0,5 ml normal pig serum Reinjection: 1,5 ml normal pig serum	0	0
15	Sensitization: 0,5 ml nephrotoxic duck serum ("7M") + 0,5 ml normal pig serum Reinjection: 1,5 ml nephrotoxic duck serum ("7M")	+++	0
23	Sensitization: 0,5 ml nephrotoxic duck serum ("7M") Reinjection: 1,5 ml nephrotoxic duck serum ("7M")	++	0
25	Sensitization: 0,5 ml nephrotoxic duck serum ("7M") Reinjection: 1,5 ml normal pig serum	0	0
39	Sensitization: 0,5 ml normal pig serum Reinjection: 1,5 ml normal pig serum	0	0

* Sensitization: October 15, 1957
Reinjection: October 22, 1957
++: Turbidity
+++: Heavy precipitate

dilates, its wall is reduced to paper-thinness and the animal dies in respiratory or circulatory failure. Post mortem the lungs are collapsed and the right ventricle is extremely dilated. Under the experimental conditions described, we have succeeded in localizing the anaphylactic reaction to the kidney. In rabbits sensitized with an ineffective dose of nephrotoxin, anaphylaxis, irrespective whether normal or nephrotoxic duck serum had been used for reinjection, gave rise within 24 hours to massive proteinuria. Thus, the latent period characteristic for the action of nephrotoxic duck serum in the rabbit disappeared. The experiments furnish direct proof of the role of the normal duck serum proteins in the pathomechanism of MASUGI's nephritis. It is clear, further, that in MASUGI's nephritis the duck serum, acting as a foreign protein, has to be regarded beside the anti-kidney specific immunglobulins as a decisive

factor. Thus, these results confirm, and lend new support to the theory of the biphasic development of MASUGI's nephritis, as postulated by KAY [11, 12].

B) *Re-evaluation of the first phase of Masugi's nephritis*

What occurs exactly in the first phase of MASUGI's nephritis, immediately after the injection of nephrotoxic duck serum ? According to KAY [11, 12], it consists in an innocuous combination of the rabbit kidney (antigen) with the anti-rabbit-kidney antibodies of the duck serum. Numerous data, however, do not fit in this simple assumption. The nephrotoxic duck serum damages the kidney directly and immediately. This has been borne out by clinical, pathological and biochemical observations. The injection of nephrotoxin is followed by a rise in blood pressure even before the appearance of renal symptoms (MASUGI [16], KORÁNYI and HÁMORI [14], ARNOTT, KELLAR and MATTHEW [1]). Others have pointed out, that using sufficiently active nephrotoxin, oliguria (MASUGI [16]) or even anuria (WEISS [32], HÁMORI and KORÁNYI [6]) develop early in the prealbuminuric period. Immediately after the injection of nephrotoxic duck serum grave hyperaemia develops in the glomeruli (HEMPRICH [8], WEISS [32]).

HÁMORI and TOMPA [7] observed that the China ink injected i. v. into rabbits treated with nephrotoxin is immediately stored in the glomerular endothelium, a phenomenon never seen in control animals. Storage by capillary endothelium (the endothelial phenomenon of JANCSÓ) has been ascribed to endogenous histamine (JANCSÓ [9]). In agreement with this, DIECKHOFF [3, 4] observed immediately after the injection of nephrotoxin a transient fall in blood pressure, a rise in the histamine content of the renal venous blood, and in the histamine output in the urine. Thus, in the rabbit treated with nephrotoxic duck serum, MASUGI's nephritis is the result of two antigen-antibody reactions, each noxious in itself : the first reaction corresponding to passive, the second to active anaphylaxis.

Prealbuminuric latency could be due to the relative weakness of the nephrotoxic duck serum, which might fail to increase renal permeability sufficiently to cause immediate proteinuria. The onset of proteinuria in these cases is due to a second antigen-antibody reaction in which antibodies produced by the rabbit participate. This second antigen-antibody reaction following the first, elicits the complete syndrom of experimental nephritis.

SEEGAL and BEVANS [26] have stressed that KAY's theory, adequate for the mechanism of delayed nephritis, cannot explain the nephritis developing immediately after the injection of nephrotoxic serum. We do not think that the two types of experimental nephritis differ in principle. The difference might be due simply to the fact that in birds a weak and in mammals a strong antiserum is produced against the mammalian kidney. For this reason in the

latter type proteinuria develops without delay, and thus the second antigen-antibody reaction remains latent.

Using a fluorescence-optical method, ORTEGA and MELLORS [17] showed, that in the blood of rats treated with nephrotoxic rabbit serum, antibodies appeared after 6 to 9 days and were present for 3 months. These anti-rabbit-sera antibodies adhered, like the anti-rat-kidney antibodies of the nephrotoxic rabbit serum, almost exclusively to the basal membrane of the glomeruli. These observations prove the biphasic mechanism of MASUGI's nephritis by demonstrating a second, autogenous antibody, which reacts with the kidney-bound nephrotoxic antibody.

Accordingly, it may be assumed, that in all nephrotoxic renal lesions a biphasic mechanism is involved. The first phase, the reaction of the antibodies of the nephrotoxic serum with the intact kidney (passive anaphylaxis) elicits the full blown nephritic syndrom only when mammalian nephrotoxic serum had been used, while applying avian nephrotoxic sera, proteinuria develops only after a latent period, although oliguria and hypertension may develop early. The second phase, the reaction of the antibodies of the recipient with the proteins of the nephrotoxic serum (active anaphylaxis) fails to manifest itself, when mammalian nephrotoxic serum had been injected, full blown nephritis being elicited in this case already by the first antigen-antibody reaction. When avian nephrotoxic serum had been used manifestation of nephritis follows only this second antigen-antibody reaction.

C) *The development of human glomerulonephritis*

The development of human nephritis is usually explained by

1. Streptococcal allergy. According to the classic view (SCHICK [27], PIRQUET [19]) the streptococcal protein sensitizes the human organism and the disease will become manifest when after an adequate period, in the course of reinfection, streptococcal proteins react with sessile antibodies.

2. According to others (SCHWENTKER and COMPLOIER [28], CAVELTI [2]) the streptococcal toxin merely alters the renal proteins, which enter the circulation acting as foreign proteins, and elicit the production of antibodies. The organism is assumed therefore to produce antibodies against its own kidney ; these react with the kidney and elicit the nephritis (autoimmunization).

3. Others (KELLETT [13], SARRE [22, 23]) postulate a mechanism of reversed anaphylaxis : the streptococcal protein is bound to the kidney, the organism produces antibodies against the foreign protein, and these react with the streptococcal proteins bound to the kidney.

None of these theories can fully explain human nephritis, and none of them can be excluded as a pathogenic mechanism. In our opinion all three of them have to be taken into consideration in the pathogenesis of glomerulo-

nephritis, which may be a result of a combination of the various mechanisms. This seems to be also an adequate explanation for the low incidence of human glomerulonephritis, compared with the frequency of streptococcal infections. A somewhat similar hypothesis was proposed by PFEIFFER and BRUCH [18], according to which streptococcal allergy and autoimmunization following each other may combine to elicit chronic glomerulonephritis, but acute nephritis is due to streptococcal allergy alone. Acute allergic (streptococcal) nephritis usually heals with the control of infection, but in some cases autoantibodies, demonstrable by suitable techniques, are formed against the lesioned kidney. Autoimmunization would be responsible for the development of chronic nephritis and secondary nephrosclerosis.

SUMMARY

Under certain experimental conditions, anaphylactic shock accelerates or aggravates the pathological process of MASUGI's nephritis in the rabbit. In the rabbit sensitized with an in itself ineffective dose of nephrotoxic duck serum, proteinuria follows the intravenous reinjection of nephrotoxin without the usual latent period. MASUGI's nephritis develops even if under the same conditions normal duck serum is injected, indicating that the reaction of anti-duck antibodies with normal duck serum protein elicits the manifestation of a so far latent pathological process. These experiments demonstrate two, linked allergic mechanisms in the pathogenesis of experimental nephritis, and these may play a role also in the human disease.

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