PART XXV

GUEST LECTURE

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TOXIC IMMUNE GLOMERULOPATHY

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Introduction

Drug or toxin induced immune glomerulopathy represent an important problem as several immunologically mediated glomerulonephritis are known to be associated with drug intake or toxic exposure. Moreover, most of the glomerulopathies are still of unknown origin raising the possibility that at least some of them are related to unknown exposure. Toxic immune glomerulopathies are also of great interest for research since the mechanisms of induction are still unknown, raising important questions concerning, for example, the dysregulation of the normal immune system induced by drugs or toxic agents. Experimental models are of major interest in this respect.

I will first review the agents known to be associated with glomerulonephritis in humans and then summarize the main experimental models that have been developed with particular attention to mercury-induced glomerulonephritis which has been extensively studied.

Drug and toxin-induced glomerulopathy in humans

A large number of drugs have been described associated with the occurrence of glomerulonephritis in humans (a complete bibliography for this section can be found in our recent reviews [1–3]). The glomerular disease may be either a membranous glomerulonephritis or the nephrotic syndrome with minimal glomerular changes. Interestingly the same drug may often induce either glomerular disease (Table I). Other glomerular lesions have occasionally been described. The responsibility of the drugs incriminated is well documented for several of them, since either a great number of cases have been reported, or/and because glomerulonephritis recurred when the drug was reintroduced (Table I). In contrast the responsibility of the drug in the appearance of glomerular lesions may be difficult to assess when only few cases have been published. The latter drugs are only mentioned in Table II.
TABLE I. Main immunologically mediated glomerular lesions induced by drugs and drugs most frequently associated

<table>
<thead>
<tr>
<th>Membranous glomerulonephritis*</th>
<th>Nephrotic syndrome with minimal glomerular changes*</th>
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<tbody>
<tr>
<td>Gold salts</td>
<td>Lithium</td>
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<tr>
<td>Mercurials</td>
<td>NSA1</td>
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<tr>
<td>D-penicillamine</td>
<td>Other drugs with sulphydril group</td>
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* The glomerular lesion mentioned is the most frequently observed associated with the corresponding drugs. However, many (in italics) may be associated with the other glomerular lesions

TABLE II. Drugs or toxins that have been found associated with immunologically mediated glomerulonephritis

**Well-documented**
- Heavy metals (gold, mercury)
- D-penicillamine
- Other drugs with a sulphydril group (thiopronine, 5-thiopyridoxine, pyrithioxine, methimazole)
- Lithium salts
- Non-steroidal and anti-inflammatory agents
- Rifampicin
- Anti-convulsant drugs (diones, hydantoin, ethosuximide)
- Drugs responsible for lupus-like syndrome (hydralazine)

**Likely**
- Drugs responsible for lupus-like syndrome (procainamide)
- Toxin-induced connective tissue disease (silica exposure, toxic-oil syndrome)
- Hydrocarbon exposure
- Interferon

**Not well-documented or few cases published**
- Ampicillin
- Probenecid
- Phenindione
- Carbutamide, tolbutamide, chlorpropamide
- Potassium chlorate
- Quinidine
- Dapsone
- PUVA
- Levamisole
- Nifedipine
- Human adjuvant disease
Glomerulonephritis induced by heavy metals

**Gold salts** Proteinuria and the nephrotic syndrome are observed in 6 to 17.2 per cent and 2.6 to 5.3 per cent respectively of the patients with rheumatoid arthritis and treated with gold salts. In a recent review of 27 publications [1–3], we found 122 such patients treated with gold salts who underwent renal biopsy. Most of them (89.5%) had a membranous glomerulonephritis and 9.6 per cent had minimal glomerular changes. Renal insufficiency is quite rare. Proteinuria, associated with the nephrotic syndrome in 57.9 per cent of the cases, is of good prognosis and subsides within four to 18 months. Gold therapy has always been stopped when proteinuria appears and reintroduction has very rarely been attempted.

Immunomorphological studies of gold-induced membranous glomerulonephritis gave results similar to those obtained in idiopathic membranous glomerulonephritis.

Most authors agree that there is a causal relationship between the occurrence of membranous glomerulonephritis and gold treatment, since such glomerular lesions have rarely been reported among rheumatoid arthritis patients who did not receive gold salts, D-penicillamine or related drugs. The occurrence of membranous glomerulonephritis is not correlated with the cumulative dose of gold, with the duration of treatment, nor with the gold salt used. Proteinuria seems, however, to occur much less frequently after treatment with the gold salt auranofin given orally. Since proteinuria is only observed in some patients and is not dose related this suggests that susceptibility is genetically determined. It has, indeed, been shown that patients with HLA B8 or DR W3 antigens are at higher risk.

**Mercurials** Mercury induced membranous glomerulonephritis has been described in patients treated with organo-mercurial diuretics, in patients using ammoniated mercury topically, or mercurious chloride-containing laxatives and in women using mercury-containing skin lightening creams.

Interestingly the nephrotic syndrome has also been observed after environmental or occupational exposure to mercurials. Eighteen cases have been published and renal biopsy exhibited either a membranous glomerulonephritis or minimal glomerular changes [1–3]. It is possible that unknown mercury exposure might account for some cases of apparently idiopathic membranous glomerulonephritis.

Glomerulonephritis induced by drugs with a sulphydryl group

**D-penicillamine** is used in the treatment of rheumatoid arthritis, Wilson’s disease, cystinuria; chronic active hepatitis and systemic sclerosis.

Proteinuria is usually the only abnormality encountered. It has been observed in seven to 20 per cent of rheumatoid arthritis patients treated with D-penicillamine. In a recent review, 190 cases were collected [1–3]. The nephrotic syndrome was present in 49.6 per cent of them. The characteristics of proteinuria
or of the nephrotic syndrome are similar to those mentioned for gold salts. Renal insufficiency is rare as well as hypertension. The occurrence of proteinuria is neither correlated with the cumulative dose of the drug nor with duration of treatment, suggesting individual susceptibility, and the frequency of proteinuria has been reported to be higher in DR W3 patients. Renal biopsies performed in 147 of these patients exhibited a membranous glomerulonephritis, quite similar to that induced by gold salts, in 85.2 per cent of the cases and more rarely (10.4%) a mesangiproliferative glomerulonephritis. Minimal glomerular changes and focal necrotizing glomerulonephritis have been observed, each in three patients and, more recently, a rapidly progressive glomerulonephritis in one. The prognosis is good in most cases and proteinuria progressively disappears. Interestingly, since D-penicillamine is given in severe diseases such as Wilson's disease, and because drug-induced glomerulonephritis usually has a good prognosis, therapy has occasionally not been interrupted. It has been reported that proteinuria may disappear despite continued treatment. Similarly, reintroduction of the drug was not always associated with recurrence of proteinuria.

Glomerulonephritis as a part of a lupus-like syndrome or associated with lung haemorrhage (Goodpasture’s syndrome) has been observed in six and nine patients respectively. In the latter situation, diffuse extracapillary necrotizing proliferative glomerulonephritis is usually observed. The prognosis is poor, although a favourable outcome has been observed after plasma exchange associated with immunosuppressive therapy. It is of note that while a linear pattern of deposition of IgG along the glomerular capillary wall has been occasionally observed, circulating anti-GBM antibodies were not detected.

Other drugs with a sulphydryl group (captopril, thiopronine, pyrithioxine, 5-thiopridoxine and methimazole) have also been reported to be associated with the occurrence of immune type glomerulonephritis.

**Lithium salts**

Although only 10 patients have been reported [1–3], a causal relationship has been well established since three patients who had recovered from a first episode of the nephrotic syndrome relapsed when rechallenged. Both lithium sulfate and lithium carbonate have been incriminated. Serum lithium was in the therapeutic range and the delay between the institution of the treatment and the occurrence of the nephrotic syndrome varied from six weeks to two years. Heavy proteinuria with the nephrotic syndrome was present in all cases, associated with renal insufficiency severe enough to require haemodialysis in two patients. The nephrotic syndrome and proteinuria rapidly disappeared and renal function returned to normal shortly after withdrawal of the drug. Even in patients who relapsed after rechallenge, the nephrotic syndrome disappeared after the drug was stopped.

Renal biopsy exhibited minimal glomerular changes with negative immunofluorescent findings and/or without electron-dense deposits in most patients. Diffuse granular IgG deposits suggestive of membranous glomerulonephritis were reported in only one patient. In another patient who developed acute renal
failure, a small collection of lymphocytes in the interstitium was described suggesting that acute renal failure could be due to an allergic interstitial nephritis as is the case for fenoprofen nephropathy. However, histological descriptions do not allow any firm conclusions.

Non-steroidal anti-inflammatory agents, and other drugs inducing similar syndromes

Twenty-eight cases of the nephrotic syndrome with acute renal failure due to fenoprofen have been published [1–3]. Females and elderly patients are at high risk. Renal abnormalities occurred after several months. Daily dosage was in the therapeutic range. Renal failure, present in all patients varies greatly in its severity and may require haemodialysis. Remission, however, occurred in most patients either spontaneously after withdrawal of the drug or after steroid therapy. Renal histological findings are quite peculiar and associate minimal glomerular changes, together with acute interstitial nephritis. Lymphocytes, plasma cells and eosinophils are found in the interstitium. Fluorescent staining is usually negative for C3 and Ig. Most of mononuclear cells (80%) were characterized as T cells with only 20 per cent B cells, the majority of which being IgE bearing cells.

Other non-steroidal anti-inflammatory agents may give rise to the same picture [1–3] although acute renal failure may be absent. The drugs implicated were ibuprofen (2 cases), naproxen (1 case), fenofenac (3 cases), diclofenac (2 cases), alclofenac (1 case), zomepirac (6 cases), tolmetin (3 cases), indomethacin (1 case), sulfonamides (1 case), phenylbutazone (5 cases) and piroxicam (1 case).

The association of the nephrotic syndrome and acute interstitial nephritis has also been described with ampicillin, rifampicin and interferon [1–3]. Other glomerular lesions have also been reported as a consequence of rifampicin therapy including severe extracapillary glomerulonephritis.

Drugs inducing lupus-like syndrome

Renal manifestations seem to be very rare during drug-induced lupus-like syndrome. We have already mentioned that D-penicillamine can induce this with renal involvement. Renal biopsies have been performed in six patients treated with procainamide who exhibited renal manifestations. Different renal lesions were reported [1–3].

Renal involvement is less rare in patients treated with hydralazine. We collected 24 cases, 16 of whom underwent renal biopsy [3–6]. Mild renal abnormalities (proteinuria, haematuria) were observed in seven of them. In the 17 other patients renal insufficiency developed in 14 of them. Renal biopsy exhibited in most instances a focal and segmental glomerulonephritis with crescents and necrotizing glomerulonephritis.

Anticonvulsant drugs, such as the oxazolidinedione derivatives, hydantoin derivatives or ethosuximide are also able to induce a lupus-like syndrome. Renal involvement has also been described. However, in most cases, renal involvement
is not associated with systemic manifestations. The nephrotic syndrome has occasionally been observed, usually in children treated with dione derivatives. Various renal lesions have been reported including membranous glomerulonephritis, minimal glomerular changes and, in one patient, a peculiar glomerular lesion defined by an infiltration of capillary loops with eosinophils [1–3]. The prognosis was favourable in all cases after withdrawal of the drug.

**Connective tissue diseases associated with occupational or accidental exposure or with cosmetic surgery**

Silica exposure may induce scleroderma, lupus-like syndrome or rheumatoid arthritis. Proliferative glomerulonephritis with occasional crescents has been reported in several patients [7–10].

The toxic-oil syndrome is responsible for scleroderma-like syndrome and has been described associated with proliferative glomerulonephritis or membranoproliferative glomerulonephritis in four patients [11].

Systemic sclerosis, rheumatoid arthritis or lupus-like syndrome have been observed, mainly in Japan, following injection of foreign substances such as silicone or paraffin (‘human adjuvant disease’). Proteinuria has been reported in five out of 46 women affected with this syndrome but renal biopsies were not performed [12].

**Hydrocarbon exposure**

We have collected 12 cases of proliferative necrotizing glomerulonephritis considered to be related to hydrocarbon exposure [13–18]. Linear IgG deposits were found in the 11 renal biopsies studied by immunofluorescence. Eight of them exhibited lung haemorrhage. Six cases of membranous glomerulonephritis have also been reported.

Several case control studies have also been performed which were recently critically reviewed by Churchill et al [19] who pointed out methodological deficiencies (such as recall bias).

**Drug and toxic-induced experimental glomerulonephritis**

In order to better understand the mechanism(s) of action of drugs in inducing immunologically mediated glomerulonephritis, several experimental models have been devised (Table III). The mercury model which has been the most extensively studied will be first described.

**Mercury-induced glomerulonephritis**

*Mercury-induced autoimmune disease in the Brown-Norway rat*

*Description of the disease* The disease observed following injections of HgCl₂ is species and strain dependent. The most interesting disease has been seen in
<table>
<thead>
<tr>
<th>Drug or toxin</th>
<th>Species</th>
<th>Glomerular lesion</th>
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<tr>
<td>Mercury</td>
<td>Rat</td>
<td>Anti-GBM GN</td>
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<td></td>
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<td>Membranous GN</td>
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<td>Mouse</td>
<td>Immune complex GN</td>
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<td>Rat</td>
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<td>39–40</td>
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<tr>
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<td>Mouse</td>
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<tr>
<td>Hydrocarbon</td>
<td>Rat</td>
<td>Nephrotic syndrome*</td>
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<td>Goodpasture's syndrome*</td>
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<tr>
<td>CC14</td>
<td>Rat</td>
<td>IgA nephropathy†</td>
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* Immunofluorescence studies not performed
† CC14 induces cirrhosis of the liver

The Brown-Norway (BN) rat [20–23]. One week after the first injection, a host of autoantibodies can be detected including antiglomerular basement membrane (GBM) antibodies, and anti-ss DNA antibodies. A striking polyclonal IgE and IgG increase is also observed. These autoimmune abnormalities reach a peak by day 15 and then progressively disappear even when HgCl2 injections are continued.

Circulating anti-GBM antibodies are readily found deposited in a typical linear and smooth pattern along the glomerular capillary wall and in other organs [24]. The circulating antibodies are directed towards collagenase digested GBM. Deposition of anti-GBM antibodies is associated with the occurrence of heavy proteinuria. Study of the kidney by light and electron microscopy at peak illness showed mild infiltration of monocytes without extracapillary proliferation [25]. Rats may die at this time, probably as a consequence of intravascular coagulation due to antibody deposition [26]. The mechanism of proteinuria is not clearly understood but has been shown to be complement independent.

When rats survive this phase of the disease, glomerular linear IgG deposits progressively diminish and granular IgG deposits are superimposed along the glomerular capillary wall and in a subepithelial position as shown by electron microscopy [21,25]. Granular IgG deposits are also found in the mesangium and in vascular walls in the kidneys and in several other organs. Circulating immune complexes transiently detected by several assays are probably responsible for it. The antigen and the antibodies constituting such complexes are unknown at present.
Genetic control of susceptibility  The BN rat strain is the only one among the 22 tested to develop such autoimmune abnormalities. Interestingly the four strains with the RT-1 I haplotype are completely resistant (the RT-1 complex is the equivalent of the HLA complex in man). In order to more precisely dissect the genetic control of susceptibility the behaviour of segregants between the resistant LEW strain and the susceptible BN strain was assessed. We were thus able to demonstrate that susceptibility is inherited as an autosomal dominant trait and depends upon three to four genes, one of which is RT-1 linked [27–29]. This is of interest since, as mentioned above, MHC linked genes are also at play in gold-induced membranous glomerulonephritis in humans.

Mechanisms of induction of mercury-induced autoimmune disease in BN rats  One tempting hypothesis to explain the occurrence of autoimmune glomerulonephritis in BN rats is that HgCl₂ could induce autoantibodies by modifying self-antigens or by acting as a hapten. It is difficult to rule out a modification of self-antigens by HgCl₂. It was, for example, tempting to speculate that granular IgG deposits occurred as a consequence of the formation of antibodies directed to the brush border antigen also present on visceral epithelial cells and responsible for Heymann's nephritis. However, such antibodies could not be detected and it must be underlined that BN rats are resistant to the induction of Heymann's nephritis while LEW rats are susceptible. It is also difficult to rule out that HgCl₂ acts as a hapten. However, as will be mentioned below, mercury was not found by autoradiography in the immune deposits of rabbits which develop a disease similar to that seen in BN rats [30].

In vivo findings in BN rats injected with HgCl₂ strongly suggest that some kind of polyclonal activation of B cells occurs. Moreover, these rats develop spleen and lymphnode enlargement from day eight and we have shown (unpublished observations) that the number of both B and T cells significantly increase in these organs. Using the plaque forming cell (PFC) assay we also observed that the number of anti-TNP and anti-sheep red blood cells (SRBC) PFC produced by the spleen was increased when compared to controls [31].

This prompted us to test whether HgCl₂ modifies lymphocyte functions in BN rats. This was studied using the popliteal lymphnode assay and mixed lymphocyte cultures. Unfractionated spleen cells and T cells from BN rats treated with HgCl₂ induce a proliferation in the draining popliteal lymphnode when injected in the footpad of naive syngeneic recipients. Both T helper cells and B cells were found to proliferate [32].

These findings were confirmed in mixed lymphocyte cultures. Irradiated T helper cells from BN rats who had received HgCl₂ or irradiated normal T helper cells exposed in vitro to HgCl₂ induced normal BN rat spleen cells to proliferate. Both normal T helper cells and normal Ia positive cells were required among responder cells. This response was specific since T suppressor/cytotoxic cells or B cells from rats injected with HgCl₂ were unable to induce the proliferation. Several hypotheses are currently under investigation to explain this abnormal cooperation. It is possible that T helper cells exposed to HgCl₂ release nonspecific factors. It is also possible that modified T helper cells induce the generation of autoreactive T helper cells recognizing Ia positive cells.

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These findings do not confirm the hypothesis put forward by Gleichmann et al [33] from chronic GVH experiments. They have shown that autoimmune manifestations in that model are a consequence of a reaction of T helper cells with allo Ia positive cells. They have suggested that Ia determinants modified by virus or drugs could function as allo Ia and stimulate autologous T helper cells. However, in our experiments we could not find any evidence for a role of modified Ia determinants.

**Spontaneous regulation of mercury induced autoimmune disease** Another interesting feature of the disease induced in BN rats is the spontaneous regulation that occurs after three weeks even when HgCl₂ injections are continued [22]. All the autoimmune manifestations subside progressively so that no abnormalities can be detected by the end of the second month in most of the animals except for the persistence of granular IgG deposits in kidney structures.

Bowman et al [34] observed that the disease cannot be induced again in animals who have recovered and also that BN rats can be rendered tolerant if they are first injected with low HgCl₂ doses.

This suggests that suppressor cells could be responsible for the spontaneous regulation observed. Indeed spleen cells from animals who have recovered are able to transfer resistance when injected into naive syngeneic recipients. Other experiments also suggest that these cells have the suppressor/cytotoxic phenotype since spleen cells depleted OH8+ cells (suppressor/cytotoxic) are unable to transfer resistance [34].

**Mercury glomerulonephritis induced in other strains of rats**

Among the other strains of rats tested [35] several developed only an immune-complex type glomerulonephritis characterized by granular IgG deposits in various locations (subepithelial, mesangial or in vascular walls).

The glomerulonephritis induced in PVG/c rats has been studied by Weening et al [36]. They found antinuclear antibodies in that strain. Moreover they obtained evidence that the occurrence of the disease was associated with an inhibition of suppressor cell function. The fact that adult thymectomy worsened the disease still supports the hypothesis of a role for inhibition of suppressor cells [37].

**Mercury induced autoimmune glomerulonephritis in other species**

Roman-Franco et al [30] have reported that HgCl₂ induces in outbred rabbits a disease quite similar to that seen in BN rats. Interestingly these authors could show by using 203 HgCl₂ and autoradiography that mercury was deposited in the proximal tubular cells but not within the immune deposits.

Several authors have studied the effect of HgCl₂ in mice [38]. Most authors have found that a mesangial glomerulopathy could be induced in BALB/c mice and SWISS mice. Granular IgG deposits along the glomerular capillary wall have also been reported in BALB/c mice.
Other experimental autoimmune glomerulonephritis induced by drugs and toxins

Several other experimental models have been described but usually the mechanisms responsible have not been sought. It has been reported that diones induce a nephrotic syndrome in Wistar rats [39] but this was not confirmed by later experiments. Nagi et al [40] have shown that a membranous glomerulonephritis occurs as a consequence of gold thiomalate administration in Wistar rats. It was suggested but not demonstrated that antibodies against the brush border tubular antigen were responsible. Wistar rats have also been shown to develop a membranous glomerulonephritis after prolonged feeding with D-penicillamine [41]. Again the fine mechanisms at play have not been elucidated. More recently, Donker et al [42] have observed that BN rats fed D-penicillamine develop a disease quite similar to that described in that strain after injections of HgCl₂. Ten Veer et al [43] have demonstrated that hydralazine may give rise to antinuclear antibodies and also to mesangial IgG deposits in mice.

Rats exposed to hydrocarbon have been reported to develop either a nephrotic syndrome or Goodpasture's syndrome [13]. However, immunofluorescence studies were not performed.

Finally CC14 induces in rats cirrhosis of the liver associated with mesangial IgA deposits [46]. This model is reminiscent of what has been observed in humans with cirrhosis of the liver.

Pathogenesis of immunologically mediated nephritis in humans

Immune complex nephritis These nephritides are the consequence either of deposition of circulating antibodies or of in situ immune complex formation. The numerous experimental models that we have described are probably the most convincing evidence that drug exposure may induce such immunologically mediated glomerulonephritis.

However, the fine mechanisms at play are usually unknown. There are only very few indications that drugs or toxins may induce renal damage by modifying self antigens or by acting as haptens. Probably the only example is given by methicillin [47,48] induced antibodies (either anti-TBM or directed towards a metabolite or methicillin). It is usually considered that gold or mercury induced membranous glomerulonephritis could be due to the induction of antibodies similar to those observed in Heymann's nephritis, but such antibodies have never been demonstrated. It has also been claimed that gold or mercury could act as haptens but neither gold nor mercury could be detected within the immune material deposited. Although D-penicillamine interferes with collagen metabolism this has not been shown to result in autoantibody synthesis.

In contrast, several experiments suggest that many drugs that induce immunologically mediated nephritis have an immunomodulatory effect. Gold, D-penicillamine and mercury may also interfere with the immune response. Besides the immunosuppressive effect of both gold and D-penicillamine, these agents may have stimulatory effect. D-penicillamine has been shown, for example, to act as a polyclonal activator in mice [49] and clearly, mercury interferes with the immune response in BN rats.
Whatever the precise mechanisms of action of the drugs, it is clear that the effect observed depends on genetic factors: 1) drug induced lupus-like syndrome, gold and D-penicillamine induced membranous glomerulonephritis are more frequently observed in patients with the DR4 [50] and DR3 [51] antigen respectively. The role of class II antigens is also confirmed from experimental studies; 2) antinuclear antibodies are more frequently encountered in slow acetylator s [52]. It is noteworthy that the acetylated form of procainamid e does not induce antinuclear antibodies and does not affect lymphocyte in vitro.

In conclusion, it is most likely that the mechanisms at play are highly complex and that one drug may act in different ways. It is of interest to mention that the results of recent experiments showing that drugs such as hydralazine interact in vitro with the fourth component of complement and may therefore modify the clearance of immune complexes [53].

**Drugs inducing the nephrotic syndrome with minimal glomerular changes** There is good evidence that in humans, drug induced nephrotic syndrome associated with minimal glomerular changes may be of immune origin: 1) only few patients exposed develop the glomerulopathy which is against a toxic effect; 2) several drugs such as D-penicillamine, gold salts or mercury compounds may induce either a membranous glomerulonephritis or nephrotic syndrome with minimal glomerular changes. This suggests that, depending on still unknown factors, either humoral immunity or cellular immunity, are involved; 3) in the same vein, the drug induced nephrotic syndrome with minimal glomerular changes is often associated with immuno-allergic acute interstitial nephritis characterized by interstitial infiltration with T lymphocytes. It is therefore tempting to speculate that activated T cells could play a role in the appearance of the nephrotic syndrome; 4) drugs like steroids and cyclophosphamide have been reported to have a beneficial effect on these drug induced nephrotic syndromes; 5) finally, there are several arguments suggesting that the idiopathic minimal-change glomerulopathy is immunologically mediated. Shaloub [54] has first suggested that lipid nephrosis could be a consequence of T cell dysfunction. Others have then suggested that lymphokines released by activated T cells could increase vascular permeability. It is therefore tempting to speculate that both lipid nephrosis and the drug induced nephrotic syndrome with minimal glomerular changes have similar pathogenesis. Unfortunately there is no experimental model of drug induced nephrotic syndrome with minimal glomerular changes of immune origin.

**Conclusion**

The various drugs or toxic agents associated with glomerulopathy have been briefly reviewed. There is good evidence that the glomerular disease is immunologically mediated in most cases. Though the prognosis is usually good after withdrawal of the drug, these drug-induced side effects are important since patients affected are then deprived of efficacious therapy. Better knowledge of the genetic factors will perhaps allow in the future the determination of patients...
at risk. Another way for research will be to discover molecules divested of deleterious side effects. It is also clear that several occupational or environmental toxins may be responsible for immunologically mediated glomerulonephritis and may account for glomerulonephritis still considered as idiopathic.

Development of experimental models will allow a better understanding of the mechanisms at play which is of major interest in basic and applied immunology.

Acknowledgment

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