

## Gold salts, D-penicillamine and allopurinol

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## Gold nephropathy

### Introduction

Gold salts have been used in the treatment of patients with rheumatoid arthritis since 1927 [1]. After a controlled study, the Empire Rheumatism Council [2], confirmed the effectiveness of gold salts for the treatment of rheumatoid arthritis. Even today, chrysotherapy has remained one of the major therapeutic modalities in the second line treatment of progressive rheumatoid arthritis. Gold salts are also used in the treatment of pemphigus vulgaris [3] and bronchial asthma [4]. Before the introduction of an orally administered gold compound, auranofin (triethylphosphine gold tetra-acetyl glycopyranoside), to clinical use [5-7], parenterally administered gold salts, such as sodium aurothiomalate and gold thioglucose comprised chrysotherapy. The frequency and severity of the side effects for patients treated with parenteral gold versus those given oral gold preparations are significantly different [8-10]. With introduction of newer parental DMARDs, toxicity has been reduced using combination therapy [10a, 10b].

### Parenterally administered gold

Despite the efficiency of injectable gold salts in the treatment of rheumatoid arthritis, they are associated with a variety of adverse effects, such as skin rashes [11-13], thrombocytopenia [14, 15], granulocytopenia [11, 16], aplastic anemia [17, 18], interstitial pneumonitis [19, 20], gastrointestinal side effects [11, 21], chrysiasis of cornea and lens [12], and proteinuria and nephrotic syndrome [11, 22, 23]. One or more of these adverse reactions have been reported in approximately one-third of patients treated with gold salts [12]. Proteinuria, including nephrotic syndrome, is the commonest manifestation of gold-induced nephropathy, occurring in 2% to 10% in patients receiving chrysotherapy [10, 22-24]. However, the decreased frequency of proteinuria has paralleled the reduction in dosage of injectable gold salts, prolonging the interval between injections and the introduction of several new disease modifying agents. The risk of proteinuria is increased at higher doses [26] and in the patients with HLA DR3 [27-30]. In one-third to half of the patients, the proteinuria is accompanied by microscopic hematuria [31, 32]. The

severity of the proteinuria varies greatly and does not correlate with the duration of treatment or the total dose of gold received [31, 33]. The peak incidence of proteinuria occurs after four to six months of treatment [33], but it may develop at any time from 1 week to 39 months after the start of treatment [33, 34]. Complete resolution of gold-induced proteinuria occurs in all patients 3 years after cessation of therapy, however, one-third of patients had resolved their proteinuria in 6 months after stopping therapy [34a]. Progressive loss of renal function following withdrawal of gold therapy is rare [34b]. Furthermore, reinstitution of gold therapy at a lower dose in patients with prior history of gold-induced proteinuria without recurrence suggests that the proteinuria may have a dose dependency [34c]. Renal function is usually normal to minimal impairment in these proteinuric patients.

### Histopathology of glomerular lesions

Histopathological examinations of the renal biopsy specimens from patients with proteinuria show predominantly membranous glomerulopathy [10, 22, 31-40]. Electron microscopy of renal tissue usually demonstrates subepithelial electron dense deposits (especially when the disease is of short duration) [22, 32-40], intramembranous electron dense deposits [32, 34, 40], and fusion and increased density of foot processes of epithelial cells [22, 32, 35-40]. Light microscopy occasionally discloses varying degrees of uniform thickening of the glomerular basement membrane. Small, fuchsinophilic deposits with associated spike like extensions of the basement membrane may be identified on trichrome-stained sections. Immunofluorescent study of the renal tissues with subepithelial electron dense deposits reveals granular deposition of IgG, IgM and/or complements [10, 33, 34, 37, 39]. In addition to membranous glomerulonephritis, there are reports of minimal change glomerulonephritis [32, 41], focal segmental glomerulonephritis [32], and mesangioproliferative glomerulonephritis with immune complex deposition in mesangial areas [10, 31, 40]. Skrifvars et al. [42] reported a highly unusual fatal renal complication induced by sodium aurothiomalate. This complication was characterized by microhematuria, impaired renal function and by a granulomatous glomerulonephritis.

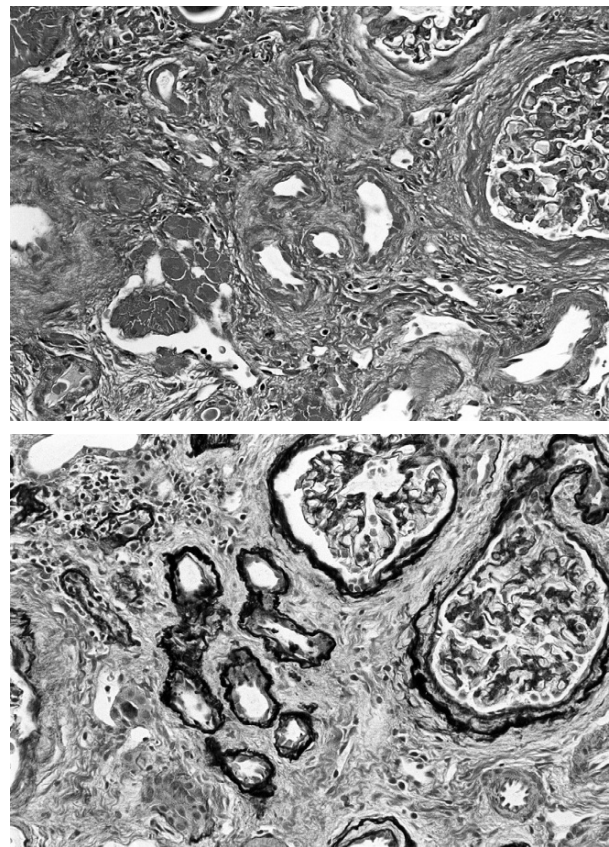
### Histopathology of interstitial lesions

In addition to the glomerular lesions mentioned above, focal tubular atrophy of variable severity is a feature of the majority of biopsy specimens of gold induced nephropathy [32, 37, 39, 43]. Interstitial fibrosis can be recognized in many of the specimens (Figure 1), and the degree of fibrosis tends to parallel the severity and extent of the tubular atrophy. However, interstitial inflammation is not usually prominent [32]. Electron microscopy reveals the existence of characteristic filamentous, electron dense cytoplasmic inclusions in various renal cells at high frequency [22, 37-39, 44, 45]. These filamentous inclusions may be complexes containing gold and other molecules [52, 50, 53]. The inclusions are concentrated in proximal tubular epithelial cells, interstitial macrophages, but rarely occur in mesangial cells and visceral epithelial cells, and spare the basement membrane or subepithelial space. They are much more prominent in patients who have received large doses of gold [22]. There may be a significant association between the degree of histological interstitial changes and the number of gold inclusions. Cramer et al. [43] reported a patient who suffered from chronic interstitial nephritis after receiving large quantities of aurothioglucose for rheumatoid arthritis. Gold deposition was seen by electron microscopy and confirmed by microprobe X-ray analysis within both tubular epithelial cells and interstitial macrophages but not the interstitium. They hypothesized that the administration of massive amounts of gold salts resulted in these depositions and the subsequent interstitial nephritis [43]. Lesato et al. [46] reported a high incidence of subtle renal tubular dysfunction in rheumatoid arthritis patients receiving gold treatment, demonstrating tubular proteinuria and the urinary excretion of large amounts of renal tubular epithelial antigen, tubular basement membrane (TBM) antigen, and  $\beta$ 2-microglobulin. However, the amounts of these proteins in urine did not correlate with the total dose of gold [46]. Renal tubular dysfunction has been induced in Hartley guinea pigs by the injection of sodium aurothiomalate, as manifested by the urinary excretion of tubular basement membrane and renal tubular epithelial antigens and tubular proteinuria. Excretion of these proteins tended to be dose dependent [47]. Following the tubular dysfunction, autoimmune tubulointerstitial nephritis with anti-TBM antibodies

developed in the animals [47].

### Pathogenesis

There are mainly two types of gold-induced nephropathy, one being immune complex type glomerulonephritis and the other limited to tubular lesions. The latter may be induced by the direct toxic action of gold, and this toxicity seems to be dose dependent. The morphological changes in the tubules usually involve gold inclusions [22, 37, 39, 44-46]. Nagi et al. [48] using large doses of sodium aurothiomalate (1 mg/week) produced renal tubular necrosis in rats, characterized by degenerative changes of the cytoplasmic contents of epithelial cells of proximal convoluted tubules. The ultracellular structure changes involved swollen mitochondria that had lost their shape. Eiseman et al. [49]

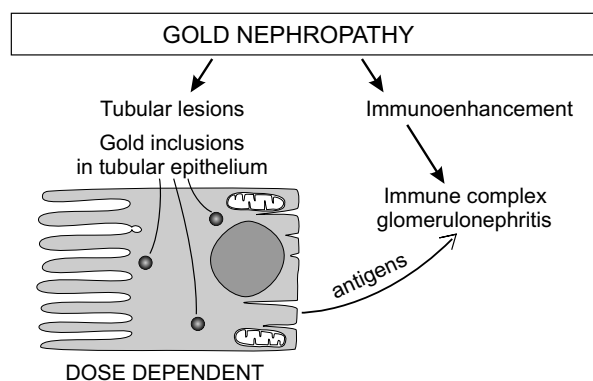


**Figure 1.** Photomicrographs of the kidney from a rheumatoid arthritis patient with gold nephropathy, demonstrating prominent interstitial fibrosis and tubular cell degeneration (magn.  $\times 340$ ). Above: Masson's trichrome staining; below: PAM staining.

reported morphofunctional and biochemical changes in rat kidneys following a single ip injection of a high dose (75 mg/kg) of gold sodium thiomalate. This included severe coagulative necrosis of the proximal tubular epithelium at one day, followed by epithelial regeneration by day 4 and nearly complete resolution by day 8. Alternations in renal heme biosynthesis and drug metabolism paralleled the morphological changes [49]. Tubular dysfunction has also been reported in rheumatoid arthritis patients receiving gold treatment [46] and in animals being treated with low doses of gold salts [47, 48].

The pathogenesis of immune complex type glomerular lesions associated with chrysotherapy remains unclear. To clarify the pathogenesis of this nephropathy, it is necessary to confirm the specificity of the antigens and antibodies responsible for the immune complex of the glomerular lesions. Gold salts may act as a hapten, and specific IgE antibodies against gold salts have been detected in the sera of rheumatoid arthritis patients with mucocutaneous and hematologic adverse reaction to gold salts [50, 51]. A positive lymphocyte transformation test to gold salts has been reported in some rheumatoid arthritis patients with hematologic side effects after chrysotherapy [52]. Derot et al. [53] reported a rare case of fatal acute tubular necrosis due to gold induced nephropathy. Allergic reaction to gold salts might have been responsible for the development of this nephritis; however, such immunological phenomena are rarely seen in the patients with gold-induced nephropathy [50, 51]. To date, no evidence for the presence of gold in renal immune deposits has been reported.

It is difficult to confirm that gold is the causal antigen or hapten in gold-induced immune complex nephropathy. Palosuo et al. [54] demonstrated a circulating antigen in a patient with gold-induced nephropathy before and after the development of nephropathy, which shared immunological determinants with tissue antigens extracted with deoxycholate from microsomal fractions of various organs including human liver, human kidney, and rat liver. Precipitating antibodies against this circulating antigen were found in the serum sample pre-dating diagnosis. This serum reacted with various tissue antigens extracted from human organs, but not with kidney specific antigen [54]. In an experimental rat model, Nagi et al. [48] reported the successful induction of slowly progressive immune complex nephropathy by weekly injections of small doses of



**Figure 2.** An illustration of possible mechanisms in the pathogenesis of gold nephropathy.

sodium aurothiomalate (0.0025 mg/week), suggesting the important pathogenetic role of renal tubular antigen released from damaged tubular epithelial cells (Figure 2). Skrifvars [55] also emphasized the possible role of autoimmunization secondary to released tubular antigens in the pathogenesis of gold-induced glomerular lesions. In the guinea pig model, renal dysfunction was also induced by injections of sodium aurothiomalate, as manifested by the urinary excretion of renal tubular antigens including renal tubular epithelial and tubular basement membrane antigens. Following the tubular dysfunction, immune complex nephropathy with circulating anti-renal tubular epithelial antibody, including deposition of renal tubular epithelial antigen in the glomerular immune complexes, developed in the animals [47]. Thus, shed renal tubular antigens from damaged tubular epithelium may play an important role in the pathogenesis of gold-induced immune complex nephropathy. There are many drugs that injure the renal tubular epithelium, but rarely induce immune complex nephropathy. Thus, in addition to tubular damage, there must be other factors that promote the development of gold nephropathy. Other tissue autoantigens released and/or altered by the effect of gold and heterogeneous antigens may also participate in the pathogenetic mechanisms.

That gold salts possess immunosuppressive effects has been demonstrated by both *in vivo* and *in vitro* studies [56-59]. In addition, they also have an immunoenhancing effect on the immune response of mice, depending on dosage [60]. BALB/c mice are highly susceptible to autoimmune interstitial nephritis, while C57BL/6 mice are genetically resistant to this nephritis

when immunized with tubular basement membrane antigen with adjuvant [61]. When both strains of mice are following pretreated with appropriate doses of sodium aurothiomalate immunization with tubular basement membrane antigen with adjuvant, BALB/c mice become resistant to the development of nephritis, but nephritis is induced in the genetically resistant C57BL/6 mice. Thus, gold salts may depress the activity of all T cells, and the phenotypical effect of gold salts on the immune response to some antigens may depend on the character of the dominant T cells [62]. Selective *in vitro* inhibition of T cells has also been shown in patients receiving chrysotherapy [63]. There must be other, as yet defined factors that are involved in the development of gold nephropathy.

### Therapy and prognosis

Proteinuria is usually slow to resolve after withdrawal of the drug. In 1970, Vaamonde et al. [31] reviewed 19 case reports of nephrotic syndrome associated with chrysotherapy. In 17 patients whose outcomes were known, 13 recovered in 3 months to 7 years. Hall et al. [33] reported a long-term study of 21 patients with rheumatoid arthritis who developed proteinuria during treatment with sodium aurothiomalate. Ten patients developed proteinuria after 6 months' of treatment, 15 after 12 months, and 18 after 24 months. When chrysotherapy was stopped the proteinuria had reached a median peak of 2.1 g/day (range 0.7-30.7 g/day) at two months (range 1-13 months) before resolving spontaneously, in 8 patients by 6 months, in 13 by 12 months, and in 18 by 24 months. All patients were free of proteinuria after 39 months, the median duration being 11 months after withdrawal. Renal function did not deteriorate, and no patient died from or needed treatment for renal failure. HLA-B8 and/or DR3 alloantigens were identified in seven of the patients [33].

Newton et al. [64] studied 27 patients with gold-induced proteinuria, and provided guidelines as to when gold should be permanently stopped in these patients. They demonstrated that proteinuria of up to 2 g/L is compatible with continued gold therapy, since the low risk of more serious nephropathy developing was low. They concluded: 1) mild proteinuria (less than 0.4 g/L) is common in rheumatoid arthritis patients on gold, and such a level may not even be re-

lated to this drug. It usually disappears spontaneously without alteration of therapy, but rarely can proceed to more serious problems. 2) moderate proteinuria (0.4-2.0 g/L) should be treated more seriously. Gold injections should be stopped. If the urine clears within three months, then further treatment with gold may be given without precipitating heavy proteinuria. 3) none of their subjects have sustained permanent renal impairment [66]. The advice of Howard-Lock et al about D-penicillamine therapy may also be suitable for gold therapy. They advocate withholding the drug if there is (1) proteinuria of 2<sup>+</sup> on the dipstick, (2) persistent (longer than 3 weeks) proteinuria of 1<sup>+</sup>, (3) if there are red cell casts, white cell casts, or hyaline casts present, or (4) if red cells >10 per high power field are present. For patients whose disease has improved but who developed proteinuria of between 300 to 1,000 mg/day but without other renal abnormality, they suggest continuing the drug cautiously at a reduced dose with close monitoring. If the proteinuria exceeds 2 g/day or the glomerular filtration rate falls, the drug should be discontinued immediately [65]. Manthorpe et al. reported a successful one year treatment with auranofin (6 mg/day) in 7 rheumatoid arthritis patients with previous proteinuria associated with parenterally injected gold salts [66].

### Prediction, prevention and monitoring of development of gold nephropathy

To predict the adverse effects of gold, the association with HLA antigen has been studied [27, 28, 67-69]. A genetic predisposition to gold toxicity was first suggested by Panayi et al. [67]. Wooley et al. [68] investigated the possible relation between HLA antigens and toxicity of D-penicillamine and sodium aurothiomalate in rheumatoid arthritis patients. Nineteen of 24 patients in whom proteinuria developed were positive for HLA-B8 and DRw3 antigens. Furthermore, all 13 episodes of proteinuria exceeding 2 g/day occurred in patients with DRw3. Several investigators confirmed the association between gold-induced proteinuria and DR3 [27-30] and B8 [30], but others were unable to confirm it [70]. Conversely, DR3 patients tended to exhibit a better therapeutic response to sodium aurothiomalate than patients with DR4 [28]. DR4 and/or DR2 positive patients may have some degree of protection against gold toxicity [28, 29]. Given the uncertainty about HLA

types and toxic reactions, together with the suggestion that patients with DR3 respond better than the more numerous DR4, and taking into account the cost involved, any suggestion of using HLA typing as a guide to therapy seems premature [71]. While Van Riel et al. [72] reported the predictive value of serum IgA for gold toxicity, the study of Ostuni et al., involving a larger population, concluded that the monitoring of serum IgA was not useful in predicting gold toxicity [73]. Recently, Ayesh et al. [74] reported the predictive efficacy of the prior measurement of sulphoxidation capacity. A patient with poor sulphoxidation capacity had a nine-fold greater risk of developing gold-induced adverse reactions including nephropathy. Hopefully this will be confirmed by prospective studies involving various races and a large population. To date, there is no confirmed method for predicting gold toxicity including nephropathy, thus it is essential to monitor patients closely for any appearance of nephropathy. However, Shah et al [74a] have evaluated the association between gold ADR's (thrombocytopenia or proteinuria) and HLA-DR3 status. Based on a cohort of 41 patients they concluded that patients with nodular disease were more likely to develop ARDs (51.3% vs. 25.6%, OR= 3.0, p=0.02 and also more likely to be HLA-DR3 positive (41.2% vs. 17.6%, OR= 3.0, p= 0.045. The authors suggest that nodular patients with HLA-DR3 should not receive parenteral gold as their primary treatment for RA.

The decline in the number of reports of parenterally administered gold-induced nephropathy may indicate that the dose of gold salts used per injection is decreased and intervals between injections are being extended to prevent adverse reactions. Furthermore, introduction of methotrexate therapy, along with several biological agents, for rheumatoid arthritis, has contributed to decreased reliance on gold salts. However, intriguing reports using nanotechnology gold in treatment of malignancies has renewed interest in gold as a therapeutic agent [74b, c].

### Auranofin nephropathy

Auranofin, a unique gold compound, has been available for clinical use for 25 years after it proved to be one of the most potent oral antiarthritic com-

pounds among alkylphosphine gold coordination complexes [75]. Initial clinical studies suggested that this compound was therapeutically active when taken by mouth, with no renal adverse effects in any of the 32 patients studied [5-7]. Subsequently, the therapeutic benefits and toxicity of auranofin have been evaluated [24, 76], compared with placebo [9, 77, 78], sodium aurothiomalate [8-10, 79], and D-penicillamine [80-82]. The incidence of proteinuria in a world-wide trial was 3% for auranofin [10, 24]. The risk of developing proteinuria with auranofin therapy is significantly less than with parenteral gold [9, 24], or D-penicillamine [82]. Histopathological findings in renal biopsy specimens from patients with moderate to heavy proteinuria are consistent with the membranous nephropathy similar to injectable gold nephropathy [33, 83, 84]. Heuer et al. [10] reported a total of 3, 475 rheumatoid arthritis patients receiving auranofin therapy in 27 countries. Proteinuria developed in 3% of the patients, resulting in drug withdrawal in 0.9%, compared with 4% proteinuria in patients receiving injectable gold, with 0.8% being withdrawn. Katz et al. [24] evaluated proteinuria in 1800 rheumatoid arthritis patients given chrysotherapy. Three percent (41 cases) of 1283 auranofin-treated patients had an abnormal 24-hour urine protein level: 15 had mild (0.15 to 1 g/day), 17 had moderate (1 to 3.5 g/day), and 9 had heavy (>3.5 g/day) proteinuria. Permanent renal impairment did not occur in any patient. In 36 patients with long-term follow-up after drug withdrawal, proteinuria cleared in 31 patients within 1 week to 24 months. Seven of 8 patients who were rechallenged once the proteinuria had cleared were able to continue treatment without recurrent episodes [24].

Pathogenic mechanism of auranofin-induced nephropathy resemble those of parenteral gold-induced nephropathy. The reason for the reduced risk of proteinuria with auranofin compared to parenteral gold salts is not known. However, differences in the pharmacokinetics of the two types of gold preparations may be important. In rats treated with auranofin or sodium aurothiomalate for one year, renal gold concentrations were 33 times higher with the latter formulation [85]. Renal elimination of an orally administered dose of auranofin in human is less than 15%, compared with greater than 70% for parenterally administered sodium aurothiomalate [86].

## D-penicillamine

### Introduction

D-penicillamine is so named because it was first isolated as an amine, from the degradation products of penicillin by Abraham et al [87]. Later studies showed the characteristic chemical behavior of D-penicillamine which involves three types of reactions, formation of disulphide links, formation of thiazolidine rings, and formation of metal complexes and chelates [67]. It was first used in 1956 in the treatment of Wilson's disease [88]. D-penicillamine has since been used in the treatment of many diseases, such as cystinuria [89], rheumatoid arthritis [90-92], systemic sclerosis [93], primary biliary cirrhosis [94], heavy metal poisoning due to lead [95], cadmium [96], and mercury [97], and hyperviscosity syndrome [99]. In rheumatoid arthritis, D-penicillamine has been widely accepted as an effective second line treatment. Despite of its effectiveness, it causes many adverse effects, such as skin rashes [99, 100], taste abnormalities [100, 101], hepatic dysfunction [102-104], gastrointestinal toxicity [99, 105], proteinuria [100, 106], hematuria [107, 108], thrombocytopenia [92, 109], aplastic anemia [110], lupus-like syndrome [111, 112], Goodpasture's-like pulmonary renal syndrome [113-115], vasculitis [116, 117], myasthenia gravis [118-122], polymyositis [123, 124], and dermatomyositis [125]. One or more of these adverse reactions was recorded in nearly 60% of patients treated with D-penicillamine [100, 126-129]. Among these adverse reactions, nephropathy developed in patients with proteinuria, hematuria, lupus-like syndrome, Goodpasture's-like pulmonary renal syndrome, and vasculitis.

### Proteinuria

Proteinuria, including nephritic syndrome, is the commonest manifestation of nephropathy, reported as occurring in between 2 and 32% of patients [100, 101, 109, 124, 126-130]. The risk of proteinuria is increased at higher doses [100, 131-133], in patients with HLA B8 and/or DRW3 antigens [68], and in patients with previous gold toxicity [134, 135]. However, others have not confirmed the relationship to the drug dosage [136], duration of therapy [137], or HLA antigens [70]. In the majority of patients, proteinuria is accompanied by

microscopic hematuria [100, 127]. The peak incidence of proteinuria occurs in the second six months of treatment, but it may develop at any time from 6 weeks to 74 months [107, 101, 138]. Proteinuria may be persistent or may slowly progress to nephrotic syndrome if therapy is continued. Up to 1/3 of the patients with significant proteinuria progress to nephrotic syndrome if therapy is continued [106]. Renal function is normal to minimal impairment in patients with isolated proteinuria.

### Histopathology

Histopathological examination of renal biopsy specimens from the patients with isolated proteinuria due to D-penicillamine shows predominant membranous glomerulopathy [139-141]. Electron microscopy of renal tissue usually demonstrates subepithelial electron dense deposits and fusion of epithelial foot processes [139-141]. The deposits on the epithelial side of the glomerular basement membrane appear to be slowly covered and later incorporated into the basement membrane. With time the deposits become fainter and move towards the endothelial side of the basement membrane [142]. Immunofluorescent study may demonstrate granular deposits of IgG and C3 in the capillary wall. These changes in glomerular histology can persist for at least a year after the withdrawal of the drug [139]. Sellars et al. [143] reviewed the renal biopsies of 30 patients with rheumatoid arthritis and clinical evidence of renal disease. They reported all 9 patients with membranous glomerulonephritis but only 6 of 13 with mesangial change had received D-penicillamine or gold. Besides membranous glomerulonephritis, there are reports of minimal change glomerulonephritis [144, 145], mild mesangioproliferative glomerulonephritis without crescent [110, 142, 146], or IgM nephropathy [147, 148] associated with D-penicillamine induced proteinuria.

### Therapy and prognosis of proteinuria

Proteinuria usually resolves slowly after withdrawal of the drug. Hall et al. [149] reported a long-term study of 33 patients with rheumatoid arthritis who developed proteinuria during treatment with D-penicillamine. Of these, fourteen patients developed proteinuria within 6 months after the start of treatment and 27 within 12 months. When treatment was stopped, the proteinuria

reached a median peak of 4.2 g/day (range 0.3-15 g/day) at one month (range 0-7 months) before resolving spontaneously by six months in 12 patients, 12 months in 21, and 21 months in all. In all their patients whose nephropathy was due to D-penicillamine the proteinuria resolved completely when the drug was withdrawn; renal function did not deteriorate, and corticosteroids were unnecessary [149]. Jaffe [150] reported that reintroduction of D-penicillamine in patients with drug induced proteinuria, starting with a daily dose of 250 mg, was usually followed by a return of proteinuria at about the same time and at about the same cumulative dose as on the first occasion. However, Hill et al. [133] reported successful reintroduction and continuation for a minimum of 13 months in 5 rheumatoid arthritis patients who developed proteinuria during the first course of the drug. They instituted the "go slow, go low" method of Jaffe [151], starting with a daily dose of 50 mg and increasing by monthly increment of 50 mg to a maintenance dose of 150 mg daily. The dose was held at 150 mg/day for 4 months and thereafter increased by 50 mg at 3-months intervals if disease remained active. Proteinuria did not recur, and improvement of disease was shown in all 5 patients [133]. Howard-lock et al. [65] advocated withholding D-penicillamine if there is (1) proteinuria of 2+ on the dipstick, (2) persistent (longer than 3 weeks) proteinuria of 1+ (3) if there are red cell casts, white cell casts, or hyaline casts present, or (4) if red cells > 10 per high power field are present. For patients whose disease has improved but who developed proteinuria between 300 to 1,000 mg/day, but without other renal abnormality, they suggest the continued use of the drug cautiously at a reduced dose with close monitoring. If proteinuria exceeds 2 g/day or the glomerular filtration rate falls, the drug should be discontinued immediately.

#### Goodpasture's-like syndrome

Besides the benign proteinuria mentioned above, proliferative glomerulonephritis with fulminant renal failure has also occurred with D-penicillamine therapy. One is Goodpasture's-like syndrome, which is characterized by pulmonary hemorrhage and rapidly progressive glomerulonephritis. Goodpasture's-like syndrome associated D-penicillamine treatment has been reported in patients with Wilson's disease [113], rheumatoid arthritis [114, 115, 152, 153], primary bil-

iary cirrhosis [154], and progressive systemic sclerosis [155]. D-penicillamine was given for at least 7 months (range: 7-84 months), and at a daily dose higher than 750 mg (range: 750-2,000 mg) preceding the onset of symptoms. Pulmonary X-rays showed bilateral extensive infiltrates in all 10 cases. Lung hemorrhage was the principle cause of death in 3 cases [113].

The histopathology of renal specimens usually showed proliferative glomerulonephritis with crescent formation in 30 to 100% of the glomeruli. Direct immunofluorescent study failed to show linear IgG deposition along the glomerular basement membrane, but granular deposition of IgG and/or C3 were present along the glomerular capillary walls in 5 of 6 patients. Subepithelial electron dense deposits were observed in 3 of 4 patients tested. Circulating anti-glomerular basement membrane antibody was not detected in any of the cases tested. In Brown Norway rats, the administration of D-penicillamine induced antinuclear antibodies and significantly high concentrations of immune complexes. In these animals there was no granular deposition of IgG, but linear deposition of IgG along the glomerular basement membrane. IgG eluted from diseased kidneys bound both *in vitro* and *in vivo* to the kidney basement membrane [156]. HLA-DR2 antigen was absent in the 2 cases where HLA phenotype was determined, whereas there is a strong association between HLA-DR2 and antibody-mediated Goodpasture's syndrome [157]. Anti-nuclear antibodies have been detected both before [115, 156] and after initiation of the drug [152, 115]. Although this syndrome is potentially life-threatening, aggressive treatment with plasmapheresis, steroids, immunosuppressive drugs such as azathioprine and cyclophosphamide, and mechanical ventilation with PEEP may be life saving [113, 152-155]. Derk and Jimenez [155a] recently reviewed the case for Goodpasture-like syndrome occurring in systemic sclerosis patients treated with penicillamine. Basically they describe rapidly progressive glomerulonephritis without anti-GBM antibodies, but with linear or granular glomerular deposits. While they raise the possibility of pauci-immune GN this could not be confirmed since ANCA was not tested in their patient. Despite their conclusions, the case report by Bienaime et al ([155b]) makes a compelling case for penicillamine induced ANCA associated RPGN in a patient with Wilson Disease. Since Wilson Disease has never been associated with pauci-immune GN, the



authors are confident that penicillamine is capable of inducing ANCA associated RPGN. To date all patients with suspected pauci-immune GN have tested positive for anti-MPO antibodies. Since this observation was limited to a patient with Wilson Disease, it remains to be confirmed that patients with systemic sclerosis or rheumatoid arthritis receiving penicillamine who develop the Goodpasture-like syndrome described as a complication of penicillamine treatment should be classified as pauci-immune GN with anti-MPO antibodies.

#### Renal vasculitis

Extracapillary glomerulonephritis with renal vasculitis is also been reported as a rare complication of D-penicillamine therapy [117, 126, 156]. Necrosis of interlobular arteries with glomerular crescent [117] and necrotic and occluded periglomerular arterioles [156] have been reported. Aggressive treatment with pulse steroid, anticoagulants, and antiplatelet agents may be beneficial. The two patients with renal vasculitis, whose outcome was known, died from bacterial infection within ten months after the onset of the disease [117, 156]. These cases mostly likely represent pauci-immune GN as reviewed in the preceding paragraph.

#### Systemic lupus erythematosus syndrome

A drug-induced systemic lupus erythematosus (SLE) with proliferative glomerulonephritis has also been described in patients treated with D-penicillamine [111, 157]. Systemic lupus erythematosus syndrome is induced in approximately 2% of patients treated with D-penicillamine [112, 158]. Unlike other forms of drug-induced systemic lupus erythematosus, anti-double-strand DNA antibodies and/or hypocomplementemia are seen in D-penicillamine-induced systemic lupus erythematosus syndrome [111, 156]. Nephropathy is rare in D-penicillamine-induced systemic lupus erythematosus syndrome [111]. Walshe [112] reported that 8 patients developed the serological change of systemic lupus erythematosus of 120 patients with Wilson's disease treated with D-penicillamine, but none of them showed nephropathy.

Chalmers [111] reported 6 rheumatoid arthritis patients with D-penicillamine-induced systemic lupus erythematosus syndrome. All patients had previous

mucocutaneous reactions to chrysotherapy. Manifestations included pleurisy in 5 of 6 patients, rashes in 3, and nephritis in 2. LE cells were present in 5 patients, anti nuclear antibodies in all 6, anti-double-strand DNA in 3, 3 were Coomb's test positive, and low C4 complement in 5 of the 6 [111]. Results of a renal biopsy from a patient with nephritis showed diffuse endocapillary proliferative glomerulonephritis with focal crescent formation and vasculitis. Electron microscopy showed scattered subendothelial deposits, and immunofluorescent study revealed granular deposition of IgG, IgM, C3 complement and C1q. The patient was successfully treated with prednisolone and azathioprine [112]. Ntoso et al. [156] reported penicillamine-induced rapidly progressive glomerulonephritis in two patients with progressive systemic sclerosis. Anti nuclear antibodies, anti-Sm antibody, and Coomb's antibodies were positive in both patients. Renal biopsies from the two patients demonstrated a diffuse, predominantly extracapillary, proliferative glomerulonephritis with crescents and focal necrosis, and by immunofluorescence, focal areas of IgG, C3, and fibrinogen were observed in areas of glomerular necrosis. Subendothelial and mesangial deposits were observed by electron microscopy. Both patients responded to pulse methylprednisolone and subsequent daily steroids [156].

#### Pathogenesis of D-penicillamine-induced nephropathy

Deposition of immune complexes in the glomerular basement membrane may play an important role in the pathogenesis of D-penicillamine-induced nephropathy, such as isolated proteinuria, Goodpasture's-like syndrome, and nephritis associated with D-penicillamine-induced systemic lupus erythematosus rheumatoid arthritis syndrome. Immunofluorescent study show predominantly granular deposition of IgG and/or C3, and electron microscopy revealed subepithelial or subendothelial electron dense deposits. In rheumatoid arthritis patients, D-penicillamine alters the circulating immune complexes [159]. D-penicillamine has the capacity to convert large complexes into small ones *in vitro* and there has been speculation that similar mechanisms *in vivo* could explain the deposition of complexes and renal damage [160]. Small immune complexes deposit in the glomeruli easier than big ones.

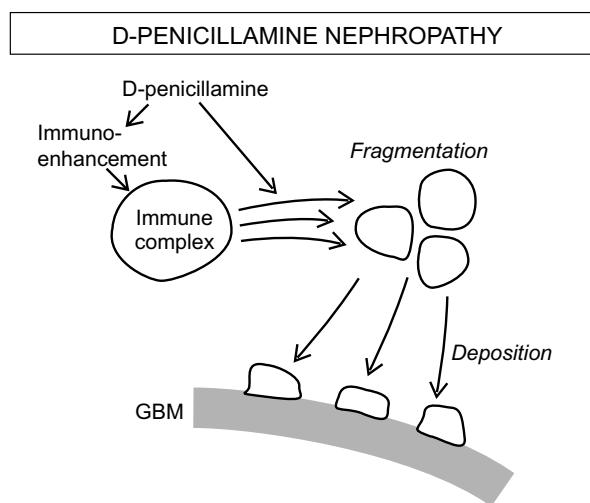
In addition to penicillamine nephropathy, other side effects of the drug may be related to the widespread deposition of immune complexes (Figure 3). Dense, granular immunoglobulin deposits have been identified at the epidermodermal junction in 4 rheumatoid arthritis patients who developed toxic reactions, such as severe rashes, thrombocytopenia, aplastic anemia, and proteinuria. Three of 4 penicillamine-induced systemic lupus erythematosus syndrome patients had similar findings on skin biopsy [161].

Besides immune complex deposition, autoantibodies against several autoantigens are frequently detected in patients treated with D-penicillamine, leading to autoimmune diseases. The exact mechanism by which this drug induces autoimmunity remains to be investigated. It may directly stimulate oligoclonal B cell activity, upset the balance between T cell subsets, or alter antigens by hapten formation. D-penicillamine can bind with various proteins, and may change the antigenicity of these proteins as a hapten. However, to date, no evidence for the presence of penicillamine in renal immune deposits has been reported. Nagata et al. [162] reported that D-penicillamine can act as a hapten for specific T cells when presented on the surface of appropriate stimulator cells, and suggested that the adverse immunological side effects of this drug in patients may have a pathogenesis similar to graft-versus-host reaction.

The possibility of ANCA associated vasculitis, as described in the case report of Bienaime et al [155b], raises an alternate explanation for the pathogenesis of penicillamine-induced vasculitis. Since all of the ANCA associated GN due to penicillamine have had anti-MPO antibodies, this suggests that an interaction with MPO is critical in triggering the ANCA induced vasculitis. However, it is not clear that penicillamine induces autoimmunity, thus the exact mechanism remains to be elucidated, although both humoral and cellular immunity are thought to play significant roles [162a].

#### Prediction and monitoring of development of D-penicillamine nephropathy

To predict D-penicillamine side effects, the association between side effects and various factors, such as HLA antigens [68, 70, 128, 130, 163, 164], autoantibodies [165, 166], and previous gold toxicity [101, 138, 167, 168] has been studied. Wooley et al. [68] investigated



**Figure 3.** An illustration of the pathogenesis of D-penicillamine induced nephropathy.

the possible interaction between HLA antigens and toxicity of D-penicillamine and sodium aurothiomalate in rheumatoid arthritis patients. Nineteen of 24 patients in whom proteinuria developed were positive for HLA-B8 and DRw3 antigens. Furthermore, all 13 episodes of proteinuria exceeding 2 g/day occurred in patients with DRw3 [68]. There is also a strong association between idiopathic membrane nephropathy and HLA-DRw3, B8 and B18 [169]. Other investigators have confirmed the association between D-penicillamine-induced proteinuria and DR3 [128, 130, 164] and B8 [70, 128, 130]. However, other investigators could not confirm a significant association between D-penicillamine proteinuria and HLA-DR3 [70, 170]. In addition to HLA antigens, Emery et al. [163] emphasized the sulphoxidation status of patients as a new predictor of outcome of drug toxicity.

Moutsopoulos et al. [165, 166] reported that anti-Ro (SSA) positive Greek rheumatoid arthritis patients experienced a significantly high frequency of side effects from D-penicillamine. Despite their dissimilar chemical structures, the thiol compounds, sodium aurothiomalate and D-penicillamine, have remarkably similar clinical effects, and this similarity extends to the incidence and type of adverse effects [138, 167]. Several investigators have noted the association between prior gold nephropathy and D-penicillamine. Billingsley and Stevens reported the significant correlation of D-penicillamine-induced proteinuria to a previous history of

gold nephropathy [134]. Patients with gold-induced proteinuria are at a higher risk for the development of proteinuria during D-penicillamine therapy ( $p < 0.001$ ), and this occurs within the first six months of treatment [138]. All six patients who developed systemic lupus erythematosus syndrome while being treated with D-penicillamine had previous mucocutaneous reactions to chrysotherapy [114]. Dood et al. [165] noted that all patients who took D-penicillamine within six months after an adverse reaction to gold developed side effects from D-penicillamine, and recommended an interval exceeding six months between treatment with gold and treatment with D-penicillamine in patients who have developed adverse reactions to gold, to reduce the risk of adverse reactions to D-penicillamine, Kean et al. [101] analyzed the influence of previous sodium aurothiomalate therapy on the toxicity pattern of D-penicillamine, but could not confirm a synergistic effect of D-penicillamine and sodium aurothiomalate leading to increased adverse reaction in patients with rheumatoid disease [101].

Although there are several predictors of adverse reactions, the most useful clinical predictor is urinalysis. Patients on D-penicillamine therapy should be closely monitored for evidence of proteinuria as the first sign of penicillamine induced nephropathy [170a].

## Allopurinol

### Introduction

Allopurinol (4-hydroxypyrazolo [3, 4-d] pyrimidine) is an inhibitor of xanthine oxidase that was successfully introduced in the treatment of primary gout about 45 years ago [171]. Allopurinol continues to be accepted as standard therapy in the treatment of primary and secondary hyperuricemia. Adverse reactions occur in about 10% of patients treated with allopurinol and are relatively mild and self-limited [171, 172]. A mild maculopapular eruption or gastrointestinal disorders are usually noted, which promptly regress with cessation of therapy. Isolated instances of alopecia [173], bone marrow depression [174], ocular lesions [175], acute cholangitis [176], various types of hepatic injuries [177, 178] temporal arthritis [179], and xanthine stones [180] have been reported. Recently, LaRosa et al [180a] have reported a case of xanthine nephropathy during treatment of childhood T-cell ALL.

Xanthine nephropathy has been reported in tumor lysis syndrome (TLS) in patients with hypoxanthine-guanine phosphoribosyl transferase (HGPRT) enzyme deficiency [180b], however, this patients' cultured fibroblasts yielded normal levels of HGPRT enzyme. Allopurinol pretreatment allows the build up of both xanthine and hypoxanthine which, in the absence of HGPRT, cannot be recycled and thus xanthine supersaturation in the urine resulting in xanthine stones with subsequent obstructive renal failure.

In 1970, reports began to appear of systemic, severe, prolonged hypersensitivity reactions occurring in patients during treatment with allopurinol, now known as allopurinol hypersensitivity syndrome (AHS) [182]. These reactions are characterized by fever, chills, malaise, generalized dermatitis, eosinophilia, abnormalities of liver function tests, and rapidly progressive renal failure [181-188]. Allopurinol-induced nephropathy is usually reported as a part of these reactions. In 1979, Gorge et al. [186] reported 3 cases of such reactions and reviewed 38 patients including their 7 patients. The average dose of the drug in these patients was 300 mg/day. The average time from initiation of the therapy to onset of the reaction was 3.8 weeks. The most common type of dermatitis was a pruritic, diffuse, erythematosus, maculopapular eruption noted in over 60% of the patients. Toxic epidermal necrosis, Stevens-Johnson syndrome, and exfoliative dermatitis were also noted in some patients. Exfoliative dermatitis has also been reported in a patient with metabolic syndrome as a delayed skin reaction heralding the onset of AHS [188a]. The presence of eosinophilia (4-53%) was noted in all but two patients. Thirty-one of 32 patients (97%) had documented impaired renal function prior to allopurinol therapy. Following the onset of the hypersensitivity reaction, further deterioration of renal function occurred in 30 of 32 patients [186]. In 1986, Singer et al. [188] reported 8 additional patients with such reactions and reviewed an additional 72 patients described in the literature. Forty of 80 patients (50%) had impaired renal function prior to allopurinol therapy. Further deterioration of renal function was found in 48 of 80 patients. Underestimation of the presence of impaired renal function in hospitalized patients with gout was recently highlighted by the findings of Petersel and Schlesinger [188b]. Based on a two year retrospective review of records of hospitalized patients with acute gout they found renal failure (serum creatinine  $> 1.5$

mg/dL) in 65% and a decreased eGRF in 73%. CKD III was present in 47%, CKD IV in 20% and CKD V in 5%. Combination therapy with Colchicine and NSAIDs was used in over 80% of the patients with renal failure and gout. Only 27% of the patients admitted with gouty arthritis were receiving allopurinol prophylaxis. In patients receiving allopurinol prophylaxis as outpatient treatment, one quarter do not have their serum creatinine monitored [188c].

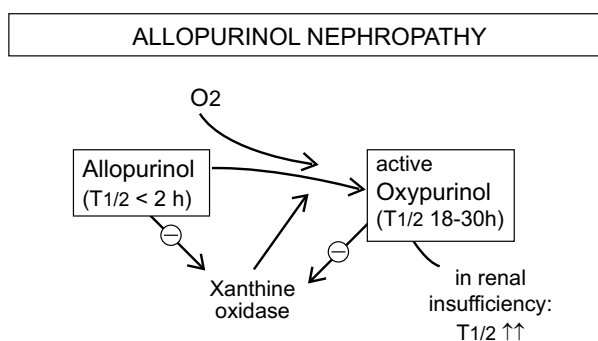
### Histopathology

Histopathological examination of renal biopsy or autopsy specimens revealed renal vasculitis [181], focal segmental glomerulonephritis [184], and acute interstitial nephritis [185, 187, 189, 190]. Jarzowski et al. [181] reported a case of the hypersensitivity type of vasculitis with fibrinoid necrosis and eosinophilic reaction, involving multiple organs, especially the kidney, resulting in uremia and death. Boyer et al. [191] also reported 3 cases of the same type including the efficacy of prednisolone in treating this type of disease. Kantor et al. [182] reported a case of glomerulonephritis associated with allopurinol-hypersensitivity. Linear deposition of IgG and complement along the glomerular basement membrane were demonstrated, and a necrotizing, hemorrhagic pneumonitis was also reported. However, no circulating anti-glomerular basement membrane antibody was detected. Acute interstitial nephritis has also been reported associated with by the administration of allopurinol [185, 187, 189, 190]. Gelbart et al. [185] reported a case of allopurinol-induced interstitial nephritis with extensive infiltration of lymphocytes, plasma cells and tubular damage. No immunoglobulins, complement, or fibrin were evident in the tubular basement membrane. This patient also had other typical symptoms of hypersensitivity reactions. Grussendorf et al. [187] also reported a case of acute interstitial nephritis with circulating anti-tubular basement membrane antibody and granular C3 deposition on the tubular basement membrane. The interstitium was diffusely widened, edematous and infiltrated with lymphocytes, plasma cells, histiocytes and numerous eosinophils. The nephritis was induced by controlled re-exposure to allopurinol in a patient who had two successive severe hypersensitivity reactions to this drug. More recently, Morel et al [191a] reported a case of allopurinol hypersensitivity reac-

tion with renal failure on admission, in which skin manifestations and renal failure recurred after initial recovery. The case was considered unique due to the presence of an ANA titer or 1:2000 on admission. Treatment consisted of intravenous and oral steroids with residual renal impairment after 7 months of therapy. A renal biopsy, at the time of recurrence, yielded deposits of C3 complement in the vessel walls. A previous skin biopsy on admission yielded leukocytoclastic, non-specific vasculitis. The authors concluded that the "findings suggested the participation of ribonucleotide alterations in the pathophysiology of allopurinol hypersensitivity syndrome".

### Pathogenesis

The pathogenesis of nephropathy associated with allopurinol-induced hypersensitivity reactions is unclear. However, pathogenic role of the immune reactions against allopurinol or its metabolites has not been excluded. Emmerson et al. [192] studied the lymphocyte reactivities to allopurinol and its active metabolite, oxypurinol, in 9 patients with previous documented adverse reactions to allopurinol. They suggested that some adverse reactions to allopurinol represented delayed type hypersensitivity to oxypurinol, but not to allopurinol. Allopurinol is oxidized by xanthine oxidase to oxypurinol, which is also an inhibitor of the enzyme (Figure 4). Allopurinol plasma half life is less than 2 hours due to rapid renal clearance and oxidation to oxypurinol [193]. Oxypurinol, because of its reabsorbance by the renal tubules, has a plasma half-life of 18 to 30 hours. The clearance of oxypurinol is diminished in renal insufficiency [194]. In addition, thiazide diuretics might be expected to cause accumulation of oxypurinol since its renal handling is similar to that of uric acid [195]. Hypersensitivity syndrome has been found to occur most frequently when allopurinol is given with thiazides or in patients with renal insufficiency [184, 188]. The immune reactions to oxypurinol may play an important role in the pathogenesis of the syndrome, including being dose dependent. The serum concentration of oxypurinol has been monitored to prevent adverse reactions [195, 196]. Recommended plasma oxypurinol concentrations are below 100  $\mu\text{mol/L}$  [196]. Several authors [195, 196] reported that no adverse reactions have occurred in patients with lower plasma oxypurinol levels; how-



**Figure 4.** Suggestion of reactions leading to allopurinol nephropathy.

ever, hypersensitivity syndrome occasionally develops in patients with a therapeutic plasma oxypurinol concentration [197]. In addition to plasma oxypurinol concentration, other factors probably contribute to the development of the syndrome.

Human herpes virus 6 (HHV 6) infection is recently attracted a great deal of attention as a possible cause of drug-induced hypersensitivity. Suzuki et al reported a case of allopurinol-induced hypersensitivity syndrome with dramatically increased anti-HHV 6 IgG antibodies. They also demonstrated the presence of HHV 6 in the skin of this patient using a polymerase chain reaction and *in situ* hybridization [198]. Thus, drug-induced hypersensitivity syndrome may not be a simple allergic reaction to drug. Further investigations regarding the relation of HHV 6 infection and drug-induced hypersensitivity syndrome may provide insight to the pathogenesis of allopurinol-induced hypersensitivity syndrome.

#### Therapy, prognosis, and prevention

Withdrawal of the drug and the prolonged administration of systemic steroids are beneficial for the hypersensitivity syndrome with renal involvement. Initial dose of steroid should be 1 to 2 mg/kg/day of methylprednisolone, with careful gradual tapering of steroids required in the majority of patients. The recovery time ranged from 1 week to 11 months. Mortality from this syndrome is high, with twenty-one of 80 patients died as a result of the syndrome [188]. In fulminant cases, such as acute renal failure complicating toxic epidermal necrosis or Stevens-Johnson syndrome, methylprednisolone 'pulse' therapy might be

beneficial. Patients with HHV 6 infection also require prednisolone therapy.

To prevent unnecessary morbidity and mortality due to the allopurinol hypersensitivity, Singer et al. [188] recommended the indications for allopurinol as follow: 1) tophaceous gout; 2) major uric acid overproduction (urinary excretion of more than 900 mg of uric acid/day on a diet with rigid purine restriction); 3) frequent gouty attacks unresponsive to prophylactic colchicines, when uricosuric agents cannot be used due to intolerance, lack of efficacy, renal insufficiency, or poor patient compliance; 4) recurrent uric acid renal calculi; 5) recurrent calcium oxalate renal calculi when associated with hyperuricosuria; or 6) prevention of acute urate nephropathy in patients receiving cytotoxic therapy for malignancies. The tumor lysis syndrome (TLS) has come under increased scrutiny with the more aggressive chemotherapeutic management of both hemopoietic and solid tumor malignancies. Because of the massive release of purine nucleotides, pretreatment with allopurinol often is inadequate to control the hyperuricemia and acute uric acid nephropathy develops [198a]. To overcome this deficiency of allopurinol protection, febuxostat, a more powerful xanthine oxidase inhibitor has been developed. However, in criticizing a recent clinical trial comparing febuxostat with allopurinol [198b], Gelber [198c] wrote "caution, however, needs to be exercised in as much as the reported frequency of adverse events leading to discontinuation of the drug occurred two and three times as often in the low-dose and high-dose febuxostat group, respectively, as in the allopurinol group". Rasburicase is a urate oxidase that converts uric acid to allantoin which is much more soluble thus precluding acute urate nephropathy in TLS [198d, h]. A combination of rasburicase and allopurinol has been successfully used in preventing hyperuricemia of TLS [198i]. While Rasburicase has been shown to be successful in preventing the hyperuricemia of TLS [198e, f, g] it should not be given to patients with G6PD deficiency, methemoglobinemia and history of anaphylaxis [198e]. Also, concern has been raised about the high immunogenicity of rasburicase and native uricase since antibodies to the drug occurred in 14% of patient in a clinical trial of TLS [198a]. There is disagreement regarding the value of allopurinol treatment for asymptomatic hyperuricemia, uncomplicated gout, and acute gouty attacks which Singer et al [188] consider counter-indicated while Kelley [199] advised

allopurinol therapy for asymptomatic hyperuricemia, but only when it is truly severe (serum uric acid level > 13 mg/dl and 24-hour urine excretion > 1, 100 mg). For the treatment of acute hyperuricemia with renal insufficiency Ronco and coworkers [198g] present compelling data supporting the use of rasburicase. The allopurinol hypersensitivity syndrome occurs most frequently when the drug is given with diuretics or in patients with renal insufficiency. CKD patients on allopurinol therapy should be closely monitored especially within

the first several weeks after initiating administration of the drug. If the AHS develops, allopurinol should be withdrawn but may be reintroduced using a gradually increasing dosage schedule [200]. Finally, patients at high risk for developing hyperuricemia should start the therapy with lower dose of allopurinol. Indications for chronic treatment of symptomatic gout in high risk patients using either rasburicase or febuxostat needs to be confirmed by clinical trials.

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