

Gold Nephropathy

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ABSTRACT

The early use of gold in medicine and dentistry dates back to the ancient Chinese and Egyptians. The discovery in 1890 that gold salts were toxic *in vitro* to tubercle bacilli led to the extensive treatment of tuberculosis with gold salts in the first three decades of this century. Eventually, gold therapy was extended to arthritis and lupus erythematosus, because of the belief that these diseases were forms of tuberculosis. Because of its beneficial effect particularly on active rheumatoid arthritis, chrysotherapy has remained one of the most widely used treatments of rheumatoid arthritis for the past half century. Toxicity of gold salts includes hypersensitivity reaction of skin and mucous membranes, bone marrow depression, and nephrotoxicity. The nephrotoxic clinical manifestations are renal insufficiency, proteinuria and hematuria, and the nephrotic syndrome. The pathologic changes are tubular degeneration, acute tubular necrosis or immune complex glomerulonephritis. The justification that any of these possible changes are the result of gold therapy rests clinically upon the time relationship of gold therapy and the renal symptoms, and pathologically upon the presence of gold inclusions (aurosomes) in proximal tubular epithelial cells. Aurosomes can at times be visualized by light microscopy, are usually seen by electron microscopy, and can be identified by microprobe analysis. Their pathology will be illustrated and pathogenic mechanisms discussed.

Introduction

Chrysotherapy has been one of the most widely used medications in the management of patients with rheumatoid arthritis for the past 50 years, despite a rather high incidence of side effects. Untoward reactions may occur early or late in the course of therapy. The incidence of toxic reaction

is most probably related to the total body concentration of gold, since only 40 percent of gold is excreted each week on a standard weekly dose, leading to a progressive increase in its body tissue stores. The most common toxic effects are those involving skin, mucous membranes, bone marrow, and the kidney. The nephrotoxic clinical and pathological manifestations

have been well documented. Proteinuria, hematuria, the nephrotic syndrome, and renal insufficiency are well recognized complications of gold therapy. The renal lesions associated with chrysotherapy include acute tubular necrosis, tubular degeneration, and immune complex glomerulonephritis. Similar lesions can be produced in experimental animals with gold salts. The pathogenesis of the tubular lesions seem to be a direct drug "toxicity" of gold ions, while the immune complex glomerulonephritis is an immunologically mediated drug toxicity.

The earliest use of gold in medicine and dentistry dates back to the ancient Egyptians and Chinese.²¹ The therapeutic use of gold in modern medicine was stimulated by the observation of Robert Koch of the adverse reaction of gold salts on the tubercle bacillus in 1890.⁸ Despite disappointing clinical results, gold was used in the treatment of tuberculosis, particularly in western Europe, until the late 1930's. Eventually gold therapy was extended to the treatment of arthritis and lupus erythematosus because of the belief of some that these diseases were forms of tuberculosis. The treatment of rheumatoid arthritis with gold, however, was first popularized by Jaques Forestier in the early 1930's.⁹ He reasoned that gold probably stimulated the defense mechanism of the body in tuberculosis and might behave similarly in rheumatoid arthritis.

Fifty years of use of gold in the management of rheumatoid arthritis has had a mixed acceptance. Despite a rather high incidence of side effects, some prognostically serious, chrysotherapy remains one of the most widely prescribed medications in the management of patients with rheumatoid arthritis.

Gold exists in monovalent and trivalent forms. All significant preparations are aureous (monovalent) salts in which gold is attached to sulfur. The strong affinity of monovalent gold for sulfur and the inhibitory affects of certain gold salts on

peruvic dehydrogenase suggest that the therapeutic effects of gold salts are due to inhibition of sulfhydryl-related enzymes.

The most commonly used gold compounds in the treatment of rheumatoid arthritis are aurothioglucose (Solganal) and gold sodium thiomalate (Myochrysin). Both compounds contain approximately 50 percent gold. Water soluble compounds are rapidly absorbed after intramuscular injection. Serum gold concentration peaks within two to four hours, after which it declines gradually. Ninety-two percent of gold in the blood is protein bound, of which 95 percent is present in the albumin fraction.¹⁰ Gold is widely distributed throughout the body.²⁰ The highest concentration of soluble compounds is found in the kidneys, while insoluble compounds are recovered in larger amounts from the reticulo-endothelial system. Gold compounds are selectively concentrated within the inflamed synovial tissue of active rheumatoid arthritis. Soluble gold compounds are excreted mainly by the kidney, while insoluble compounds are excreted in the bile. However, only 40 percent of administered gold is excreted each week during standard treatment; therefore, with weekly injections, the body stores increase progressively. Gold was found to persist in various tissues up to 23 years after chrysotherapy was stopped. In the past, unduly large doses of gold compounds used in the treatment of tuberculosis and later of rheumatoid arthritis resulted in a high incidence of severe toxic reactions.³ Untoward reactions to gold may occur early or later in the course of therapy. The incidence of toxic reactions to gold is unrelated to its plasma levels but is probably related to its total body concentration. The most common toxic effects of chrysotherapy are those involving the skin and the mucous membranes. Less common but more severe in their consequences are the hematologic and renal manifestations of gold toxicity.^{6, 13}

Renal symptoms of gold toxicity range from renal proteinuria and hematuria and the nephrotic syndrome^{13,14} to renal insufficiency and even fatal anuric failure.^{3,11} The renal lesions associated with chrysotherapy have been well documented. Large doses of gold salts produce acute tubular necrosis.³ The main lesion is confined to the proximal convoluted tubules. The evolution of the tubular lesion was extensively studied in experimental animals.^{12,17,18}

By light microscopy, in hematoxylin and eosin stained sections, the proximal tubular cells appear swollen and show areas of rarification or vacuolization in which at times small yellowish-brown, refractile, poorly defined granules can be recognized. These may be shown in light microscopic sections to be gold by a photochemical method described by Gilg,⁷ or recognized by their distinct morphologic structure by electron microscopy or identified by electron probe microanalysis (figure 1).

Gold deposits (aurosomes) of soluble gold compounds consist of electron dense granules, their projecting rod like and linear structure giving them a feathery appearance, whereas aurosomes produced by colloidal gold are made up of aggregates of spherical electron dense structures (figure 2).^{12,17,18,20}

The primary site of gold deposition in the kidney is the mitochondria of the proximal convoluted tubules. The damage to the mitochondria is proportional to the amount of gold injected. Accumulation of gold results in mitochondrial disruption and consequent degeneration and necrosis of the lining cells. The tubular basement membrane remains intact. The distal tubules become filled with cast of cellular debris and clumps of gold deposits.^{12,17,18}

The percentage of patients reported who develop proteinuria or the nephrotic syndrome during chrysotherapy varies from 0.2 to 10 percent. Although most patients presenting with proteinuria have

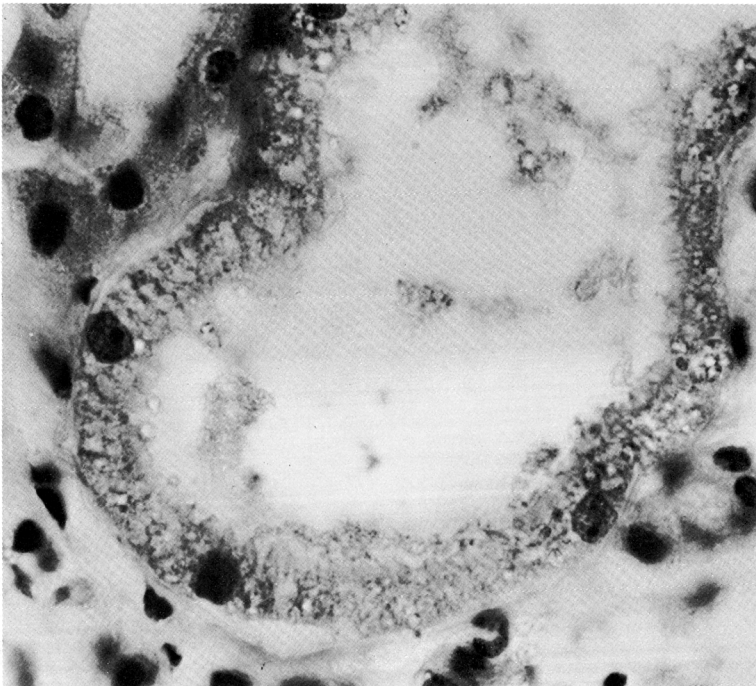
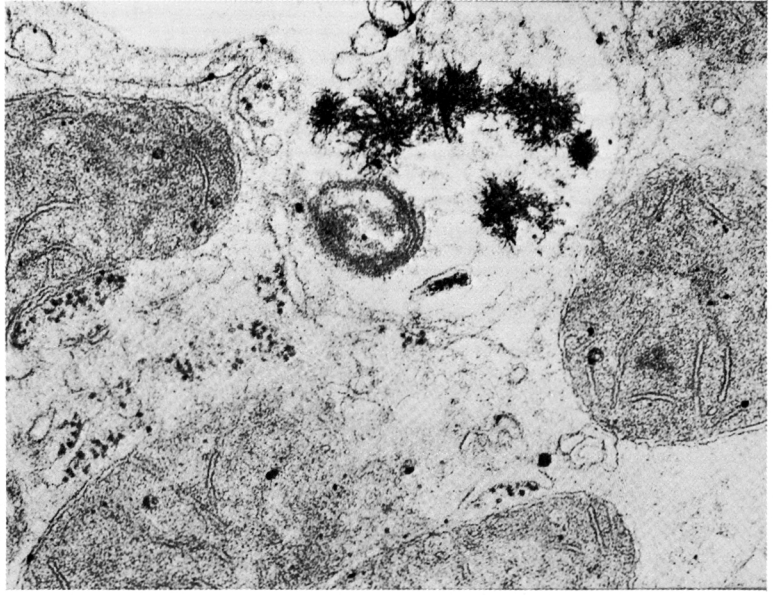


FIGURE 1. Light microscopic section of proximal convoluted tubule. The cytoplasm is vacuolated and shows poorly defined refractile granules. Hematoxylin and eosin $\times 630$ (AFIP 80-10684).

FIGURE 2. Electronmicrograph of a portion of proximal convoluted tubules, showing degenerating mitochondria and gold inclusions. $\times 10,800$ (AFIP 80-10685).



received a substantial amount of gold, proteinuria has been reported after as little as 10 mg of gold sodium thiomalate. The glomeruli in renal biopsies of these patients viewed by light microscopy may appear normal, or show minimal increase

in endocapillary cells, or show focal or diffuse thickening of capillary walls (figure 3). The thickened capillary walls in methenamine silver stained sections show basement membrane spiking and, in trichrome stained sections, granular

FIGURE 3. Light microscopic section of glomerulus showing focal thickening of capillary walls. Hematoxylin and eosin $\times 280$ (AFIP 80-10683).

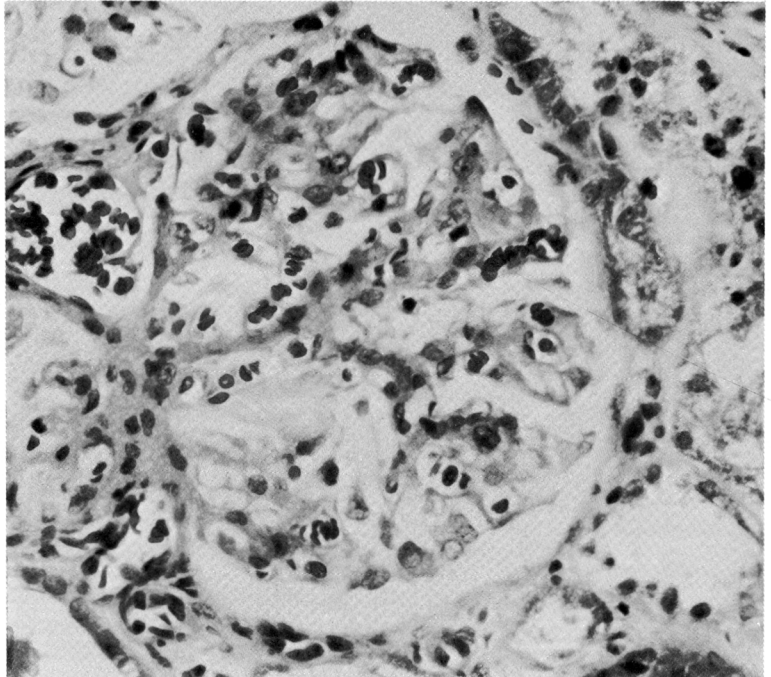




FIGURE 4. Electron micrograph of a portion of glomerulus. Widely spaced subepithelial deposits with early basement membrane spiking is present. There is diffuse effacement of epithelial cell foot processes. $\times 3700$ (AFIP 80-10686).

magenta red deposits. By electron microscopy, electron dense deposits are seen on the epithelial surface of the glomerular capillary basement membranes (figure 4).^{2,4} Depending on the time interval between the first gold injection, the appearance of proteinuria, and the day of the kidney biopsy, the deposits may be few and the underlying basement membrane intact, or there may be basement membrane spiking or finely incorporation of deposits into the thickened remodeled basement membrane. Thus, all stages of membranous glomerulonephritis may be seen in gold glomerulonephropathy except that in the latter, irrespective of the stage, the number of deposits varies and a number of loops may be totally free of deposits.¹⁶ If properly searched for, auroosomes will be found in proximal tubular epithelium and rarely, visceral glomerular epithelial cells.^{18,19} Fluorescence microscopy shows the deposits to contain IgG and complement in a granular pattern along the glomerular capillary basement membrane. If gold therapy is discontinued soon after the proteinuria appears, and the glomerular lesions are early and

segmental, the prognosis is good. First, there is progressive and, finally, complete disappearance of proteinuria, followed by loss of deposits and restoration of glomerular capillary basement membrane as revealed by repeated biopsies.⁴

The tubular damage in the course of chrysotherapy is caused by the deposition of gold inside mitochondria, which appear to be the target organelles of injury.^{17,23} The exact pathogenesis of mitochondrial injury is not known, but gold probably enters the mitochondria in ionic form, since it can be seen in mitochondria which have an intact outer membrane. It is possible that they become overloaded by large numbers of gold ions, which interfere with their normal functions of selective binding and unbinding of cations.

Several hypothesis have been proposed concerning the pathogenesis of the immune complex glomerulonephritis related to gold therapy. It was originally suggested that gold acts as a hapten when combined with tissue proteins; however, up to date it has never been detected within the immune deposits. It has been

suggested that the deposits may be complexes of rheumatoid autoantibodies and that gold may facilitate the glomerular deposition.¹⁵ Another hypothesis, recently widely supported, is that the gold-damaged tubules liberate autoantigens, which are then deposited with antibody in the glomeruli.¹¹ Finally, there is growing evidence that immunologically mediated drug toxicity may be controlled by genes of the histocompatibility system. It is known that patients with rheumatoid arthritis may have HLA-88 or HLA-DRw3 antigens. It was recently reported that DRw3 positive patients with rheumatoid arthritis have a high titer of rheumatoid factor and treatment with aurothiomalate¹ results in a high incidence of proteinuria.²²

The diagnosis of gold induced membranous glomerulonephritis is justified only when there is a relationship between gold therapy and renal symptoms, and auroosomes are found in the proximal convoluted tubules. At times they are difficult to detect in conventionally stained electron microscopic sections, but they are relatively easily visualised in unsmicated unstained sections.⁵

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