



Penicillamine

Updated: September 28, 2014.

OVERVIEW

Introduction

Penicillamine is a chelating agent used to decrease copper stores in Wilson disease, which also has immunomodulatory activity in rheumatic diseases such as rheumatoid arthritis, scleroderma and systemic lupus erythematosus. Penicillamine is capable of causing hypersensitivity reactions, some of which are accompanied by liver injury which is typically cholestatic.

Background

Penicillamine (pen" i sil' a meen) is the d-isomer of dimethylcysteine, a breakdown product of penicillin, which was originally isolated from the urine of patients with liver disease receiving penicillin. It was later found to have chelating properties against copper and used in Wilson disease. Penicillamine was also found to lower levels of immune complexes, which led to its use in several rheumatic and immune disorders such as rheumatoid arthritis, scleroderma, systemic lupus erythematosus and primary biliary cirrhosis. Penicillamine was approved for use in Wilson disease in 1960 and is still widely used for that rare indication. The use of penicillamine for rheumatic disorders has decreased markedly with the availability of more modern, potent and less toxic agents. Penicillamine is available in generic forms and under the brand names of Cuprimine and Depen in capsules of 125 and 250 mg and tablets of 250 mg. The usual dose is 250 mg four times daily, increasing based upon effect and tolerance to a maximum of 2 grams daily. Lower doses were used in rheumatic diseases. Common side effects include gastrointestinal upset, metallic taste, bone marrow suppression, rash, pruritus, induction of autoimmune diseases and drug fever.

Hepatotoxicity

Penicillamine has been linked to a characteristic pattern of liver injury arising 1 to 6 weeks after starting therapy, with a distinctly cholestatic pattern of serum enzyme elevations. The jaundice due to penicillamine can be severe and prolonged and result in protracted, symptomatic cholestasis, but most cases are self-limited. Immunoallergic manifestations of rash, fever and eosinophilia are common, but not invariable. Other toxicities of penicillamine therapy such as bone marrow suppression, neutropenia and severe dermatologic features can accompany the hepatic injury. Furthermore, in instances with severe nonhepatic penicillamine toxicities, some degree of hepatic involvement such as mild-to-moderate serum enzyme elevations may occur. Long term toxicities of penicillamine include induction of autoimmune conditions (glomerulonephritis, pneumonitis, lupus-like syndrome) that may be accompanied by autoantibody formation, but autoimmune hepatitis-like syndromes have not been reported.

Mechanism of Injury

The liver injury caused by penicillamine appears to be due to hypersensitivity as shown by its brief latency and the frequency of immunoallergic symptoms and signs. Susceptibility to penicillamine hypersensitivity has been linked to HLA DR3, sulphoxidation status and previous gold allergy, but these factors have not been specifically linked to hepatotoxicity from penicillamine.

Outcome and Management

The hepatotoxicity of penicillamine is typically self-limited, although recovery may be delayed. However, there have been several instances of progressive cholestasis resulting in death or need for liver transplantation arising after acute, severe cholestatic liver injury due to penicillamine. While the pathology of these cases has stressed the chronic cholestatic features and progressive fibrosis, there is little information on bile duct injury and loss. Nevertheless, these instances probably represent vanishing bile duct syndrome. While ursodiol and corticosteroids are often used in patients with prolonged cholestasis after hepatotoxicity from penicillamine (and other drugs), there is little evidence that they are beneficial. There may be cross reactivity between penicillamine hypersensitivity and allergic responses to penicillin, but this is not invariable. Nevertheless, caution should be employed in use of penicillins in patients with severe penicillamine hypersensitivity.

Drug Class: [Antirheumatic Agents](#); [Chelating Agents](#), [Wilson Disease Agents](#)

Other Drugs in the Subclass, Wilson Disease: [Dimercaprol](#), [Trientine](#), [Zinc](#)

CASE REPORT

Case 1. Immunoallergic hepatitis due to penicillamine.

[Modified from: Rau R, Weber S, Böni A. [Allergic-toxic liver damage due to D-penicillamine]. Schweiz Med Wochenschr 1972; 102: 1226-8. German. [PubMed Citation](#)]

A 58 year old woman with scleroderma accompanied by arthritis, Raynaud's phenomenon, skin tightening over the face and hands, and lung involvement was placed on penicillamine in a dose of 1.8 g daily. Three weeks later she developed fever and generalized maculopapular rash, followed two days later by dark urine and jaundice. All medications were stopped. She had no previous history of liver disease or drug allergies and did not drink alcohol. Over-the-counter medications included vitamins only. Laboratory testing showed serum bilirubin of 7.4 mg/dL, mild ALT elevations (90 U/L), and marked increases in alkaline phosphatase levels (Table). She had mild eosinophilia (5%) and leukocytosis. Over the next few days, fever and rash resolved and 3 weeks after onset, laboratory tests had returned to normal or near normal.

Key Points

Medication:	Penicillamine (1.8 g daily)
Pattern:	Cholestatic (R=0.3)
Severity:	2+ (jaundice, not hospitalized)
Latency:	3 weeks
Recovery:	3 weeks
Other medications:	Vitamin B6

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (BEU/L)	Bilirubin (mg/dL)	Other
Pre	Pre	19	1.1	<1.0	
14 days	0	Worsening fever over 4 days followed by rash and jaundice			
24 days	0	90	33.4	7.4	5% eosinophils
26 days	2 days	43	32.4	5.8	
33 days	9 days	21	14.5	1.6	
39 days	15 days	9	7.8	0.9	
Normal Values		<30	<4.5	<1.2	

Comment

An early report without viral serology to exclude acute viral hepatitis or modern imaging to exclude biliary obstruction, but the progression of symptoms and laboratory test abnormalities were very typical of drug induced hypersensitivity and liver injury. The latency to onset of symptoms of fever, rash and malaise was 2 to 3 weeks, with jaundice appearing soon thereafter. Immunoallergic symptoms and signs were present and the pattern of serum enzyme elevations was distinctly cholestatic, features that are typical of penicillamine induced liver injury. The features of hypersensitivity usually resolve within a week of stopping therapy, whereas the cholestasis and jaundice are slower to improve. Corticosteroids appear to improve the immunoallergic symptoms and signs promptly, but their effect on the liver injury is less clear.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Penicillamine – Generic, Cuprimine®

DRUG CLASS

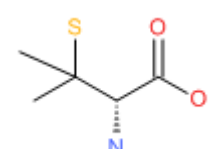
Antirheumatic Agents

Chelating Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Penicillamine	52-67-5	C ₅ H ₁₁ N-O ₂ S	

ANNOTATED BIBLIOGRAPHY

References updated: 28 September 2014

Zimmerman HJ. Drugs used in rheumatic diseases: penicillamine. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 542.

(Expert review of hepatotoxicity published in 1999; mentions that there have been 18 published cases of jaundice due to penicillamine, almost all cholestatic with latency of 2-4 weeks and features of hypersensitivity).

Byrns MC, Penning TM. Penicillamine. Environmental toxicology: carcinogens and heavy metals. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, p. 1875.

(Textbook of pharmacology and therapeutics).

Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. Am J Med 1956; 21: 487-95. PubMed PMID: 13362281.

(Initial studies on efficacy of oral penicillamine [β,β -dimethyl cysteine, a monothiol] in inducing cupruresis in Wilson disease and lack of effect of cysteine and methionine; no toxic reactions were observed).

Walshe JM. Toxic reaction to penicillamine in patients with Wilson's disease. Postgrad Med J 1968; Oct Suppl: 6-8. PubMed PMID: 5706614.

(Summary of side effects of penicillamine representing 126 patient years of use in Wilson disease; important toxicities included nephrotic syndrome, lupus-like syndrome, thrombocytopenia, urticaria and one case of a 9 year old with urticaria, fever, malaise and jaundice, with positive rechallenge and inability to tolerate the drug and resultant death from Wilson disease).

Sternlieb I, Scheinberg IH. Prevention of Wilson's disease in asymptomatic patients. N Engl J Med 1968; 278: 352-9. PubMed PMID: 5635646.

(Among 42 asymptomatic persons who were diagnosed with Wilson disease and treated with penicillamine for up to 8 years, none developed symptomatic disease).

Rau R, Weber S, Böni A. [Allergic-toxic liver damage due to D-penicillamine]. Schweiz Med Wochenschr 1972; 102: 1226-8. German. PubMed PMID: 5055042.

(58 year old with scleroderma developed fever, rash and jaundice 2-3 weeks after starting penicillamine with bilirubin 7.4 mg/dL, ALT 90 U/L, Alk P 8 times ULN, with resolution within 2 weeks of stopping: see Case 1).

Walshe JM. Copper chelation in patients with Wilson's disease. A comparison of penicillamine and triethylene tetramine dihydrochloride. Q J Med 1973; 42: 441-52. PubMed PMID: 4728043.

(Trientine induced a cupruresis in 18 patients with Wilson disease, which was less than with penicillamine, but was substantial particularly in patients who had never been treated, suggesting that it might be an alternative for patients intolerant to penicillamine therapy).

Siegmund H. [Intrahepatic cholestasis after therapy with d-penicillamine and indomethacin]. Med Welt 1976; 27: 172-4. German. Not in PubMed

(38 year old woman with rheumatoid arthritis developed jaundice 5 weeks after starting penicillamine and indomethacin [bilirubin 5.5 mg/dL, ALT 120 U/L, Alk P 10 times ULN], jaundice resolving within 4 weeks of stopping both drugs, but Alk P remained high).

Sacher M, Thaler H. Toxic hepatitis after therapeutic doses of benorylate and D-penicillamine. Lancet 1977; 1: 481-2. PubMed PMID: 65582.

(13 year old girl with rheumatoid arthritis developed jaundice 5 months after starting penicillamine with recovery in 3 months; no specifics given; benorylate is an ester of acetylsalicylic acid and acetaminophen).

Barzilai D, Dickstein G, Enat R, Bassan H, Lichtig C, Gellei B. Case report: cholestatic jaundice caused by D-penicillamine. *Ann Rheum Dis* 1978; 37: 98-100. PubMed PMID: 629612.

(56 year old man with rheumatoid arthritis developed jaundice and pruritus 4 weeks after starting penicillamine [bilirubin 15 mg/dL, ALT 203 U/L, Alk P 3 times ULN]; underwent laparotomy, with subsequent rise in bilirubin to 88 mg/dL, renal failure and death).

McLeod BD, Kinsella TD. Cholestasis associated with D-penicillamine for rheumatoid arthritis. *Can Med Assoc J* 1979; 120: 965-6. PubMed PMID: 436073.

(41 year old woman with rheumatoid arthritis developed jaundice 3 weeks after starting penicillamine [bilirubin 3.3 mg/dL, AST 117 U/L, Alk P 1132 U/L], jaundice resolving within 2 weeks and enzyme elevations within 11 weeks of stopping).

Crickx L, Leger JM, Auquier L. [Granulomatous hepatitis and parotiditis induced by d-penicillamine in a case of rheumatoid arthritis]. *Nouv Presse Med* 1979; 8: 212. French. PubMed PMID: 554085.

(50 year old woman with rheumatoid arthritis developed cholestatic jaundice and parotiditis soon after starting penicillamine, liver and parotid biopsies demonstrating granulomas; no specifics given).

Jaffee IA. Penicillamine in rheumatoid arthritis: clinical pharmacology and biochemical properties. *Scand J Rheumatol* 1979; Suppl 28: 58-64. PubMed PMID: 146201.

(Reports that penicillamine leads to improvements in stiffness and pain in rheumatoid arthritis after 8-12 weeks of therapy and can induce a variety of autoimmune conditions including pemphigus, myasthenia, glomerulonephritis, polymyositis, hemolytic anemia, lupus, Sjögren's syndrome and thrombocytopenic purpura).

Baum J. The use of penicillamine in the treatment of rheumatoid arthritis and scleroderma. *Scand J Rheumatol* 1979; Suppl 28: 65-70. PubMed PMID: 377472.

(In review of literature on 1190 patients treated with penicillamine for 4-12 months, beneficial response rates averaged 62%, but significant side effects found in 37% of patients).

Hill HFH. Penicillamine in rheumatoid arthritis: adverse effects. *Scand J Rheumatol* 1979; Suppl 28: 94-9. PubMed PMID: 156393.

(Review of skin adverse events and fatalities due to penicillamine, deaths largely due to bone marrow toxicity; no mention of hepatotoxicity or cholestasis).

Wollheim FA, Lindström CG. Liver abnormalities in penicillamine treated rheumatoid arthritis. *Scand J Rheumatol* 1979; Suppl 28: 100-7. PubMed PMID: 287188.

(Among 99 patients followed prospectively during penicillamine therapy, 6 developed serum enzyme abnormalities without jaundice, reversible within weeks of stopping in all, not always recurring with restarting penicillamine at lower doses).

Rosenbaum J, Katz WA, Schumacher HR. Hepatotoxicity associated with use of D-penicillamine in rheumatoid arthritis. *Ann Rheum Dis* 1980; 39: 152. PubMed PMID: 7387219.

(Two patients with rheumatoid arthritis with penicillamine hepatotoxicity; 43 year old woman developed enzyme elevations [normal bilirubin, AST 440 U/L, Alk P ~2 times ULN] without symptoms 2 months after starting penicillamine, resolving rapidly on stopping and recurring with rechallenge; 60 year old man developed jaundice 2 weeks after starting penicillamine [bilirubin 2.2 mg/dL, AST 128 U/L, Alk P 8 times ULN], resolving slowly over next 9 months).

- Seibold JR, Lynch CJ, Medsger TA. Cholestasis associated with D-penicillamine therapy: case report and review of the literature. *Arthritis Rheum* 1981; 24: 554-6. PubMed PMID: 7213433.
- (26 year old woman with lupus developed fever and rash after 10 days of penicillamine which improved on stopping, but recurred after a single tablet of penicillamine with fever, rash, arthritis followed by jaundice [bilirubin 7.9 mg/dL, ALT 315 U/L, Alk P 358 U/L], resolving within 7 weeks).*
- Jensen OH. [Penicillamine induced liver involvement]. *Ugeskr Laeger* 1981; 143: 3471-2. Danish. PubMed PMID: 7336507.
- (64 year old man with rheumatoid arthritis developed jaundice after a year of penicillamine therapy and had sudden worsening when it was inadvertently restarted with fever and jaundice [bilirubin ~3.0 mg/dL, Alk P and AST 3 times ULN], symptoms resolving rapidly on stopping and liver tests returning to normal within 3 months).*
- Multz CV. Cholestatic hepatitis caused by penicillamine. *JAMA* 1981; 246: 674-5. PubMed PMID: 7253120.
- (53 year old woman with rheumatoid arthritis developed jaundice 4 weeks after starting penicillamine [bilirubin 6.4 mg/dL, AST 390 U/L, Alk P 820 U/L], jaundice resolving in 2 weeks; remission in arthritis during period of jaundice).*
- Job-Deslandre C, Delrieu F, Rondier J, Guedri M, Delbarre F. Hepatite cholestatique et anticorps anti-DNA induits par la d-penicillamine. *Nouv Presse Med* 1982; 11: 2356-7. PubMed PMID: 6981100.
- (33 year old with rheumatoid arthritis treated with penicillamine for 4 years developed jaundice and lupus-like syndrome [bilirubin not given, ALT 61 U/L, Alk P 3.6 times ULN, ANA 1:500], liver abnormalities resolving within 2 months, but ANA remaining positive).*
- Grauer JL, Fonteille J, Zarski JP, Gintz B, Phelip X, Cabanel G. [Erythema nodosum and cholestatic hepatitis during treatment with D-penicillamine]. *Presse Med* 1983; 12:1997. French. PubMed PMID: 6225106.
- (62 year old with rheumatoid arthritis developed fever 20 days after starting penicillamine, resolving on stopping and reappearing 2 months after restarting along with rash, but no jaundice [bilirubin not given, AST 1.5 times, Alk P 4.5 times ULN], resolving within 2 weeks of stopping again).*
- Emery P, Panayi GS, Huston G, Welsh KI, Mitchell SC, Shah RR, Idle JR, et al. D-penicillamine induced toxicity in rheumatoid arthritis : the role of sulphoxidation status and HLA-DR3. *J Rheumatol* 1984; 11: 626-32. PubMed PMID: 6334741.
- (Among 66 patients with rheumatoid arthritis treated with penicillamine, adverse events [largely renal, bone marrow and skin toxicities] were more common in those with low sulphoxidation indices [60%] than in those with normal values [17%], and with HLA DR3 [60% vs 29%], without interaction of the two predictive factors).*
- Gefel D, Hrats N, Lijovetsky G, Eliakim M. Cholestatic jaundice associated with d-penicillamine therapy. *Scand J Rheumatol* 1985; 14: 303-6. PubMed PMID: 4048879.
- (35 year old man with cystinuria developed fever and rash 16 days after starting penicillamine followed by jaundice [peak bilirubin 14.9 mg/dL, ALT 149 U/L, Alk P 553 U/L], biopsy showing intrahepatic cholestasis; prednisone was started when bilirubin worsened; jaundice resolved within 3 months and abnormal Alk P within 9 months of stopping).*
- Devogelaer JP, Huaux JP, Coche E, Rahier J, Nagant de Deuxchaisnes C. A case of cholestatic hepatitis associated with D-penicillamine therapy for rheumatoid arthritis. *Int J Clin Pharmacol Res* 1985; 5: 35-8. PubMed PMID: 3997313.
- (72 year old man with rheumatoid arthritis developed pruritus and jaundice 1 month after starting penicillamine [bilirubin 16.2 mg/dL, ALT 227 U/L, Alk P 290 U/L], jaundice resolving within 3 weeks and serum enzymes within 6 weeks of stopping).*

- Abadia R, Jammet P, Christoforov B, Cremer GA. [Hepatotoxicity of drugs commonly used in rheumatology]. *Ann Med Interne (Paris)* 1985; 136: 590-600. PubMed PMID: 2868682.
- (Review of hepatotoxicity of rheumatologic agents; mentions 16 cases of penicillamine induced liver injury, typically with immunoallergic features and cholestatic pattern with resolution in 2-4 weeks, recurrence after reexposure in 5 instances; one fatality).*
- Kumar A, Bhat A, Gupta DK, Goel A, Malaviya AN. D-penicillamine-induced acute hypersensitivity pneumonitis and cholestatic hepatitis in a patient with rheumatoid arthritis. *Clin Exp Rheumatol* 1985; 3: 337-9. PubMed PMID: 4085166.
- (45 year old woman with rheumatoid arthritis developed rash, fever and hypersensitivity pneumonitis 10 days after starting penicillamine, responding to prednisone therapy but with subsequent jaundice [peak bilirubin 30 mg/dL, ALT 300 U/L, Alk P 5 times ULN], resolving within 4 weeks of stopping; recurrence of dyspnea and jaundice after unintentional rechallenge).*
- Choudhuri G, Tandon RK. D-penicillamine induced cholestatic jaundice. *J Assoc Phys India* 1986; 34: 299-300. PubMed PMID: 3759835.
- (45 year old woman with rheumatoid arthritis developed rash, fever and dyspnea within 2 weeks of starting penicillamine [initial bilirubin 7.0 mg/dL, ALT 200 U/L, Alk P 5 times ULN]; allergic alveolitis responding rapidly to prednisone, but bilirubin rising to 30 mg/dL; positive rechallenge; appears to be same patient as described by Kumar [1985]).*
- Roux H, Bonnefoy-Cudraz M, Antipoff GM. [Liver complications caused by D-penicillamine. Apropos of a case]. *Rev Rhum Mal Osteoartic* 1986; 53: 21-3. French. PubMed PMID: 3704507.
- (60 year old woman with rheumatoid arthritis developed rash and pruritus followed by jaundice 6 weeks after starting penicillamine [bilirubin 8.2 mg/dL, ALT 61 U/L, Alk P 2158 U/L, 14% eosinophilia], resolving slowly upon stopping).*
- Scheinberg IH, Jaffe ME, Sternlieb I. The use of trientine in preventing the effects of interrupting penicillamine therapy in Wilson's disease. *N Engl J Med* 1987; 317: 209-13. PubMed PMID: 3600712.
- Cooperative Systemic Studies of Rheumatic Disease Group. Toxicity of longterm low dose D-penicillamine therapy in rheumatoid arthritis. *J Rheumatol* 1987; 14: 67-73. PubMed PMID: 2952797.
- (Among 148 patients with rheumatoid arthritis continued on long term penicillamine, side effects included rash, gastrointestinal upset, proteinuria, bone marrow suppression, myasthenia, myositis, drug fever and pemphigus; no late hepatotoxicity).*
- Bernelot Moens HJ, Ament BJ, Feltkamp BW, van der Korst JK. Longterm followup of treatment with D-penicillamine for rheumatoid arthritis: effectivity and toxicity in relation to HLA antigens. *J Rheumatol* 1987; 14: 1115-9. PubMed PMID: 3437418.
- (HLA testing done on 86 patients with rheumatoid arthritis started on penicillamine including 22 on long term [5-7 years] therapy; HLA-DR4 was associated with thrombocytopenia [94% vs 67%] and HLA-B8/DR3 with proteinuria [60% vs 9%], but no association with effectiveness; no cases of hepatotoxicity).*
- Berbis P, Fabre JF, Privat Y. [Cholestatic hepatitis: a rare complication of the treatment with D. penicillamine]. *Ann Dermatol Venereol* 1987; 114: 377-9. French. PubMed PMID: 3605968.
- (22 year old woman with scleroderma developed fever, rash, and weakness followed by jaundice 10 days after starting penicillamine [bilirubin 1.5 mg/dL, ALT 381 U/L, Alk P 409 U/L with mild eosinophilia], resolving within 3 weeks of stopping).*
- Guerrero Navarro L, Molina Lorente E, Mur Villacampa M, Revillo Pinilla P. [Cholestatic hepatitis caused by D-penicillamine]. *Rev Esp Enferm Apar Dig* 1988; 73: 221. Spanish. PubMed PMID: 3375535.

- (61 year old man developed fever, rash, pruritus and jaundice 3 days after starting penicillamine [peak bilirubin 10.6 mg/dL, ALT 198 U/L, Alk P 336 U/L], resolving within 2 weeks).
- Fishel B, Tishler M, Caspi D, Yaron M. Fatal aplastic anaemia and liver toxicity caused by d-penicillamine treatment of rheumatoid arthritis. *Ann Rheum Dis* 1989; 48: 609-10. PubMed PMID: 2774703.
- (65 year old woman with rheumatoid arthritis developed thrombocytopenia 3 months after starting penicillamine [platelet count 10,000/ μ L, white cell count 3000/ μ L, hemoglobin 6.7 gm/dL] and subsequently developed jaundice [bilirubin 10.0 mg/dL, AST 80 U/L, Alk P 120 U/L], dying 17 days later with bone marrow, renal and hepatic failure).
- Jacobs JW, Van der Weide FR, Kruijsen MW. Fatal cholestatic hepatitis caused by D-penicillamine. *Br J Rheumatol* 1994; 33: 770-3. PubMed PMID: 8055207.
- (37 year old woman with rheumatoid arthritis developed fever, granulocytopenia and jaundice 10 days after starting penicillamine [without rash or eosinophilia], with intrahepatic cholestasis on liver biopsy and subsequent persistent jaundice and cholestasis and death from sepsis 14 months later).
- Barthel HR, Hiepe F. [Lupus erythematosus and liver diseases]. *Dtsch Med Wochenschr* 1995; 120: 1253-7. German. PubMed PMID: 7671785.
- (Review of liver abnormalities in lupus erythematosus; penicillamine can induce a lupus-like syndrome which resolves when the drug is stopped, although ANA positivity may persist).
- Harders H, Cohnen E. Preparation of and clinical experiences with trien for the treatment of Wilson's disease in absolute intolerance of D-penicillamine. *Proc R Soc Med* 1997; Supple 3: 10-2. PubMed PMID: 122652.
- (28 year old woman who was intolerant to penicillamine was successfully treated with trientine prepared by an improved method, with prompt cupruresis and improvement in neurologic symptoms).
- Chalasanani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; 135: 1924-34. PubMed PMID: 18955056.
- (Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to penicillamine).
- Roberts EA, Schilsky ML, AASLD. Diagnosis and treatment of Wilson disease: an update. *Hepatology* 2008; 47: 2089-111. PubMed PMID: 18506894.
- (Thorough review of the cause, natural history, diagnosis and treatment of Wilson disease with specific recommendations for use of penicillamine, trientine and zinc).
- Walshe JM. The conquest of Wilson's disease. *Brain* 2009; 132 (Pt 8): 2289-95. PubMed PMID: 19596747.
- (History of the initial description of Wilson disease, its link to copper accumulation, and therapies several of which were developed by the author).
- Weiss KH, Stremmel W. Evolving perspectives in Wilson disease diagnosis: treatment and monitoring. *Curr Gastroenterol Rep* 2012; 14: 1-7. PubMed PMID: 22083169.
- (Review of the diagnosis and management of Wilson disease, including the role of genetic testing and the choice of medical therapies).
- Weiss KH, Thurik F, Gotthardt DN, Schäfer M, Teufel U, Wiegand F, Merle U, et al.; EUROWILSON Consortium. Efficacy and safety of oral chelators in treatment of patients with Wilson disease. *Clin Gastroenterol Hepatol* 2013; 11: 1028-35. PubMed PMID: 23542331.

(Retrospective analysis of 380 patients with Wilson disease from referral centers in Germany and Austria, including 141 who were treated with trientine and 326 with penicillamine, found higher rate of improvement with penicillamine, but also higher rate of adverse events leading to discontinuation [29% vs 7%], although there were no therapy related deaths; reasons for discontinuation in the trientine group included arthralgias, gastrointestinal upset, myalgias, leukopenia, rash, lupus erythematosus and increase in ANA titers; no mention of ALT elevations or hepatotoxicity).