GOUT: MANY DISEASES WITH A COMMON EXPRESSION

I. Clinical Features and Epidemiology

Case 1. [redacted] [redacted]

This 39 WM was admitted for the final time on [redacted]-63, for peritoneal dialysis because of chronic tophaceous gout present since age 8. For the previous 2 years, he had experienced almost continuous attacks of acute gouty arthritis and had maintained elevated serum uric acid levels in the range of 8-14 mg%. Little or no effect on his clinical disease or serum uric acid levels had been produced by maximum medical therapy (800 mg of sulfinpyrazole, 3 grams of probenecid, 300 mg of phenylbutazone, alkalinizing agents and 0.5-2.0 mg of colchicine daily). Blood urea nitrogen had gradually increased above normal and ranged from 50 mg% down to 24 mg% on admission.

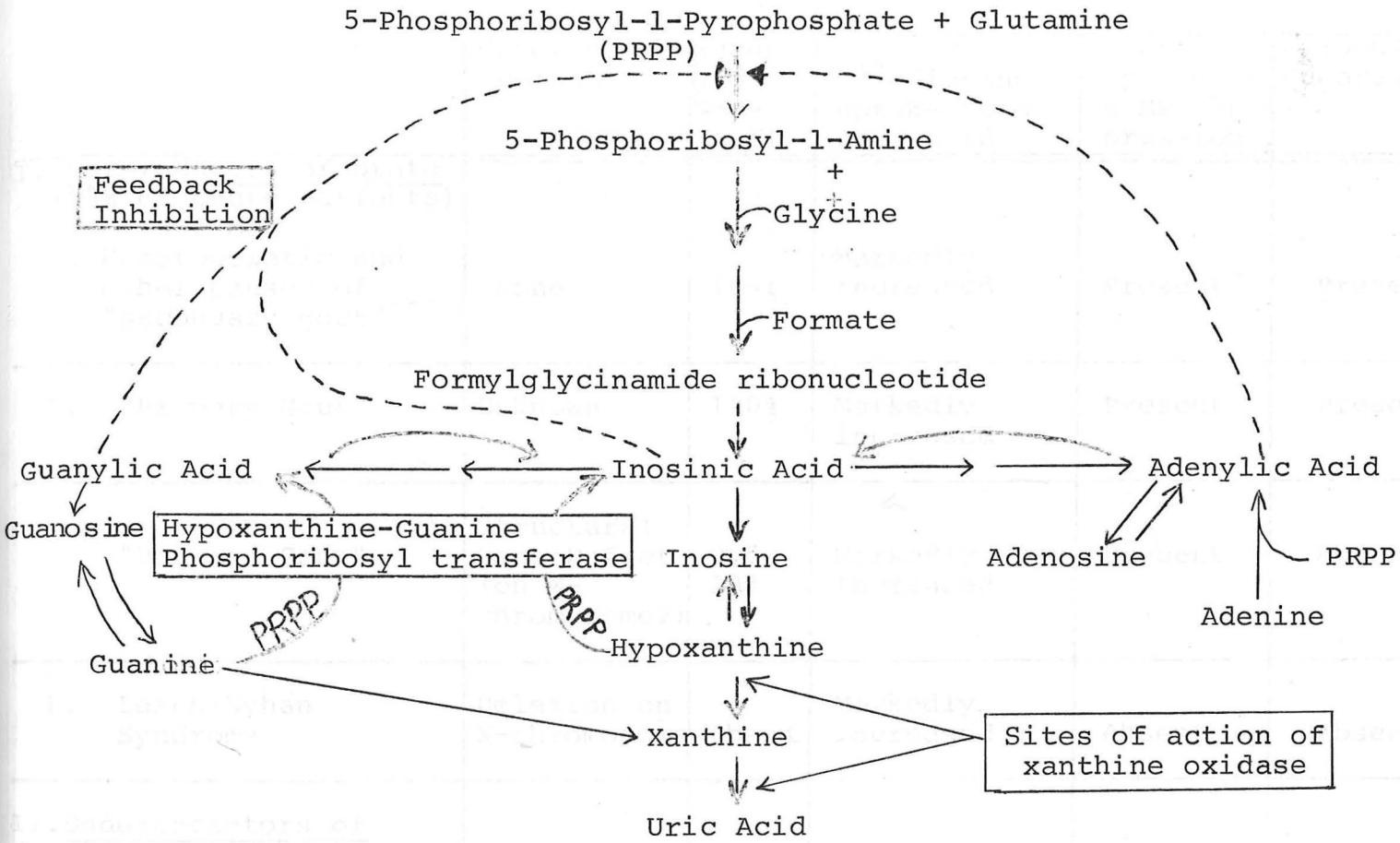
It was hoped that improved response to maximum uricosuric therapy would follow the dialysis procedure. Unfortunately, the patient developed pseudomonas peritonitis on the third day of peritoneal dialysis, responded poorly to antibiotics and died.

Table I. Epidemiology of Gout and Hyperuricemia (Ref. 1, 2)

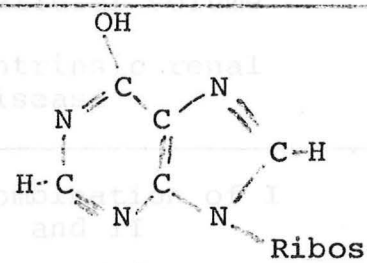
1.	Peak age of new gouty attack	40 years
2.	Population fraction with hyperuricemia >7 mg% (males 9.2%, females 0.4%)	4.8%
3.	Population fraction having had one or more attacks of acute gout by age 58	1.5
4.	Likelihood of acute gouty attacks based on serum uric acid level	
	6.0-6.9 mg%	1.8
	7.0-7.9	11.8
	8.0 or above	36.0
5.	Fraction of acute attack patients who had had podagra in at least one attack	84.0
6.	Impaired renal function (Talbott)	25.0
	urinary calculi if hyperuricemic	11.0
	if gouty arthritis	12.0
7.	Hyperuricemia more frequent in persons with higher hemoglobin levels and larger body build. Its frequency is <u>not</u> increased with diabetes.	

<u>The Unitary Concept of Gout</u>. Regardless of the many possible causes of hyperuricemia, the common clinical expression of the gouty attack depends on the local precipitation of urate. Influx of PMN's bring phagocytosis and release enzymes which produce pain and inflammation. Elimination of PMN's blocks this effect of local urate crystals (Ref. 49) and prevention of PMN lysosomal enzyme release by colchicine also blocks the gouty attack (Ref.58-62).

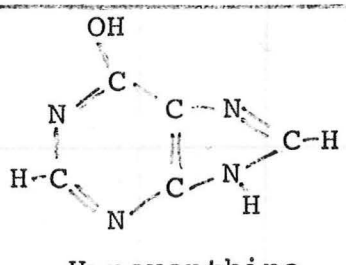
PURINE BIOSYNTHESIS AND INTERCONVERSIONS



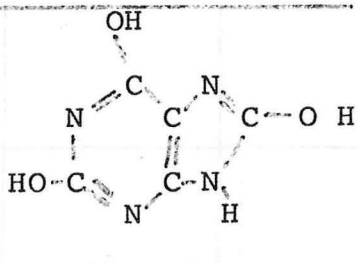
The exciting new discoveries of the past two years concern an important enzyme pathway which enhances the feedback regulation of uric acid synthesis (indicated above by dotted lines). At the terminal portion of the chain of enzymes responsible for uric acid formation, an enzyme reconverts guanine and hypoxanthine back into earlier forms which in turn suppress new purine synthesis when present in sufficient concentration. This enzyme, hypoxanthine-guanine phosphoribosyltransferase (HGPRT), has been shown to be markedly reduced in some patients with gout and absent in a congenital neurological disorder of children associated with hyperuricemia.



Inosinic Acid



Hypoxanthine



Uric Acid

Table II. Metabolic Classification of Hyperuricemia
(Ref. 3-48)

	Genetic Defect	HGPR Transferase (% of Normal)	De Novo Purine Synthesis		
			C^{14}-Glycine uptake into uric acid	Azathioprine or 6-MP Suppression	Allopurinol Suppression
I. Overproducers of urate (65% of gouty patients) (600 mg)					
A. Hematopoietic and other causes of "secondary gout"	None	100%	Markedly Increased	Present	Present
B. "Primary Gout"	Unknown	100%	Markedly Increased	Present	Present
C. "Primary Gout"	Structural Gene Defect (on X-chromosome?)	0.5-10%	Markedly Increased	Present	Absent
D. Lesch-Nyhan Syndrome	Deletion on X-chromosome	Absent	Markedly Increased	Absent	Absent
II. Underexcretors of urate (260 mg) (35% of patients)					
Lactic acidosis Ketoacidosis Hyperparathyroidism Diuretic or other acquired contraction of extracellular volume Intrinsic renal disease	Unknown or None	100%	Normal	Present	May or may not be present (Absent in extensive tophaceous gout)
III. Combination of I and II					

Conclusion: Overproducers of uric acid representing about 65% of all cases of gout are a heterogeneous group who have different genetic abnormalities which are phenotypically expressed as gout. The remaining gout patients may be genetically normal as far as purine biosynthesis is concerned.

Table III. Specific activity of phosphoribosyltransferase of erythrocyte hemolysates from normal and hyperuricemic subjects (Kelley et al, Refs. 5 and 7)

Subject	Urinary Uric Acid mg/kg/day	Phosphoribosyltransferase Activity Mμ moles/mg protein/hr		
		Hypoxanthine	Guanine	Adenine
Normal (32)	6.1	103 ± 18	103 ± 21	31.2 ± 6.0
Gout				
Normal uric acid production (6)	6.1	99 ± 13	106 ± 10	31.2 ± 6.9
Excessive uric acid production (10)	8.0	103 ± 18	104 ± 22	30.4 ± 5.3
Mutant enzyme				
J. family				
F.J.	18.4	1.3	0.6	45.8
R.J.	15.8	1.5	0.8	43.2
T.J.	16.4	1.8	0.8	56.4
L. family				
F.L.	23.9	11.8	0.5	74.0
M.L.	29.0	8.7	0.5	63.8
Lesch-Nyhan				
D.F.	16.0	0	0	--
F.H.	20.0	0	0	65.0

Biochemical observations leading to the discovery of allopurinol for treatment of hyperuricemia. (Ref. 71)

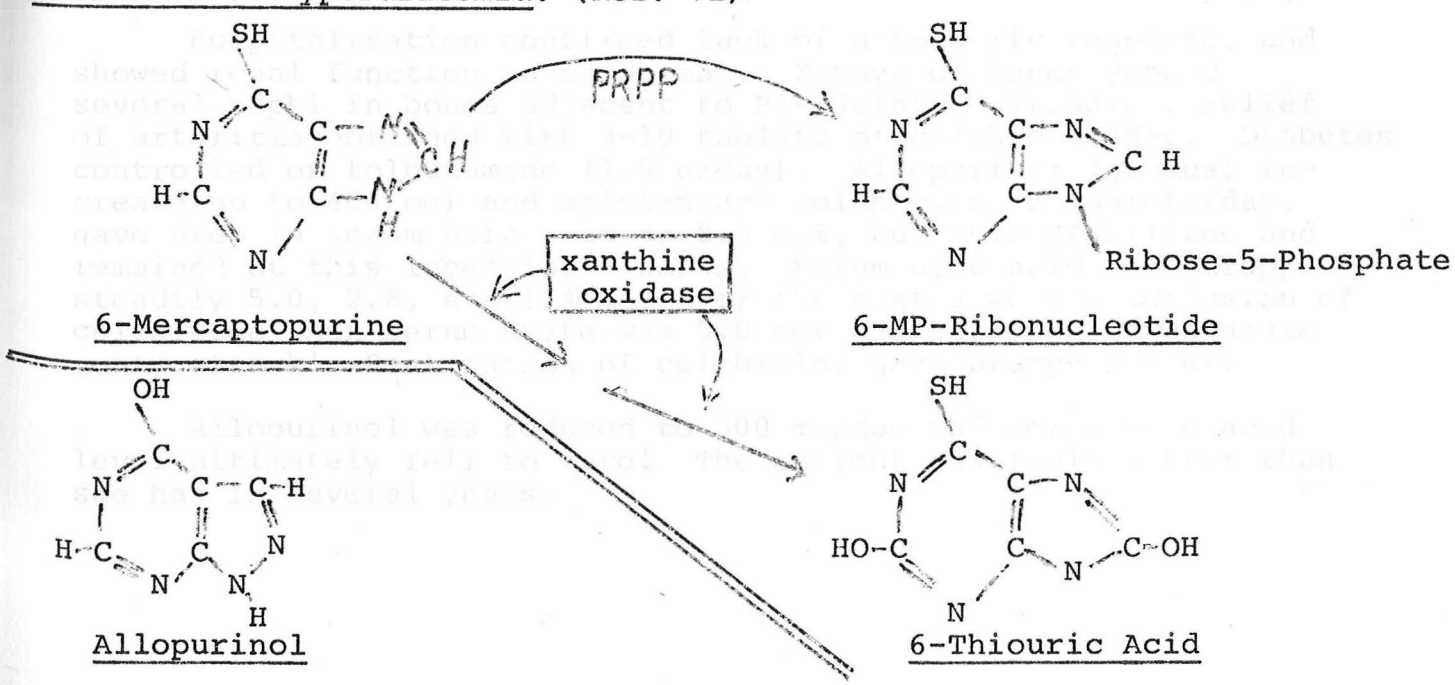


Table IV. Conditions requiring Allopurinol therapy

1. Primary gout with renal disease (25%).
2. Gout associated with metabolic disease:
   a. Diabetes mellitus, especially with ketosis.
   b. Obesity with fasting.
   c. Glycogen storage disease (Von Gierke's).
3. Secondary gout or marked hyperuricemia of hematopoietic or neoplastic disorders.
4. ?Lesch-Nyhan syndrome (hyperuricemia, mental retardation, choreoathetosis and self-destructive biting).

Case II. Metabolic disease with severe gout

[redacted]. This 48 CF, 300 lb. diabetic experienced bilateral ankle and knee arthritis in acute attacks of 2-3 weeks which began soon after menopause. These required bedrest and semi-enforced fasting. Podagra suggested gout. Off aspirin, a uric acid level of 10.0 mg% was found in the serum.

In spite of probenecid (3 g/day) and sulfinpyrazole (0.8 g/day) serum urate rose over next several months (11.3, 12.7, 13.0, and 16.5).

Hospitalization confirmed lack of uricosuric response, and showed renal function to be normal. X-rays of hands showed several tophi in bones adjacent to PIP joints. Transient relief of arthritis obtained with 3-10 tablets of colchicine/day. Diabetes controlled on tolbutamide (1.0 g/day). Allopurinol (gradual increase up to 400 mg) and maintenance colchicine, 3 tablets/day, gave drop in serum uric acid to 8.0 mg%, but this stabilized and remained at this level for 9 weeks. Serum uric acid then dropped steadily 5.0, 2.8, and 1.4 mg% over the next 3 weeks. Omission of colchicine when serum urate was 5.0 mg% was followed by an acute gouty attack! Restoration of colchicine gave prompt relief.

Allopurinol was reduced to 300 mg/day and serum uric acid level ultimately fell to zero! The patient now feels better than she has in several years.

Table V. Comparison of untoward effects of Allopurinol and Probenecid (Rundles et al, Ref. 70, 71 and Goodman and Gilman Pharmacology)

	Probenecid (% of patients treated)	Allopurinol (% of patients treated)
Gastrointestinal (anorexia, nausea)	2	infrequent
Skin rash	1	11
Fever, chills	-	4
Malaise, myalgias	-	4
Acute gouty attacks	1	1
Hematopoietic (anemia, leukopenia, aplasia)	rare	rare

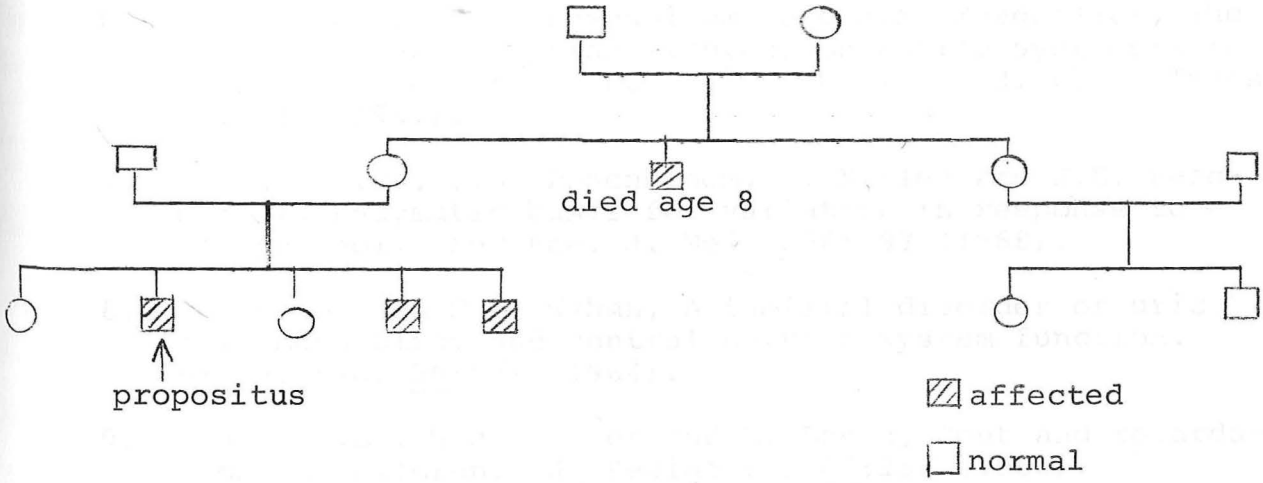
Table VI. Effect of uricosuric drugs upon serum urate concentrations (Velayos and Smyth, Ref. 64)

Changes in Serum Urate	Probenecid 28 Pts.		Sulfinpyrazole 42 Pts.	
	No.Pts.	%	No.Pts.	%
None	0	0	3	7.1
Decreased				
<1 mg%	5	17.9	4	9.5
1-2 mg%	12	42.9	9	21.4
2-4 mg%	6	21.4	17	40.5
4-6 mg%	2	7.1	6	14.3
>6 mg%	1	3.6	1	2.4
Increased	2	7.1	2	4.8

Case III. Lesch-Nyhan syndrome.

[redacted] [redacted]. This infant was delivered on [redacted]66 and diagnosed as having the Lesch-Nyhan syndrome on the basis of a uric acid level of 18 mg% shortly after birth and a positive family history shown in the diagram below. At 3 weeks of age, the child was begun on 40 mg of Allopurinol per day with a dramatic drop in serum uric acid to normal. At 8 weeks examination showed a normal infant and growth continued normally. However, possible hypotonia was observed at 10 weeks which became definite at 24 weeks and marked at 28 weeks of age. Although this hypotonia decreased by 14 months, tensionathetosis was noted at 17 months and self mutilation began at 19 months of age. Irregular intake at home of Allopurinol produced wide fluctuations in serum level, but the conclusion of Drs. Marks, Keele and Kay was that Allopurinol had not prevented development of the neurological syndrome.

Family with hyperuricemia, mental retardation, and choreoathetosis



Pseudogout (Chondrocalcinosis) Ref. 74-77.

1. Characterized by acute and chronic attacks of inflammatory arthritis of larger joints due to calcium pyrophosphate crystal induced synovitis.
2. Appears to mimic gout clinically except patients older as a group (average 67) and have associated osteoarthritis. Diabetes, hypertension or hyperparathyroidism seen in some cases.
3. Calcified articular cartilages of the hip, knee, wrist, fibrocartilage of the symphysis pubis; annulus fibrosus of spine and menisci of knee seen in most, but not all, patients with the disorder.

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