PARKLAND MEMORIAL HOSPITAL

MEDICAL GRAND ROUNDS

January 24, 1963

GOUT

"For that old enemy the gout has taken him in toe."

-Thomas Hood (1799-1845)

Case # 1.

[redacted] a thirteen-year old [redacted] male was first seen with a two week history of enlarged cervical nodes and bleeding gums. The family history was negative for arthritis though a serum uric acid on the father was 7.2 mg. per cent. He had massive cervical lymphadenopathy and hepatosplenomegaly. The WBC was 281,000, 98% lymphs. Serum uric acid was 11.7 mg. per cent. The bone marrow showed 90% large immature lymphoblasts. He was originally given prednisone for two weeks followed by 6MP. The WBC and serum uric acid fell to normal and the organs receded. Two months later following vomiting and weight loss he was readmitted. The WBC was 2300 with a marked hypocellular marrow. The organs were still not palpable. He developed oliguria with increased BUN (172 mg. per cent) and potassium 7.2 meq/L. This improved before death. At this time he developed acute gouty arthritis with a serum uric acid of 72 mg. per cent. The urine during this period was milky with uric acid crystals. The arthritis responded markedly to I.V. colchicine.

Case # 2.

[redacted]) is a 39 year old WM with a 31 (?) year history of gouty arthritis. At age 8 following an episode of nausea, vomiting, and diarrhea, he had the acute onset of a hot, painful, left elbow and right ankle. This recurred every few years becoming more frequent until recently when he has had attacks within a two week period. Uric acids first determined at age 34 were 11 and 13 mg.% and with continued uricosuric therapy since 1957 have not been lower than 9.6 mg.%. Acute episodes which were initially well controlled with colchicine became more difficult to control with colchicine and phenylbutazone. Three tophi had to be surgically removed because their local pressure on nerves produced parasthesias (ulnar nerves and hip). The family history was nil for gout.

BUN's have steadily risen from about 20 in 1957 to 40-50 now. PSP from 45% to 16%. I.V. pyelograms show small kidneys. He is now on Anturan and colchicine with good control.

I. Primary or Genetic

1. Primary familial (gout)
2. ? Diabetes mellitus
3. ? Myocardial infarction
4. ? Renal (gout)
5. ? Hyperparathyroidism (gout)
6. ? Primary hypercholesterolemia

II. Secondary

A. Renal

1. Decreased renal function in general
   a. Chronic renal disease
   b. Hyperparathyroidism
   c. ? Sarcoidosis
   d. Mongolism
   e. Myxedema
   f. Puerperium (following toxemia)

2. Increased reabsorption or decreased secretion

   a. Glycogen storage disease (gout)
   b. Toxemia of pregnancy
   c. ? Diabetic ketoacidosis
   d. Drugs (ASA in low doses, Pyrizinamide, Thiazides, Acetazolamide)

B. Metabolic (Overproduction)

1. Psoriasis (plus sarcoidosis → gout)
2. Polycythemia primary and secondary (gout)
3. Neoplastic disease of the bone marrow (gout)
4. ? Diabetic ketoacidosis
5. ? Drugs (Thiazides, Thiadiazole)

BIBLIOGRAPHY

A. Genetic, epidemiological and diagnostic features.

1) Smyth, C.J., Hereditary factors in gout, Metabolism, 6:218, 1957.

Best review of hereditary features.

2) Rodnan, G.P. and Golomb, M.W., Gout in the Negro female, Am. J. Med. Sci. 236:269, 1958.

Possible in some that transmission of the gouty trait occurred via a non-Negro ancestor. None of the 6 patients bore progeny. Renal disease present in all.

3) Popert, A.J. and Hewitt, J. V., Gout and hyperuricemia in rural and urban populations. Ann. Rheum. Dis. 21:154, 1962.

Support for the view that a diet high in protein is one of the principle factors determining the high incidence of gout in some hyperuricemic families.

4) Decker, J. C., Gout and hyperuricemia in a Pacific population group, Eugenics Quarterly, 9:54, 1962.

High incidence of hyperuricemia and gout in Philipinos with a uric acid frequency curve suggesting inheritance by a single gene with alleles.

5) Shepherd-Wilson, W. and Gelfand, M., Gout in the African: report of a case, Cent. Afr. J. Med., 8:181, 1962.

Never seen until this prosperous, well-fed African appeared.

6) Turner, R.E., Frank, M. J., Ausdal, D. Van, Bollet, A.J., Some aspects of the epidemiology of gout., Arch. Int. Med. 106:400, 1960.

No significant racial differences, but incidence of gout in females was about 1/3 of male cases.

7) Logan, W.P.D. and Cushion, A.A. Morbidity statistics from general practice, H.M.S.O., Vol. 1, 1958.

Incidence of gout in a general practitioner survey based on consultations was 1.2 per 1000 men and 0.4 per 1000 women (33% incidence).

8) Talbott, J. H. and Lilienfeld, A., Longevity in gout, Geriatrics, 14:409, 1959.

Conclusion that the general mortality rate in gout is no higher than that of the general population.

9. Goldthwait, J. C., Butler, C.F. and Stillman, J. S., The diagnosis of gout: significance of an elevated serum uric acid value, N.E.J.M., 259:1095, 1958.

In 225 patients with elevated serum uric acid less than half had gout. Kidney disease, polycythemia, neoplastic disease of the bone marrow and a family history of gout explained the hyperuricemia in less than half the remaining group.

10) Grayzel, A.I., Liddle, L., and Seegmiller, J.E., Diagnostic significance of hyperuricemia in arthritis, N.E.J.M., 265:763, 1961.

Emphasis on the role of low doses of salicylates in the production of increased serum urate levels seen clinically.

11) Brailsford, J.F., The radiology of gout, Brit. J. Radiol. 32:472, 1959.

Good x-ray films of gouty arthritis.

12) Chung, E. B., Histologic changes in gout, The Georgetown Medical Bulletin, 15:269, 1962.

Concise pathological description with excellent photographs.

13) Sokoloff, L., The pathology of gout, Metabolism, 6:230, 1957.

A standard reference especially good in its description of the renal lesions.

14) Talbott, J. H., Terplan, K. L., The kidney in gout, Medicine, 39:405, 1960.

Emphasis on the frequency of renal damage in gout (irrespective of any role the kidney may play in pathogenesis) Detailed pathology.

15) Duncan, H. and Dixon, A. St. J., Gout, familial hyperuricemia, and renal disease, Quart. J. Med., 29:127, 1960.

Close association of hyperuricemia and renal disease in a young family (only 1 member with gouty arthritis). Can hyperuricemia per se lead to renal damage?

16) Keilin, J., The biological significance of uric acid and Guinine excretion, Biol. Rev., 34:265, 1959.

A fascinating phylogenetic study of uric acid.

17) Pepper, H. and Mann, L., Leg ache: a symptomatic indication of irregular gout, Int. Med., 54:267, 1961.

9 patients with initial symptoms of gout presenting as myalgia in thigh and calf muscles. Negative family history in all. Questionable diagnosis.

18) Golding, D.N. and Thompson, M., A non-articular manifestation of gout, Proc. Roy. Soc. Med., 55:406, 1962.

5 males with "tennis-elbow" of the right elbow as the initial manifestation of gout. Other reported sites in the literature are bursae, tendons, carpal tunnel, ligaments, muscles, amputation stump, renal parenchyma, heart, cornea, and sclera.

B. The role of uric acid in gouty arthritis.

19) Seegmiller, J. E. and Howell, R., The old and new concepts of acute gouty arthritis, A & R, 5:617, 1962.

The new concepts of the causation of gouty arthritis based on the demonstration that the acute attack is caused by crystalline urate.

20) McCarty, D.J., Jr., Kohn, N. N. and Faires, J. S., The significance of calcium phosphate crystals in the synovial fluid of arthritic patients: the "pseudogout syndrome", Ann. Int. Med., 56:711, 1962.

Description of an uncommon but clinically distinctive syndrome usually involving the knee and apparently relieved by aspiration or colchicine. Distinctive crystals of calcium pyrophosphate were identified.

21) Faires, J. S. and McCarty, D.J., Acute arthritis in man and dog after intrasynovial injection of sodium urate crystals, The Lancet, II-682, 1962.

The direct relationship between crystalline sodium urate and acute arthritis. There was also a direct correlation with the amount injected.

22) Seegmiller, J. E., Howell, R.R. and Malawista, S.E., The inflammatory reaction to sodium urate, JAMA, 180:469, 1962.

The development of acute gouty arthritis requires needle-like crystals of sodium urate and an inflammatory reaction as manifest by leukocytic phagocytosis of urate crystals.

23) McCarty, D. J. and Hollander, J. L., Identification of urate crystals in gouty synovial fluid, Ann. Int. Med. 54:452, 1961.

Polarized light microscopy was used to identify urate crystals in 15 of 18 patients with clinical gout. The concentration of urate in the synovial fluid during the acute attack is probably higher than that found in the serum.

24) Yu, T.F. and Gutman, A.B., Efficacy of colchicine prophylaxis in gout: Ann. Int. Med. 55:179, 1961.

Establishment of the efficacy and safety of prophylaxis with and without uricosuric agents.

C. Therapy

25) Zuckner, Jack, Responses to colchicine therapeutic trial in rheumatoid arthritis, N.E.J.M., 267:682, 1962.

10 of 20 patients with rheumatoid arthritis said to give a good enough response to colchicine to cast doubt on its use as a diagnostic aid. The major differential point was failure of maintenance of improvement in the rheumatoid.

26) Kaplan, H., Sarcoid arthritis with a response to colchicine, N.E.J.M., 263:778, 1960.

3 patients with proven sarcoidosis, arthritis and normal uric acid levels who responded to colchicine.

27) Fruhman, G., Inhibition of neutrophil mobilization by colchicine, Proc. Soc. Exp. Bio. Med., 104:284, 1960.

Maximum effect immediately after injection; still present at 72 hours.

28) Duncan, H., Elliott, W., Horn, D.B., Kerr, D.N.S., Pearson, D.T., and Robson, A.M., Hemodialysis in treatment of gout, Lancet, 1:1209, 1962.

Successful but would require multiple dialyses to be effective.

29) Goldberg, M., Castleman, L., Friedman, I.S. and Wallace, S.L., The artificial kidney in the treatment of chronic tophaceous gout, JAMA, 182:132, 1962.

30) Larmon, W. A. and Kurtz, J.F., The surgical management of chronic tophaceous gout, J. Bone & Jt. Surg., 40-A:743, 1958.

A comprehensive review and discussion.

31) Bartels, E.C., Available uricosuric agents, Med. Clin. N. Amer., 44:453, 1960.

Feels that patients with renal disease respond most favorably to sulfinpyrazone (Anturan).

32) Marson, F.G.W., Studies in gout, with particular reference to the value of sodium salicylate in treatment, Quart. J. Med., 22:331, 1953.

On doses from 3.6 to 8.4 gms. of sodium salicylate 20 of 29 patients had complete relief of joint symptoms. Dosage had to be maintained at high levels for effect.

33) Seegmiller, J. E., Role of the newer uricosuric agents in management of gout, Bull. Rheum. Dis., 11:241, 1961.

Acetaminophen can be used in place of ASA as an analgesic since it has no antigonistic effect on urate excretion.

34) Harrington, R.T., Fallon, H. J., Uric acid nephropathy in leukemia, the use of acetazolamide in its management, N.E.J.M., 266:934, 1962.

35) Bartels, E.C. and Matossian, G.S., Gout:six-year follow-up in probenecid therapy, Arth. & Rheum., 2:193, 1959.

The number of attacks are decreased and tophi shrink with prolonged therapy. 10% had minimal side effects.

D. The role of the thiazides.

36) Ayvazian, J.H. and Ayvazian, L. Fred, A study of the hyper-uricemia induced by hydrochlorothiazide and acetazolamide separately and in combination, JCI, 40:1961, 1961.

Hydrochlorthiazide has more hyperuricemic activity than acetazolamide and they are additive in effect. In low doses hydrochlorothiazide increased the excretion of uric acid with an associated hyperuricemia.

37) Henley, L.A., Magid, G.J., and Decker, J.L., Uric acid retention due to hydrochlorothiazide, N.E.J.M., 261:1358, 1959.

Hydrochlorothiazide administration resulted in elevation of the serum uric acid in 14 of 15 patients. Probenecid 1.0 gm. daily reversed this effect completely.

38) Aronoff, A., Acute gouty arthritis precipitated by chlorothiazide, N.E.J.M., 262:767, 1960.

It is possible that the patients in whom gout develops are predisposed to this disease by having latent gout, acute attacks being precipitated by a further retention of uric acid.

39) Warshaw, L.J., Acute attacks of gout precipitated by chlorothiazide - induced diuresis, J.A.M.A., 172:802, 1960.

Two cases in which the acute attack occurred within 2-3 days of onset of therapy.

40) Demartini, F.E., Wheaton, E.A., Healey, L.A., and Laragh, J.A., Effect of chlorothiazide on the renal excretion of uric acid, Am. J. Med., 32:572, 1962.

While oral administration over prolonged periods caused renal retention of urates, I.V. doses of more than 100 mg. produced uricosuria. More evidence for tubular secretion of urate.

41) Smilo, R.P., Beisel, W.R., and Forshan, P.H., Reversal of thiazide-induced transient hyperuricemia by uricosuric agents, N.E.J.M., 267:1225, 1962.

Uricosuric agents entirely prevented hyperuricemia without effect on the excretion of uric acid. They postulate an extrarenal mechanism for thiazide induced hyperuricemia.

E. Overproduction vs. underexcretion (and uricolysis)

42) Wyngaarden, J.B., On the dual etiology of hyperuricemia in primary gout, Arth. & Rheum, 3:414, 1960.

A summary of the more recent data on incorporation studies and renal studies in gout. The pendulum appears to be settling.

43) Seegmiller, J.E., Gryzel, A.I., Laster, L. and Liddle, L., Uric acid production in gout, JCI, 40:1304, 1961.

The hyperuricemia of gout may be the result of a variety of metabolic and physiological disturbances.

44) Jones, O. W., Jr., Ashton, Doris M. and Wyngaarden, James B., Accelerated turnover of phosphoriosyl pyrophosphate, a purine nucleotide precursor in certain gouty subjects, JCI, 41:1805, 1962.

1. Dilution studies have shown major increases in the miscible pool of uric acid in almost all gouty subjects studied.

2. Incorporation studies have demonstrated unequiv. abnormalities of uric acid production only in those gouty patients showing excessive basal urinary excretions of uric acid (about 28% of the gouty population).

45) Gutman, Alexander B., A view of gout as inborn error of metabolism, Am. J. of Med., 24:545, 1960.

Strong presentation of gout as overproduction rather than underexertion.

46) Lathem, W. and Rodnan, G.P., Impairment of uric acid excretion in gout, JCI, 41:1955, 1962.

Demonstration of decreased excretion and clearance of urate in patients with gout. Due to either augmented tubular resorption or impairment of tubular secretion of urate.

47) Gutman, A.B. and Yu, T.F., A three-component system for regulation of renal excretion of uric acid in man, Tr. A. Am. Physicians, 74:353, 1961.

Summarization of the evidence (sparse) for tubular secretion of uric acid by the mammalian kidney.

48) Gutman, A.B. and Yu, T.F., Renal function in gout, Am. J. Med., 23:600, 1957.

Data for the overproduction theory and normal renal handling of uric acid in gouty patients.

49) Yu, T.F., Berger, L., and Gutman, A.B., Renal function in gout II effect of uric acid loading on renal excretion of uric acid, Am. J. Med., 33:829, 1962.

Gouty can excrete large loads of uric acid as easily as the normal. The fault in gout is not renal.

50) Sorenson, L.B., The pathogenesis of gout, Arch. Int. Med., 109:379, 1962.

Emphasis on and attempts to prove the existence of primary and secondary renal gout.

51) Yu, T.F. and Gutman, A.B., Study of the paradoxical effects of salicylate in low, intermediate and high dosage on the renal mechanisms for excretion of urate in man, JCI, 38:1298, 1959.

Retention at low doses and uricosuric effect of high doses with a possible explanation by invoking tubular secretion of urate.

52) Gutman, A.B., Yu, T.F., and Berger, L., Tubular secretion of urate in man, JCI 38:1778, 1959.

The renal regulation of urate excretion in man involves glomerular filtration, tubular reabsorption and tubular secretion.

53) Nugent, C.A., MacDiermid, W.D., and Tyler, F.A., Renal excretion of uric acid in leukemia and gout, Arch. Int. Med., 109:540, 1962.

In leukemics (as well as in normals) increased levels of serum uric acid leads to greater excretion of uric acid than in patients with primary gout.

54) Nugent, C.A. and Tyler, F.H., The renal excretion of uric acid in patients with gout and in non-gouty subjects, JCI, 38:1890, 1959.

Strong support for the theory of abnormal renal excretion of uric acid as an important cause of hyperurecemia in some patients with gout.

55) Sorenson, L.B., The elimination of uric acid in man, Scand. J. of Clin. & Lab. Invest., Vol. 12, supp. 54, 1960.

An extensive review with the authors own work showing at least a three to four times increase in pool size in gout as well as a demonstration of the extensive uricolysis (up to 1/3 of daily turnover) by intestinal bacteria.

F. Hyperuricemia with and without secondary gout.

56) Herman, J.B., Gout and diabetes, Metabolism, 7:703, 1958.

Impaired carbohydrate tolerance (glucose tolerance test) found in a high percentage of gouty patients.

No information as to status of disease. The point is not proven.

57) Bartels, E.C., Balodinos, M.C., Corn, L.R., The association of gout and diabetes mellitus, M. Clin. North Amer., 44:433, 1960.

38 patients of 500 (3.9%) are reported with the onset of diabetes following gout in all. In 15 patients the gout improved after diabetic onset.

58) Lee, F.I. and Loeffler, F.E., Gout and pregnancy, J. Obs. Gyn. Brit. Comm., 61:299, 1962.

Renal damage in a 27 year old female after 2 years and only 3 classical attacks.

59) Fuller, Roy W., Luce, Morton, W. and Mertz, Edwin T., Serum uric acid in mongolism, Science, 137:868, 1962.

Highly significant increase in average uric acid levels in mongoloids. Best explanation is probably decreased renal efficiency associated with commonly seen mal-developments of many organs in mongolism.

60) Leeper, R. D., Benoa, R.S., Brener, J.L. and Rawson, R.W., Hyperuricemia in myxedema, J. Clin. Endoc. & Metab., 20:1457, 1960.

Possible relationship between thyroid function and uric acid metabolism or excretion in the human. The effect of thyroid hormone on uric acid in myxedematous patients is mediated primarily through an effect on the kidney.

61) Kohn, P.M. and Prozan, G.B., Hyperuricemia relationship to hypercholesterolemia and acute myocardial infarction, JAMA, 170:1909, 1959.

In 35 patients hyperuricemia (79%) and hypercholesterolemia present to about the same degree.

62) Harris-Jones, J.N., Hyperuricemia and essential hypercholesterolemia, Lancet, 1:857, 1957.

No firm evidence for either a genetic or metabolic basis.

63) Lovering and Longobardi, A., Hyperuricemia in myocardial infarction, Rhode Island Med. J., 44:467, 1961.

In 50 patients with acute M.I., hyperuricemia was more common than hypercholesterolemia (of 12 who died 8 had hyperuricemia, 2 had hypercholesterolemia).

64) Mintz, D.H., Canary, J.J., Carreon, G. and Kyle, L.H., Hyperuricemia in hyperparathyroidism, N.E.J.M., 265:112, 1961.

Hyperuricemia in 4 of 8 patients with primary hyperparathyroidism. Gout or a positive family history in 2 of 4 and decreased renal excretion in 3 of 4.

65) Eisen, A.Z. and Seegmiller, J.E., Uric acid metabolism in psoriasis, JCI, 40:1486, 1961.

50% of patients with psoriasis showed hyperuricemia. This was apparently related to the degree of skin involvement.

66) Kaplan, H., Klatskin, G., Sarcoidosis, psoriasis, and gout: syndrome or coincidence, Yale J. Bio. Med. 32:335, 1960. (also Ann. Int. Med., 57:1018, 1962.)

3 cases, two male, one female. None with a familial history. In 109 cases of sarcoidosis 36% were hyperuricemic.

67) Lewis, J.G., Gout and the hemoglobin level in patients with cardiac and respiratory disease, BMJ, 1:24, 1961.

Gout present in 4 of 90 patients with a hemoglobin of 120% or more. Seen more often in cardiac disease than in respiratory. Highest values of serum uric acid in congenital cyanotic heart disease.

68) Ficarra, B.J., Hyperuricemia in gastric cancer, Surgery, 19:223, 1946.

Not proven.

69) Handler, J.S., The role of lactic acid in the reduced excretion of uric acid in toxemia of pregnancy, JCI, 39:1526, 1960.

Suggests that an increased level of lactic acid (higher in toxemic patients than in normal pregnancy) causes increased net tubular reabsorption of filtered urate and is responsible to some degree for the low uric acid clearance in toxemia of late pregnancy.

70) Treadwell, B.L.J. and Dixon, A. St. J., Puerperal hyperuricemia, Ann. Rheum. Dis., 20:186, 1961.

Hyperuricemia persisted well into the puerperium then gradually fell off. Since lactate is rapidly metabolized this persistent effect may reflect reversible renal damage produced by toxemia of pregnancy.

71) Padova, J. and Bendersky, G., Hyperuricemia in diabetic ketoacidosis, N.E.J.M., 267:530, 1962.

Gluconeogenesis with increased purine release is said to account for the hyperuricemia. However renal mechanisms were not considered at all.

72) Alepa,F.P., Howell, R.R., and Seegmiller, J.E., The occurrence of glycogen storage disease with tophaceous gout, A & R, 5:634, 1962.

Two patients with markedly elevated serum lactate levels that caused hyperuricemia and gout.

73) Ludwig, G.D., Saturnine gout - a secondary type of gout, AMA Arch. Int. Med., 100:802, 1957.

An attempt to relate plumbism to hyperuricemia and gout.

74) Lynch, E.C., Uric acid metabolism in proliferative diseases of the marrow, Arch. Int. Med., 109, 639, 1962.

An excellent review of secondary hyperuricemia and gout.

75) Talbott, J.H., Gout and blood dyscrasias, Medicine, 38:173, 1959.

Gout in association with hematological disease. A too-broad assumption that these are all secondary gout.

76) Yu, T.F., Weissmann, B., Sherney, L. Kupfer, S. and Gutman, A.B., On the biosynthesis of uric acid from glycine - N^{15} in primary and secondary polycythemia, Am. J. Med. 21:901, 1956.

Demonstration that hyperuricemia of secondary gout is a result of increased turnover of hematopoietic tissue and not through the "shunt" of primary gout.