PHYSIOPATHOLOGY, CLINICAL MANIFESTATIONS, AND TREATMENT OF GOUT*

PART 1. PHYSIOPATHOLOGY AND PATHOGENESIS

BY

L. VILLA, A. ROBECCHI, AND C. B. BALLABIO

*From the Rheumatological Department of the Medical Clinic of the University of Milan
and of the San Giovanni Battista Hospital, Turin*

This report deals with our experience with about 100 patients investigated by the laboratory tests and methods set out in Table I.

Any definition of gout must take into account the two fundamental aspects of the disease: the metabolic disturbance on the one hand, and the anatomical and clinical picture on the other.

The first, which characterizes the so-called "gouty diathesis", is seen in a 20- to 30-fold increase in the uric acid pool, as demonstrated by radio-isotope technique, and is accompanied in most cases by a rise in the blood uric acid level (Benedict, Forsham, and Stetten, 1949; Benedict, Forsham, Roche, Soloway, and Stetten, 1950; Bishop, Garner, and Talbott, 1951; Bishop, Rand, and Talbott, 1955; Talbott, 1957). The second aspect is represented by the suggestion of an allergic component in the clinico-pathological picture.

A metabolite may accumulate in the body because of inadequate breakdown, reduced excretion, or excessive formation. The absence of uricase in man has been fairly well established, and the possibility of uric acid oxidation by other enzymes, such as cytochrome oxidase or veridoperoxidase, has been considered (Agner, 1943; Margules and Griffith, 1950). We have already demonstrated (Villa, Polli, and Bussi, 1953) the uricolytic properties of leucocyte extracts, and we have found, after further investigation, that this action is not of the uricase type, and resides preferentially in cells of the myeloid series (Ratti and Ciria, 1957).

The importance of the kidney in regulating the uric acid pool is demonstrated by the low rate of urate clearance which, according to our findings (Sala, Ballabio, and Amira, 1955; Sala, Ballabio,

TABLE I
METHODS USED IN LABORATORY TESTS

Investigation	Method	
	Authors	Date
Plasma uric acid	Brown	1945
Urinary uric acid	Benedict and Franke	1922
Urinary uric acid (C ¹⁴)	Benedict, Forsham, and Stetten	1949
Plasma and urinary uric acid	Praetorius and Poulsen (Uricase Leo)	1953
Uric acid electrophoresis	Salteri and Ciria	1956
Sodium thiosulphate	Brun	1950
P.A.H.	Smith, Finkelstein, Aliminos, Crawford, and Graber	1945
Plasma and urinary endogenous creatinine	Bonsnes and Taussky	1945
Urinary 17-ketosteroids	Callow, Callow, and Emmens	1938
Plasma 17-ketosteroids	Ceresa and Cravetto	1957
Urinary 17-hydroxycorticosteroids	Silber and Porter	1954
Plasma 17-hydroxycorticosteroids	Ceresa and Cravetto	1957
17-ketosteroid chromatography	Dingenmanse, Huis in't Veld, and Hartogh-Katz	1952
Urinary purine	Williams	1950
Purine chromatography	Horrigan	1954
	Weismann, Bromberg, and Gutman	1954
	Lucchelli and Crosti	1956
Lipoprotein electrophoresis	Fasoli and Salteri	1955
Lipoprotein ultracentrifugation	Green, Lewis, and Page	1951
Cholesterolaemia	Bloor	1916

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Amira, Ratti, and Cirila, 1956) and those of other authors (Brøchner-Mortensen, 1939; Mugler, Pernet, Pernet, and Friedrich, 1955), amounts to between 8 and 10 ml./min. in normal subjects. Excretory insufficiency is regarded as a result of diminished glomerular filtration caused by physico-chemical changes in the blood uric acid. The possibility that plasma uric acid may be present in a non-dialysable form, *i.e.* bound to plasma proteins, has been investigated by several authors, including Wolfson, Levine, Guterman, Hunt, Cohn, and Rosenberg (1948) and Adlersberg, Grishman, and Sobotka (1942). According to the latter group of workers, in certain pathological conditions, especially in gout, the bound uric acid may reach 65 per cent. On the other hand, Yü and Gutman (1953, 1955) state that the plasma urate is completely filtered by the glomerulus, while Bordley and Richards (1933) have demonstrated that the concentration of uric acid in the tubular urine of the frog was the same as that in the blood.

We have investigated the electrophoretic behaviour of uric acid in 160 samples from 42 subjects, and we have reached the following conclusions (Fig. 1):

- (1) Under specific experimental conditions the electrophoretic migration of serum uric acid can be readily differentiated from that of serum protein by its characteristic band before the peak of albumin. The result is the same when uric acid is added to serum *in vitro*.
- (2) Elution of this band leads to the recovery of 85 to 100 per cent. of the serum uric acid, but only insignificant amounts can be recovered from other sections of the paper. These findings suggest that uric acid lacks the power to bind protein, and that ultrafiltration is complete;

Fig. 1.—Electrophoretic behaviour of uric acid in 160 samples from 42 subjects.

they do not support the idea that insufficient glomerular filtration may be due to physico-chemical peculiarities of the plasma uric acid.

The following results were obtained in a study of the renal excretion of uric acid in 56 subjects (Fig. 2, opposite):

- (1) In the normal subject, with an average plasma uric acid value of 4.4 mg. per cent. and a urinary urate excretion of 0.405 mg./min., the urate clearance was calculated to be 9.2 ml./min. This signifies that, with a glomerular filtration of 111 ml./min., 91.7 per cent. of the filtered urate was reabsorbed.
- (2) In gouty subjects, with corresponding values of 8.30 mg. per cent. and 0.393 mg./min., the urate clearance was 4.7 ml./min. This signifies that, with a glomerular filtration rate of 112 ml./min., 95.8 per cent. of the filtered urate was reabsorbed. Thus in 74 per cent. of our gouty subjects there was an increase in the tubular reabsorption of urate.
- (3) An adaptation of the tubule cell to an increased excretion of uric acid is noted in other pathological conditions, and our studies in leukaemic subjects have revealed that the amount reabsorbed by the tubules may be as low as 86 per cent. The urinary urate excretion increased and the urate clearance rose to 14.2 ml./min.; in single cases the urate clearance value rose to 34 ml./min.

A reduction in the amount filtered by the glomerulus intensifies the excretory insufficiency, but in the gouty subject with renal insufficiency the ratio of filtered urate to excreted urate reveals the same type of tubular dysfunction as is seen in gouty patients without renal insufficiency (Ballabio and Ortenzi, 1957). These results are significant within the 5 per cent. limit ($P < 0.01$) and do not agree with those of certain other authors (Berglund and Frisk, 1935; Coombs, Pecora, Thorogood, Consolazio, and Talbott, 1940; Brøchner-Mortensen, 1939), but the findings of Mugler and others (1955) in a large series of cases are in essential agreement with ours.

The significance of the tubule in regulating the miscible urate pool has been emphasized by the recently discovered uricosuric action of Benemid (Probenecid), which inhibits tubular reabsorption of urate (Bishop and others, 1951; Bishop and Talbott, 1953; Friedman, 1948; Sirota and Yü, 1952; Sirota, Yü, and Gutman, 1952; Ballabio, Ratti, and Amira, 1954; Talbott, 1957).

Paton, Brodie, Yü, Burns, Chenkin, Steele, and Gutman (1955) and Ballabio and Ortenzi (1957) suggest that the uricosuric action of G 25671 operates by a similar mechanism. We have also confirmed the claim of Gleason, Street, and Kahn (1956) that Pyrazinamide is capable of augmenting

Fig. 2.—Renal excretion of urate in 56 normal, gouty, and leukaemic subjects.

plasma urate levels and lowering urinary urate excretion, by studying its effects in sixteen normal and gouty subjects. Fig. 3 shows the increase in plasma urate levels produced by Pyrazinamide. In a normal subject, the urate levels rose from 4 to 7.6 mg. per cent., and in a gouty patient they rose from 9.8 to 12.2 mg. per cent. Urinary urate excretion and urate clearance both decreased simultaneously.

Fig. 3.—Effect of Pyrazinamide on uric acid excretion in a normal subject and a gouty patient.

Studies of the endogenous creatinine, thiosulphate, and *p*-aminohippurate clearances, as well as the

ratio of urate excreted to urate filtered, has shown that the renal tubule cell is the operational centre, Pyrazinamide having an effect opposite to that of Benemid.

Uric acid synthesis in the organism has been studied in recent years by the injection of labelled radioactive substances (isotopes), and it has been learned that uric acid is synthesized from relatively simple units, such as carbon dioxide, "formate", and NH_3 as obtained from the nitrogen pool, particularly glycine, glutamine, and aspartic acid (Buchanan, Sonne, and Delluva, 1948; Greenberg, 1951; Shemin and Rittenberg, 1947; Stetten and Fox, 1945). The first link in the biosynthetic chain is formed by a condensation of glutamine with 5-phospho-ribosyl-pyrophosphate, giving rise to a phospho-ribosyl-amine. Further synthesis results in a 4(5)-amino-5(4)-imidazol-carboxamide ribotide which is converted to inosinic acid (hypoxanthine ribotide). At this point purine metabolism may progress either to the classical synthesis of purine bases up to nucleic acids, or directly to hypoxanthine and uric acid.

Investigations with N^{15} -glycine (Benedict, Roche, Yü, Bien, Gutman, and Stetten, 1952; Bishop, Rand, and Talbott, 1955; Muller and Bauer, 1953), with 4- C^{13} -4-amino-5-imidazolcarboxamide (Seegmiller, Laster, and Stetten, 1955; Seegmiller, 1957), and with C^{14} -formate (Spilman, 1953), have demonstrated an increased biosynthesis of uric acid in certain gouty subjects, particularly in the presence of an increased urinary excretion of urate. We have also followed the fate of C^{14} -formate (100 microcuries) in a normal subject and in a patient with

chronic gout exhibiting typical tophi and low uraturia (Fig. 4). In this gouty patient there was no evidence of an increased incorporation of the isotope into the uric acid excreted in the urine. These data confirm that the increased production of uric acid is not a constant finding in the gouty subject (Benedict and others, 1953); Muller and Bauer, 1954), but recent work by Wyngaarden (1955, 1957) and Wyngaarden and Blair (1955) with C^{14} -glycine has shown that this increased biosynthesis is present in practically all gouty individuals.

Fig. 4.—Incorporation of C^{14} formate into urinary uric acid in a normal subject and a patient with chronic gout.

According to Wolfson and Levine (1948), Wolfson and others (1948), and Wolfson, Guterman, Levine, Cohn, Hunt and Rosenberg (1956), the pathogenesis of gout may be attributed to a specific endocrine alteration, consisting in a diminished urinary excretion of 17-ketosteroids. This decrease may arise from the production of abnormal androgens in the adrenal cortex, a manifestation of adrenocortical insufficiency, which in turn is the result of decreased ACTH production. A certain degree of adrenocortical insufficiency may frequently be present in gouty subjects, and the metabolic changes which precede and follow an acute attack (described by Talbott (1957) as the "cycle of gout"), the frequency with which an acute attack follows a state of stress, and the rapid relapse when ACTH therapy is discontinued, all support the idea of such a deficiency. The urinary excretion of 17-ketosteroids was followed in 73 gouty subjects (Table II).

TABLE II
URINARY EXCRETION OF 17-KETOSTEROIDS
IN 73 GOUTY SUBJECTS

17-ketosteroids (mg./24 hrs)	Cases		Average (mg./24 hrs)
	No.	Per cent.	
< 6	10	13.7	4.5
6 to 11	42	57.6	8.2
>11	21	28.7	13.2

A reduction was noted in 71 per cent. of these patients and this reduction was less than 6 mg./24 hrs in only 13 per cent. Chromatographic analysis in four cases showed that the diminution involved either the adrenocortical or the gonadal androgens. Blood and urinary 17-hydroxycorticosteroids and blood 17-ketosteroids were not far from normal values. It therefore appears that, considering the age and sex of the individuals involved, the abnormal gonadal and adrenocortical secretions do not play an important role in the pathogenesis of gout.

The difficulty of confining the problem of gout to that of uric acid metabolism has created interest in the possibility that certain quantitative or qualitative abnormalities in the degradation of nucleoproteins may be responsible for the disorder. According to our findings in thirteen gouty subjects, the quantitative purinuria (Fig. 5, opposite), in terms of the hypoxanthine, and xanthine excreted, is equal to that in normal subjects, in contrast with acute leukaemia in which both urate and purine excretion is considerably increased (Ratti and Cirila, 1957). Recent column and paper chromatographic studies (Weisman, Bromberg, and Gutman, 1957; Horrigan, 1954) have revealed in normal subjects an entire series of purine bases in addition to uric acid: xanthine, hypoxanthine, adenine, 7-methylguanine, guanine, 1-methylguanine, 1-methylxanthine, 7-methylxanthine, paraxanthine, and other substances not yet identified chemically.

Our work has been based on the method of Horrigan (1954), and we have carried the study of eluates a stage further by additional chromatography, using the technique of Cohn (1949), and on paper (Fig. 6, opposite). We are still identifying further purine bodies, but, on the basis of analyses in five gouty subjects, we have found no significant

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Fig. 5.—Excretion of uric acid and purines in normal, gouty, and leukaemic subjects.

Fig. 6.—Chromatography of urinary purines in a gouty subject. Thickness of circles indicates intensity of colour.

difference from the normal.

The frequent association of obesity and arteriosclerosis with the clinical picture of gout has suggested to several authors the possibility of a derangement in lipid metabolism (Greppi, 1956; Isemein, Ciaudo, Hawthorn, Lègre, Courtieux, and Ramis, 1956). The distribution of serum lipoproteins was studied in eighteen gouty subjects by

paper electrophoresis and in nine cases by ultracentrifugation. The results (Tables III and IV) are as follows:

- (1) Paper electrophoresis showed a reduction in the α_1 -lipoproteins in gouty subjects, and a higher proportion of β -lipoproteins. This change is statistically significant ($P < 0.001$).
- (2) Studies with the ultracentrifuge showed a statistically significant ($P < 0.05$) reduction in the α_1 (Class $S_{1.21.0-15}$) fraction. The most marked change ($P < 0.001$) was an increase in the β -fraction of lowest density (Class $S_{1.21.60-400}$).
- (3) The alteration in the lipoprotein equilibrium which is frequently present in gouty subjects suggests that the ability to elaborate large lipoprotein molecules is reduced.
- (4) The average cholesterol value in 62 gouty subjects was 218.8 mg. per cent.
- (5) These changes were not sufficiently characteristic to permit differentiation from the more general "atherogenic" type.

The possibility that gout has an allergic basis is suggested by several factors:

- (1) The difficulty of interpreting the disease on the basis of a single metabolic alteration.
- (2) The presence of an acute attack of gout with normal blood uric acid levels or alternatively the presence of primary or secondary hyperuricaemia during an entire life-time without gouty manifestations.
- (3) The analogous appearance of acute gout and anaphylaxis.
- (4) Hypersensitivity and vascular phenomena suggesting increased permeability in gouty subjects.
- (5) The dissociation between therapeutic results and metabolic alterations.

TABLE III
LIPOPROTEIN PATTERN
ELECTROPHORESIS

Subjects	No. of Cases	Alb.- α_1		α_1 - β_1		β_2	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
Normal ..	16	29.5	9.1	56.1	8.3	14.4	4.4
Gouty Patients ..	18	12.5	5.3	73.4	6.0	14.1	4.4

TABLE IV
LIPOPROTEIN PATTERN
ULTRACENTRIFUGATION

Subjects	No. of Cases	- $S_{1.21.0-15}$		15-25		25-33		33-60		60-400	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Normal ..	9	31.3	7.3	4.1	1.3	39.5	8.0	14.9	7.6	10.2	5.8
Gouty Patients ..	9	23.7	6.9	3.9	1.7	35.9	6.4	16.0	6.0	20.5	6.0

Fig. 7.—Biopsy of synovial membrane from a patient suffering from a first attack of gout, showing acute and mainly exudative inflammation without urate deposits.

Fig. 8.—Biopsy of synovial membrane from a patient with chronic relapsing gout, showing granulomatous inflammation with giant cells related to advanced urate deposits.

The characteristic histological changes resulting from gout were studied in biopsies of affected tissue. Fig. 7 shows biopsy material from a patient suffering a first acute attack of gout, whereas previous studies have only shown tissue removed from chronic cases. There is acute inflammation in the absence of urate crystals, and this is in marked contrast to Fig. 8, taken from a patient with chronic gout, which shows urate deposits accompanied by a typical foreign-body reaction with giant cells. Sokoloff (1957) has recently reported the presence of uric acid crystals during an early attack of acute gout, which, however, was not the first one.

Association between clinical phenomena and metabolic alterations may be noted according to the type of therapy used. This is particularly apparent with colchicine, the therapeutic action of which appears to us to be independent of any direct metabolic interference. The contrary is observed with Benemid, which has no therapeutic value in the acute episode but, because of its uricosuric action, is the drug of choice for the treatment of chronic gout. Administration of Pyrazinamide does not induce acute gout, even in gouty subjects, whose plasma urate values may reach extraordinarily high values (personal observations). According to other authors, rheumatic complaints develop only after administration of this substance for several months.

SUMMARY OF PART ONE

The pathogenesis of gout is far from being solved, but the most recent findings and our own present

results make it possible to draw the following conclusions:

- (1) In gout there is an increase in the miscible urate pool.
- (2) An increased tubular reabsorption of uric acid and a diminished urate clearance are present in gouty subjects, even when the amount of urate excreted does not significantly exceed normal values.
- (3) The possibility that uric acid biosynthesis is augmented in certain gouty subjects has been demonstrated. This is attributed to a biosynthetic shunt at the inosinic acid level, which may be transformed directly to hypoxanthine and uric acid.
- (4) Increased production and increased tubular reabsorption contribute to increase the urate pool.
- (5) The derangement which causes the accumulation of uric acid results in a deposition of urate crystals in the tissues, which is characteristic of chronic gout.
- (6) Acute gout is characterized by an inflammatory reaction of an allergic nature, which cannot be explained by the presence of uric acid crystals in the synovia or by abnormalities of purine metabolism.
- (7) Interference by other metabolic factors (*i.e.* uricolysis by routes not associated with uricase activity) or hormonal reactions (*i.e.* diminished production of gonadal and adrenocortical androgens) appear to be less likely possibilities.

PART 2. CLINICAL AND THERAPEUTIC STUDIES

BY

S. de SÈZE, A. RYCKEWAERT, J. LEVERNIEUX, AND R. MARTEAU

From the Viggo-Petersen Rheumatological Centre, Lariboisière Hospital, Paris

The clinical study which follows is based on 100 cases definitely diagnosed as gout, because of typical acute attacks (in the great toe or in one or more other joints) relieved by colchicine, or because of the presence of tophi.

From the first attack of gout, the disease had lasted:

Less than 10 years in 20 patients
More than 10 or less than 20 years in 28 patients
20 years or more in 52 patients

The patients' ages were distributed as follows:

From 30 to 39 years: 1 case
From 40 to 49 years: 20 cases
From 50 to 59 years: 45 cases
From 60 to 69 years: 27 cases
Over 70 years: 7 cases

I. AETIOLOGY

Sex Ratio.—Our series of one hundred patients included only four women.

Family History.—37 patients knew of at least one