

CLINICAL AND METABOLIC STUDIES  
WITH URICOSURIC AGENTS IN GOUT

A therapeutic assessment of Benemid  
and an experimental account of Tromexan

THESIS

presented for the degree of

DOCTOR OF MEDICINE

by

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SECTION I

PREFACE

CHAPTER 1. THE RELATION OF URIC ACID TO THE CLINICAL FEATURES OF GOUT

A. ORIGINS OF HYPERURICAEMIA

- 1. Historical note
- 2. Determining influences
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- 3. Mechanism of hyperuricaemia
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B. ROLE OF URIC ACID IN ACUTE GOUTY ARTHRITIS

C. URIC ACID IN CHRONIC TOPHACEOUS GOUT

- 1. Pathogenesis of chronic gout
- 2. Clinical results of urate deposition

D. RELATION TO RENAL AND VASCULAR LESIONS

E. LOGIC OF URICOSURIC THERAPY

PREFACE

Gout in Cape Town is a common disease. In this city of half a million inhabitants, hundreds have been found in a relatively short time to be suffering from the condition. To many of them, as well as to their doctors, this fact has come as a surprise and the local prevalence of the disease has evoked much interest.

At the Groote Schuur Hospital, teaching centre of the University of Cape Town's Department of Medicine, studies in gout began early in 1952 at the suggestion of Dr. Mark Horwitz, head of the Arthritis Clinic. Having met several gout patients while working on rheumatoid arthritis in 1948, he proposed that we both interest ourselves in what was probably not a rare disease and tackle some of its many problems.

Like most metabolic disorders, gout has a compelling fascination for students of medicine in general and research workers in particular. Few diseases can boast an earlier historical recognition, more illustrious victims or clinical descriptions as painstaking and colourful; but we are not yet in a position to deride what Thomas Sydenham ruefully wrote in 1683:

'Either men will think that the nature of gout is wholly mysterious and incomprehensible, or that a man like myself, who has suffered from it for thirty-four years, must be of a slow and sluggish disposition not to have discovered something respecting the nature and treatment of a disease so peculiarly his own'.

Much remains 'wholly mysterious' about gout to-day, contributing in part to the readiness with which this investigation was begun. A puzzle presents at every turn: the overwhelming male incidence of the disease, not explicable by genetic sex-linkage; the mode of accumulation of uric acid, and the factors leading to its visible deposition in the tissues of some of those affected; the nature of the sudden explosive inflammatory attacks in or about joints, and their precipitation

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by a gallimaufry of causes, or more often by nothing recognizable; the curious specificity of colchicine in relieving the acute episodes, and the relative immunity, as far as can be judged, of certain races from the disease, taking the African native as an example.

Several authorities have remarked on the diminished prevalence of gout in the British Isles in modern times, an observation difficult to accept for a condition shown to be primarily hereditary and only secondarily influenced by diet, social circumstances and occupation. In contrast come many reports of its impressive frequency in the U. S. A., and the finding in the past three years, by two interested people in private and hospital practice, of nearly three hundred patients with undoubted gout in Cape Town.

The scope for investigation in such a field is virtually endless, being limited chiefly by considerations of time, organization and technical facilities. The most illuminating contributions to an understanding of gout are currently being made by the use of isotopes in studying the origins of uric acid and the nature of the purine disturbance. Coupled with this are provocative new concepts, far from proven, of gout as a specific disturbance of endocrine functions. Both are spheres of research into which few can journey without adequate equipment in scientific knowledge, laboratory apparatus and technical assistance. There remains ample reason, however, for following certain lines of investigation, both established and new, in so large a group of patients, and it is against this background that the material of my study has been gathered.

The objects of this thesis are three:

First, it aims at drawing attention to the prevalence, at least in this part of the world, of gout in all its clinical phases, and emphasizing its timely recognition and appropriate treatment. It is not generally realized that gout frequently masquerades as a variety of musculo-skeletal disorders, is a potential cause of much disability and withal is strikingly amenable at its worst to suitable therapy. The opportunity is also taken of re-evaluating certain aspects of the natural history of gout, especially the perplexing association at all

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stages with a high incidence of renal disease, exemplified by our patients.

Secondly, the thesis, after considering the extent to which the pathological and clinical features of gout may directly be attributed to a disturbance of uric acid metabolism, demonstrates the therapeutic results of measures aimed primarily at enhancing the elimination of urate from the body. While in itself a time-honoured approach to the treatment of gout, the chances of assessing such a regime over a long period were recently much improved by the introduction of benemid (also known as probenecid), a synthetic compound of the highest potency in increasing the drainage of urate through the kidneys. Although used originally, like its predecessor carinamide, for slowing the renal excretion of penicillin, benemid was shown a few years ago by workers in the U. S. A. to be the most effective addition yet to the list of drugs called uricosuric agents. Initial reports, gleaned late in 1951, suggested a negligible incidence of side effects and an absence of simultaneous antiphlogistic or anti-rheumatic properties which confuse the appraisal of other urate-eliminating drugs. It seemed worth while, having this partially tried substance of unestablished therapeutic value, and the nucleus of a growing number of gout patients, to investigate for ourselves the possible benefits to be derived from long-term uric acid depletion.

Clinical, biochemical and radiographic criteria of assessment are presented on fifty patients who have received benemid for six to thirty months, and the long-range effects of such treatment on the course of gout - including its renal lesions - considered. For reasons which will be discussed, a few patients were treated with small regular doses of cortisone in addition to benemid, and the results of this measure are believed to contribute partially to the understanding and management of the disease.

The third function of this thesis is to recount the experimental discovery, in man and animals, of a hitherto unrecognized uricosuric agent known as tromexen. This substance, ordinarily used in clinical medicine for its anticoagulant prop-

erties, was shown to have a marked effect on the urinary excretion of urate as well as on certain other renal functions. Such an action, related to the biochemistry of gout and to one important aspect of its treatment, was studied experimentally as far as circumstances permitted, and the chemical, physiological and therapeutic significance of the observation weighed.

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CHAPTER I.      THE RELATION OF URIC ACID TO THE CLINICAL  
FEATURES OF GOUT

Gout is an inherited disorder of uric acid metabolism mainly affecting males. It is usually characterized by recurrent attacks of painful arthritis starting in middle life, which initially subside completely between episodes, but progress in later years to a state of chronic multiple joint disease punctuated by acute exacerbations, and featuring urate tophi in and around joints, bursae, cartilages and tendons. Levels of serum urate are typically excessive in the patient and frequently in symptomless members of his family, and early as well as late in the development some degree of renal damage is commonly in evidence. The impact of gout on its victims may vary from an occasional nuisance to a malignant illness, the outlook generally being worse the earlier the age of its onset.

The extent to which this picture depends on a bodily excess of urate, and the consequent logic of uricosuric therapy, will now be considered.

## A. THE ORIGINS OF HYPERURICAEMIA.

### 1. Historical note

Though clinically recognized by Hippocrates and other ancients, gout was first related to uric acid by Wollaston's identification, in 1797, of 'lithic acid' in material from gouty tophi.<sup>129</sup> Fifty years later, by means of the 'thread experiment', a technique humbling in its ingenious crudity, Sir Alfred Garrod demonstrated excessive amounts of uric acid in the blood of gout patients. On the biochemical side, no other compound has had the honour of being the subject of investigation by four such masters of organic chemistry as the nineteenth century scientists Liebig, Wöhler, Baeyer and Emil Fischer. In 1897 the latter established the molecular structure of uric acid and its relationship to other purine compounds, and relatively little was added to the detailed knowledge of its metabolism until recent years.

### 2. Influences determining hyperuricaemia

(a) Genetic. Modern studies by Smyth and Stecher's groups provide strong evidence that hyperuricaemia is primarily determined by genetic factors, and is transmitted by a single dominant autosomal gene whose penetrance, for obscure reasons, is much greater in males than females.<sup>109,111</sup> Among such families with 'essential' hyperuricaemia, only a portion of those exhibiting the trait develop clinical manifestations of gout. Statistical biochemical studies of this sort were stimulated by the old-standing clinical observation of the familial incidence of gout, and it may be significant in the pathogenesis of symptoms that hyperuricaemia should so strongly correlate with the hereditary predisposition to the disease.

(b) Endocrinal. Wolfson has presented evidence in an attempt to prove that hyperuricaemia in gout is a function of an abnormal androgen. In normal people serum urate is on the average higher in adult men than women, and lowest in children of both sexes before puberty; after the menopause, urate levels in women approximate those of men.<sup>124</sup> These data are interpreted as evidence of androgenic influence

on normal urate metabolism, and Wolfson believes that the agency responsible for mediating genetically determined hyperuricaemia is an abnormal androgen, the activity of which is not necessarily accompanied by features of over-masculinisation <sup>124</sup>. Confirmation is needed of the observations on which this interesting hypothesis is based.

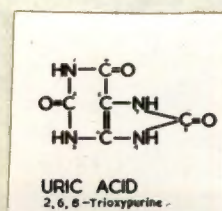
(c) Body build. Gertler and White <sup>53</sup>, while studying the problem of coronary heart disease in young men, found the mean serum urate normally to be significantly higher in dominant endomorphs, that is, men of wide frame and rotund appearance. Gutman and Yu <sup>59</sup> suggest that body urate, most of which is formed in the liver, may arise partly in muscle and bone marrow, which would help to explain the sex difference in serum urate concentration and incidence of gout, and the propensity of gout to attack heavy-set men.

### 3. Mechanism of production of hyperuricaemia

Recognition of the hereditary character of 'essential' hyperuricaemia in subjects with and without clinical gout does not in itself explain the mechanism by which the genetically transmitted influence operates. None of the following possibilities has yet gained sole confirmation <sup>5</sup>:

- (a) overproduction of urate; (b) under-excretion;
- (c) diminished degradation.

(a) Overproduction of urate. Recent studies with isotopes have revealed that, while uric acid is the end-product of purine metabolism in man, its formation is contributed to by several simple carbon and nitrogen compounds like carbon dioxide, formate, lactate, acetate, glycine and serine, which are utilized in the body's biosynthesis of purines, <sup>9, 102, 110.</sup>



This evidence narrows the customary distinction between exogenous and endogenous sources of uric acid, as even 'endogenous' purine synthesis derives part of its fabric from exogenous food molecules. It is still true, however, that a high intake of preformed nucleoprotein substances is directly reflected by increased quantities of excreted urate.

Talbott <sup>115</sup>, and Gutman and Yü <sup>59</sup>, strongly favour the belief that hyperuricaemia and urate accumulation in gout represent 'an inborn error . . . based upon an alternative and slightly divergent path of metabolism' as Garrod suggested, and that molecules are deviated from the general metabolic pool towards excessive purine synthesis, with resultant overproduction of urate.

The evidence for this view is coupled with experimental isotope studies of the 'miscible pool' of uric acid in normal and gouty subjects <sup>10, 18, 34, 52</sup>. This new approach, dependent on several technical assumptions, has shown that the amount of body urate which can mix with tracer injections is greatly increased in gout, even without detectably impaired excretion, further implying its primary overproduction.

(b) Under-excretion of urate. Since Garrod first considered a renal cause for hyperuricaemia in gout, rejection or proof of this possibility has been hampered by the liability of patients to some degree of kidney damage at the time of investigation. The modern studies of Talbott's team, Bröchner-Mortensen and Friedman and Byers <sup>38, 27, 48</sup>, indicate that in many patients in the earlier years of the disease, renal functions both by routine and specialised techniques of testing are unimpaired. Evidence of an intrinsic, constitutional defect purely for urate excretion is also lacking, and workers have in fact been impressed by the preservation of effective urate clearance even when undoubted kidney disease supervenes.

Similarly, the argument that daily urate excretion in gout subjects is normal or reduced - implying a renal origin of hyperuricaemia rather than overproduction - has fallen away since the demonstration, with newer analytical methods, that many gout patients do in fact excrete significantly more urate in 24 hours on a purine-free diet than non-gouty controls <sup>59</sup>. In those with overt renal damage this phenomenon is more likely to be masked.

It appears, therefore, that hyperuricaemia does not arise

through a primary defect of renal excretion of urate, which early on is not objectively impaired. The kidneys do, however, play a secondary part in aiding the accumulation of urate in gout according to the presence and extent of complicating renal disease.

(c) Diminished degradation. Significant uricolysis has not been demonstrated to be a normal function of human tissues, and its impairment cannot therefore be regarded as important in the development of hyperuricaemia.

(d) Conclusion. While most of the evidence briefly cited above tends to the view that hyperuricaemia is chiefly an expression of excessive urate production in those genetically predisposed, there is probably justification for Bauer and Klemperer's cautious opinion<sup>5</sup> that a single operative mechanism to explain all cases has not conclusively been demonstrated, and that possibly both factors, increased production and decreased excretion of urate, may be involved simultaneously in the pathogenesis of gouty hyperuricaemia.

B.      ROLE OF URIC ACID IN ACUTE GOUTY ARTHRITIS.

Remarkably little is known of the mechanism of production of the violent, inflammatory features characterising the acute attack of gout. There is no proof that the active deposition of urate crystals on the joint surface is an integral part of the pathology of an attack, nor, as Wood Jones points out <sup>73</sup>, that the seat of the disease is in the articulation itself. Uric acid per se is pharmacologically inert, and acute gout cannot be produced in either normal or gouty men by uric acid feeding or by its intravenous or periarticular injection <sup>5</sup>.

Further objections to ascribing acute episodes directly to hyperuricaemia include its common presence in symptomless members of gouty families, and the fact that serum urate levels are almost constantly raised in patients without special relation to the occurrence of attacks. Gutman and Yü have concluded <sup>59</sup> that there is no definite pattern of change in serum urate levels before, during or after an attack, and that the previous belief in initial urate retention followed by a urinary 'flood' is unfounded. In other conditions featuring hyperuricaemia (renal failure, marrow dysplasias) gouty episodes are a rare development.



Fig. (1).      Acute gout.

A final refutation of the role of urate in acute gout is offered by certain observations concerning therapeutic agents. Colchicine, of such striking relief in the paroxysms, is not effective in lowering serum urate levels, while the administration of uricosuric drugs may not only fail to diminish the frequency of attacks, but appears at times directly to precipitate them soon after successfully reducing circulating urate. This phenomenon was remarked on by Graham<sup>56</sup> for cinchophen, by Benedict for salicylates<sup>7</sup>, and by several workers reporting on benemid<sup>58, 64, 90, 98</sup>.

Despite ingenious alternative theories to explain the occurrence of acute gouty arthritis, the absence of a solution to this problem constitutes perhaps the widest gap in the understanding of the whole disease. Certainly urate itself is incriminated with difficulty.

## C. URIC ACID IN CHRONIC TOPHACEOUS GOUT

### 1. Pathogenesis of chronic gout

When uric acid is formed in the body at a rate greater than its effective excretion - regardless of which is at fault - it tends to be deposited as the mono-sodium salt ('sodium biurate'). The readiness with which precipitation occurs in the tissues of gout subjects is another puzzle of the disease, since the colloidal properties of plasma successfully keep urate dispersed in supersaturated solution in other hyperuricaemic states, even though the critical concentration of 6.5 to 8 mg./100 ml. <sup>5, 37</sup>, is exceeded. The tissues specially chosen are cartilage, synovial membrane, bursae, tendons and subcutaneous tissue, in all of which a basic pattern is elicited of a chronic, foreign-body inflammatory response to the presence of urate crystals. Such a reaction involving articular structures leads eventually to chronic joint degeneration - a chemical osteoarthritis.



Fig. (ii). Doubly refractile crystals of sodium bi-urate from a gouty olecranon bursitis, photographed in polarized light. (x375).



Fig. (iii). Chronic gouty arthritis of first metatarsophalangeal joint. Note degeneration of articular cartilage due to urated deposition on surface and sub-chondrally. There were no clinical tophi. (Case 28).



Fig. (iv). Doubly refractile, needle-like crystals of sodium urate in sub-chondral bone at edge of same joint. (Polarizing photomicrograph x 75).



Fig. (v). Histological appearance of gouty tophus showing central hyaline zone from which crystals have dissolved, and surrounding chronic inflammatory reaction with many 'foreign-body' giant cells and fibrous tissue. (x90).

Uric acid deposition is much more widespread in gout than clinical or radiographic search for tophi reveals. Proof of this, apart from post-mortem discovery of urate in sites previously unsuspected, is offered by the size of the miscible urate pool as estimated with isotopes in gout patients <sup>7, 10</sup>. This may be so large, even in those without visible tophi, that in order to explain it the participation of urate in the solid phase must be assumed. It is interesting that Graham first inferred this by much simpler methods from the large quantities of urate excreted as a result of cinchophen therapy in chronic gout <sup>56</sup>.

2. Clinical results of urate deposition.

Whatever its role in the acute gouty attack, urate appears directly responsible for much of the clinical picture in chronic tophaceous gout. Persistent joint symptoms may progress to a state of chronic, deforming arthritis, disfiguring swellings due to urate accumulation and non-healing ulcers over erupted tophi. Radiographs at that stage testify to the skeletal damage which may result from unrestricted urate deposition.

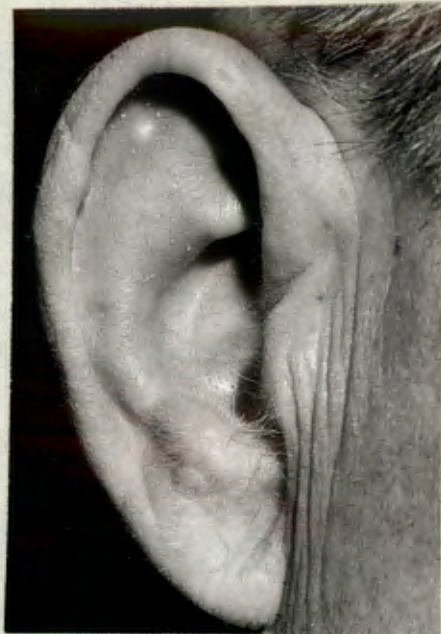


Fig. (vi). Tophus in cartilage of ear pinna.



Fig. (vii). Chronic, polyarticular tophaceous gout (case 4).



Fig. (viii). Destructive uratic lesions of joints and bones (case 4).



Fig. (ix). Lower extremities of same patient (case 4). In addition to tophi, note urate sinus over right big toe joint, and chronic dermatitis.



Fig. (x). Widespread destruction of most foot bones, with soft-tissue shadows due to overlying tophi.



Fig. (xi). Lower limbs  
(case 4).

Fig. (xii). Radiograph  
of knee  
region (case 4). It is  
rare to find such  
advanced uratic erosions  
in or near large joints.



D. RELATION OF URIC ACID TO RENAL AND VASCULAR LESIONS

The high incidence of renal disease among gout patients has been remarked by many <sup>5,101,115</sup> and is supported by this thesis (Section II). Unlike the late joint complications, the renal and vascular lesions which may be associated with gout are less easily ascribed to the <sup>dire</sup> effect of uric acid. <sup>43</sup> Dunn and Polson's demonstration that kidney damage resulted in rabbits from massive intravenous injections of urate is not acceptable evidence that hyperuricaemia per se is toxic in man. At autopsy a variety of renal changes may be encountered, including nephrosclerosis, interstitial deposition of urate, renal calculus, pyelonephritis and glomerulonephritis <sup>33,115</sup>. Accumulation of sodium urate in kidney tissue, whether by escape from renal tubules or precipitation from the blood stream, calls forth a similar cellular reaction to deposits elsewhere, and such 'urastosis' or 'renal tophus' formation when it occurs, is a hallmark of gout. The resultant interstitial fibrosis, in addition to urate blockage of tubules, is thought to explain a certain amount of impaired renal function in gout, and secondary infection in obstructed nephrons would account for further damage. It is perhaps reasonable, therefore, to blame uric acid fairly directly for much of the kidney pathology occurring in patients with gout of some duration, but its role, if any, in contributing to an unusually high incidence of nephrosclerosis and possibly glomerulonephritis <sup>33, 101</sup> is obscure.

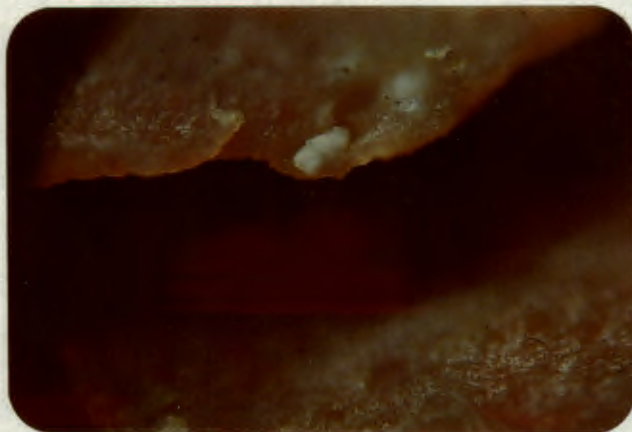


Fig. (xiii). Urate deposit in renal medulla adjacent to collecting tubule (case 111, advanced tophaceous gout). Photographed through dissection microscope.

The idea that premature vascular degeneration is an inherent accompaniment of the gouty state has been expressed in the aphorism that 'gout is to the arteries what rheumatism is to the heart' <sup>53</sup>. Morbid anatomical and clinical evidence for this concept is provided by the frequency of renal vascular disease and systemic arteriosclerosis and hypertension among patients with gout <sup>5</sup>. The relationship, which would seem to be significant, is reminiscent of diabetes mellitus which has become recognized as a state of vascular hazard. Gertler and White <sup>53</sup> have recently correlated coronary atherosclerosis with the presence of abnormally raised serum urate levels in 100 young men with coronary heart disease. Adlersberg <sup>1</sup> and Wolfson <sup>125</sup> had already independently observed the coincidence of hyperuricaemia and hypercholesterolaemia as hereditary biochemical abnormalities in certain families, and there seems to be grounds for believing that uric acid, whether by surface action on the intimal lining or in some even more obscure way, is related to arterial disease as closely as cholesterol may be.

#### E. LOGIC OF URICOSURIC THERAPY

It is plain from the foregoing discussion that much remains to be explained in the aetiology of gout as well as in some of its clinical manifestations. Whatever relationship the hyperuricaemic state itself may bear to acute gouty arthritis, there is little doubt that precipitation of urate in selected tissues is responsible for most of the clinical picture of chronic tophaceous gout. Prevention or correction of this process is an aim which, if achieved, would have a therapeutic value second only to fundamental cure of the disease.

It is part of this thesis to show the extent to which the biochemical and clinical abnormalities of gout can be corrected, by the continued use of substances enhancing urate elimination.

## SECTION II

## EXPERIMENTAL STUDIES OF URICOSURIC AGENTS

CHAPTER 2. THE BIOCHEMICAL BASIS OF URICOSURIC ACTION

- A. RENAL FUNCTIONAL CONSIDERATIONS
- B. MECHANISM OF RENAL EXCRETION OF URATE IN MAN
- C. FUNCTIONAL INTER-RELATIONSHIP OF URICOSURIC AGENTS
  - 1. Known uricosuric compounds
  - 2. Mode of action and biochemical properties of
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    - (b) Benemid
    - (c) Salicylate
    - (d) Cinchophen
    - (e) Phenylbutazone
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- D. PRESENT CONCEPT OF RENAL TUBULAR TRANSPORT MECHANISMS
  - 1. Secretion and reabsorption
  - 2. Mechanisms of interference
  - 3. Proposed scheme of tubular transport, with criticisms.

## CHAPTER 2. THE BIOCHEMICAL BASIS OF URICOSURIC ACTION

### A. RENAL FUNCTIONAL CONSIDERATIONS

Modern gout therapy and new techniques of investigation lend special importance to an understanding of the renal mechanism of urate excretion. The writing of this section was further prompted by the discovery that tromexan (ethyl biscoumacetate), a drug hitherto used clinically for its anticoagulant action, is also a potent uricosuric agent in man and animals. The demonstration of its marked effect on renal tubular function is a new finding of considerable interest and possible value.

The formation of urine by the kidney comprises three phases. They are (1) glomerular filtration, (2) tubular secretion and (3) tubular reabsorption.

Glomerular filtration involves the passive ultra-filtration of part of the plasma water from the blood circulating through the glomerular tuft. The capsular fluid, as it reaches the cells of the proximal tubule, has the same composition as the parent plasma, except for most of the proteins and certain other materials which are precluded from filtration by their molecular size.

Glomerular filtration rate may be determined with a compound that is not bound to plasma proteins, not secreted by the tubules and not reabsorbed either actively or passively from the lumen of the tubule. Under such circumstances the amount excreted is equal to the amount filtered. The most reliable test substance for measuring glomerular filtration in all vertebrates is the starch-like polymer, inulin. Mannitol, thiosulphate and creatinine have been used for the purpose, and the validity of creatinine established as an index, i.e., in the dog and cat but not entirely in man, whose tubules contribute to its clearance by some degree of active secretion.

Renal clearance is a concept that relates the total amount of a substance excreted in unit time to its plasma concentration. Thus if  $U$  is its urinary concentration in mg./ml., and  $V$  the rate

of formation of urine in ml./min., then UV is the rate of excretion in mg./min. If P is the concentration of the substance in mg./ml. of plasma, it follows that UV/P is the volume (ml.) of plasma required to supply the amount of substance excreted per minute. A compound like inulin, excreted solely by glomerular filtration, will have a renal clearance equal to the glomerular filtration rate. Thus in man:

$$C_{\text{inulin}} = \text{GFR} = \begin{array}{l} 127 \text{ ml. (males)} \\ 117 \text{ ml. (females)} \end{array}$$

these values being corrected to a standard surface area of  $1.73 \text{ m}^2$ .<sup>107</sup>

A simple but unreliable measure of glomerular filtration rate is available in the so-called endogenous creatinine chromogen clearance. Its inaccuracy in man is due both to associated tubular secretion and to the fact that the plasma substance yielding the 'creatinine' colour reaction with alkaline picrate is not wholly creatinine but includes other chromogenic material with low clearance properties whose effect is to give an erroneously low total chromogen clearance value. The margin of error is further widened by the smallness of the average plasma concentration of endogenous chromogen in man (0.64 to 1.10 mg./100 ml.)<sup>29</sup> which forms the denominator of the clearance formula. Despite the pure glomerular handling of creatinine in animals such as the dog and cat, the other fallacies of the estimation are similarly applicable to them.

It is noteworthy, however, that for all its faults, the endogenous creatinine clearance has been vindicated as a useful estimation of filtration rate in man by the careful work of Steinitz and Turkend<sup>112</sup> and Brod and Sirota<sup>29</sup>. It would appear to approximate inulin clearance values even more closely than does exogenous creatinine clearance, and as a rule the absolute difference between the chromogen and inulin clearances, even in renal disease, is so small that the chromogen clearance is a fair test of the filtration rate. The use of new methods aimed at separating true endogenous creatinine from non-creatinine chromogen by absorption of the former on Lloyd's reagent confers greater reliability on the procedure, though adding to its length technically.

Tubular secretion involves the active elimination of a substance in addition to the amount filtered at the glomerulus. Para-aminohippurate (PAH) is filtered by the glomeruli and is secreted by the tubules with such thoroughness that it is totally extracted from the renal circulation and its clearance is therefore a measure of the total renal plasma flow. The clearance of such a compound is greater than the glomerular filtration rate and bears a ratio to it exceeding 1.0.

Active tubular reabsorption, illustrated in its most complete form by the handling of glucose, involves the extraction of a substance from the glomerular filtrate and its transfer from the lumen of the tubule to the blood stream.

## B. MECHANISM OF RENAL EXCRETION OF URATE IN MAN

Of living creatures other than insects, arid reptiles and birds, only man, apes and the Dalmatian coach hound excrete substantial amounts of uric acid in the urine. There is no explanation for this apparent biochemical stasism on the part of the primates; they do not share the need of the lower orders for conserving water which nitrogen-excretion in the form of uric acid facilitates <sup>107</sup>. The Dalmatian, on the other hand, displays a renal tubular anomaly genetically parallel with its singular spotted appearance.

The technical difficulties of specifically estimating urate in blood and urine have contributed to the variability of urate clearance values recorded by many investigators. All are agreed, however, that urate clearance in man is but a fraction (about 1/10) of glomerular filtration, for which the following explanations are possible:

- (a) A large fraction of the plasma urate may be non-filterable;
- (b) Totally filtered urate may undergo active tubular reabsorption;
- (c) Some degree of both these possible factors may contribute jointly to the low clearance ratio.

Filterability of plasma urate. Two groups of workers have supported the non-filterability of the greater part of circulating urate: Adlersberg <sup>2</sup> presented evidence that between 4 and 24% of plasma urate was protein-bound and therefore retained at the glomerular membrane; in gout this fraction was greater and thought to play an important part in the biochemical and clinical abnormalities of the disease. Wolfson's group <sup>127</sup> demonstrated a similar proportion of plasma urate to be non-filterable, and believed that the basis for this was polymer-formation yielding large molecular complexes.

Most other studies, however, notably by Berliner<sup>14</sup> and Yü and Gutman<sup>131</sup> using ultrafiltration techniques reveal that all plasma urate, both in normal and gouty subjects, is completely diffusible. They also point out that the fraction which has been claimed to be non-filterable would in any event not account for the discrepancy between urate clearance and glomerular filtration. Furthermore, Bordley and Richards<sup>107</sup> showed that, at least in frogs and snakes, the glomerular filtrate contained the same concentration of urate as the plasma over a wide range of values.

Partial tubular reabsorption of urate by an active transport mechanism must then be invoked to explain its small clearance, and modern confirmation of such a process is ample. Talbott's extensive work<sup>115</sup> on the uricosuric effects of several compounds actively handled by the renal tubules (diodrast, phenol red, hypertonic glucose, salyrgan) strongly implied an active mechanism for urate reabsorption which could be inhibited or otherwise interfered with. Berliner and his co-workers have since convincingly demonstrated that such a transport mechanism exists, presumably enzymatic in nature, that the urate reabsorptive capacity of the tubules has a limit ( $T_m$ ) of about 15 mg. per minute, and that this capacity is so much greater than the normal load of filtered urate that it is not the limiting factor for tubular reabsorption (and hence net excretion) of urate. The detailed factors which adjust the exact amount of urate excreted in the urine therefore have yet to be identified.

It seems established, from the above, that all the plasma urate is in a form filterable through the glomeruli, and that about 90% of it is then actively reabsorbed in the proximal tubules. Why a metabolic end-product should be economized so assiduously by the kidneys in man remains a mystery.

## C. FUNCTIONAL RELATIONSHIPS OF URICOSURIC AGENTS

### 1. Known uricosuric compounds

The list of substances known to increase the rate of uric acid excretion in man or rats, with a resultant urate clearance rise relative to glomerular filtration, reads as follows in Smith's review <sup>107</sup>:

Cinchophen  
Salyrgan  
Salicylate  
Acetylsalicylic acid  
Diodrast  
Cerinamide  
Renin  
Glycine  
Phenol red  
Hypertonic glucose.

To these may be added the following newer and important drugs:

Benemid  
ACTH  
Cortisone  
Phenylbutazone

Many other substances have been reported less convincingly to have uricosuric properties, sometimes refuted by other workers: Pyruvic acid, bicarbonate, sodium benzoate, piperazine, adrenalin, pilocarpine, ergotamine, sorbitol, o-aminobenzoic acid, acetanilide, phenacetin, metenilic acid, sulphenilic acid, caffeine and theophyllin. The latter two drugs are methylxanthine compounds whose own excretion causes a fallacious increase in colorimetric estimations of urinary urate <sup>27</sup>. Piperazine, as well as alkalies, are good in vitro solvents of uric acid but have no proven pharmacological effect of any note. (Gutman and Yü <sup>59</sup> found that large doses of sodium bicarbonate appeared to potentiate the uricosuric effect of large doses of salicylate, though alone producing no increase in urate elimination).

In contributing to the foregoing tally of drugs, Talbott <sup>115</sup> also noted that certain substances excreted by the renal tubules, or otherwise of interest in renal physiology, did not affect

urate clearance: Inulin, mannitol, creatinine, sodium hippurate, PAH and pitressin. Colchicine in his hands, as in those of all other workers, had no uricosuric action. Of this group of 'negative' compounds perhaps the most surprising is PAH, whose tubular transport is closely related to that of urate; some data will be shown later which question Talbott's finding.

2. Mode of action of uricosuric agents

The theoretical possibilities are reviewed at length in Hueper's appraisal of cinchophen <sup>68</sup>.

(i) Effect on renal autonomic nerve supply: The abolition of cinchophen uricosuria by renal denervation in dogs was advanced by Grabfield and his co-workers as evidence for <sup>107</sup> the neural mediation of the drug's action. Smith discounts this view on the basis of uncontrolled simultaneous changes in renal dynamics and tissue metabolism.

(ii) Effect on intermediate nucleoprotein metabolism leading to accelerated urate production and hence excretion: This mechanism is untenable for cinchophen as for newer agents on the grounds that total nitrogen and phosphate excretion are not simultaneously raised as from nucleoprotein catabolism, and serum urate falls rather than rises.

(iii) Effect by mobilizing pre-formed uric acid depots: The drug is thought to render tissue stores of uric acid more soluble and assist their passage in a watery medium to the kidney for excretion. This concept might have explained its longer-lasting uricosuric effect in tophaceous gout patients, with obvious 'tissue stores'; but evidence of increased blood urate on its way to be excreted was lacking.

(iv) Effect on colloidal urate complexes rendering a greater fraction of circulating urate ultrafilterable: Wolfson <sup>127</sup> suggested this mode of action of uricosuric drugs in keeping with his views on the renal excretion of urate, neither of which, however, are acceptable in the face of contrary experimental evidence.

(v) Effect by increased permeability of the kidney: Although Hueper found little support for a literal physico-chemical mechanism of this sort, current knowledge

of renal cellular processes confirms that the site of action of uricosuric compounds is primarily the nephron itself. This concept derives from modern data on the mechanism of urate excretion by total filtration and partial tubular reabsorption, and from the disturbance by uricosuric drugs of other tubular transport mechanisms.

As examples, the properties of the following better known uricosuric agents may be briefly considered (Fig.1) :

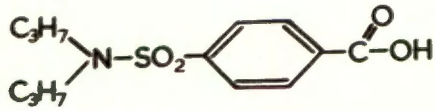
(a) Carinamide. This substance was first used by Beyer in 1947 in the study of renal tubular transport mechanisms. With his co-workers he showed it <sup>17</sup> to inhibit the renal tubular secretion of the penicillins, PAH and phenol red (PSP). It is believed to act by inhibiting a definitive enzyme in one or more phases of the secretory process. The energy requirements of this process seem comparable with those for the oxidative conjugation of glycine with p-aminobenzoic acid, which carinamide can block in vitro. Wolfson <sup>127</sup> noted its uricosuric effect after ingestion of amounts of the order of 10 G., and observations on its clinical use in gout were reported by Gutman <sup>58</sup> who remarked on the impractical dosage. Carinamide has also been shown to diminish tubular secretion of diodrast (a pyridone derivative used in studies of tubular function and renal plasma flow estimations), and of p-aminosalicylic acid (PAS). Though without effect on glomerular filtration rate, Bucht <sup>107</sup> reported a lowering of creatinine/inulin clearance ratios in normal men, implying inhibition of the tubular secretory fraction of creatinine output by carinamide. In other hands the creatinine clearance was unaffected and no change was produced in the tubular handling of glucose, arginine, urea and sulphonamide. Beyer's concept of the drug's inhibitory action on a specific enzyme reaction has been challenged by others who regard it as competing for transport within the tubules against the other substrates.

(b) Benemid. Like carinamide, to which it is structurally related, (Fig.1), benemid was synthesized in the laboratories of Sharp and Dohme, and first reported on by Beyer and his group. To date it has been the most potent

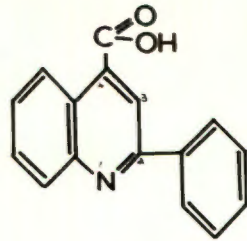
uricosuric agent known and the one with lowest toxicity. Its qualitative biochemical effects are identical with those of carinamide, and are essentially a property of the sulphamylbenzoic part of the molecule (as they are of the sulphonamidobenzoic acid part in carinamide). Its quantitative superiority over members of the carinamide series and over structural variants in its own series is apparently a function of the alkyl side-chains (di-propyl for benemid) which determine a far greater physiological economy of the compound for the body <sup>17</sup>.

The actions of benemid are as follows:

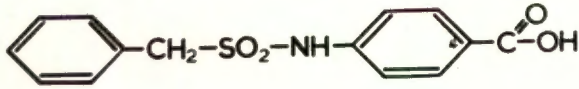
- (i) It increases urate elimination in man by inhibiting its tubular reabsorption.
- (ii) It selectively and reversibly inhibits the transport mechanism responsible for the tubular secretion of the penicillins, PAH, PSP, PAS and diodrast.
- (iii) It does not inhibit all tubular secretory systems since it has no effect on the renal elimination of N'-methylnicotinamide (NMN), a quaternary ammonium base excreted by a different tubular mechanism from the foregoing group of compounds.
- (iv) Benemid increases the excretion of uric acid by the ordinary dog, but not by the Dalmatian coach hound (whose urate clearance may in fact be diminished).
- (v) It does not effect glomerular filtration rate or the reabsorption of glucose, arginine, urea, potassium or phosphate.
- (vi) While Beyer observed no changes in the clearances of sodium, chloride and sulphonamides, Sirota, Yü and Gutman reported slight but significant increases in sodium and chloride clearances, and the renal excretion of certain sulphonamide compounds may be diminished <sup>40</sup>.
- (vii) Benemid does not enhance blood levels of aureomycin, terramycin, chlorsamphenicol or streptomycin.
- (viii) An interesting additional action of benemid is to diminish the urinary excretion of 17-ketosteroids in men



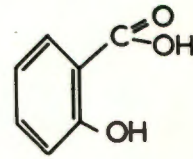
**BENEMID**  
p-(di-n-propylsulphonyl)-benzoic acid



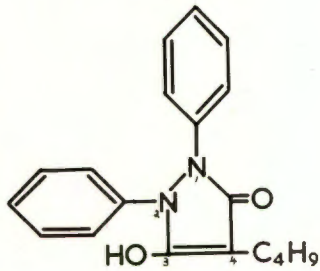
**CINCHOPHEN** (α-phenyl cinchoninic acid)  
2-phenylquinoline-4-carboxylic acid



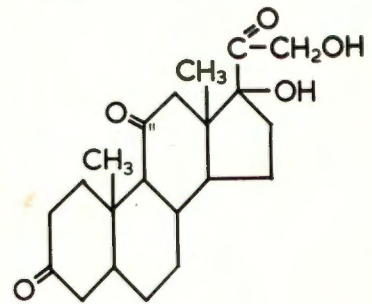
**CARINAMIDE**  
4-carboxyphenylmethane sulphonanilide



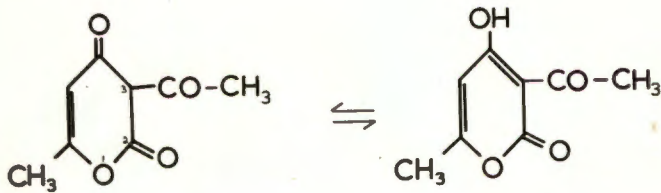
**SALICYLIC ACID**  
α-hydroxybenzoic acid



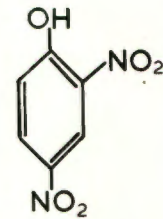
**PHENYLBUTAZONE**  
3,5-dioxo-1,2-diphenyl-4-n-butyl pyrazolidin



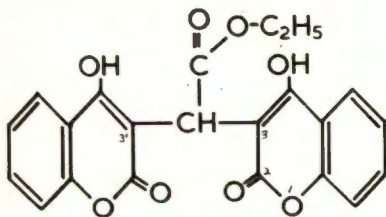
**CORTISONE**  
17-hydroxy-11-dehydrocorticosterone



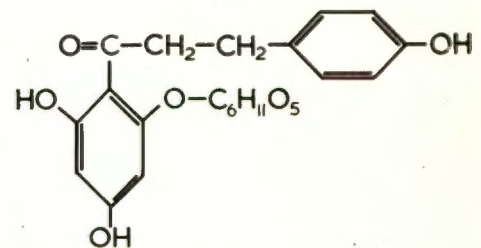
**DEHYDROACETIC ACID (DHA)**  
3-acetyl-6-methyl-1,2-pyran-2,4-dione



**DNP**  
2,4-dinitrophenol



**TROMEXAN** (Ethyl biscoumacetate)  
3,3'-carboxymethylene-bis-(4-hydroxycoumarin) ethyl ester



**PHLORIZIN**

**Fig. 1.** Uricosuric agents and other compounds suppressing renal tubular transport.

apparently by interference with a tubular secretory process related to that for urate and penicillin transport.

Benemid is so slowly metabolized and excreted that less than 2% is lost in the urine during 24 hours after a single intravenous dose in dogs, and determinable plasma concentrations persist for 48 hours. Though, like many foreign compounds, it is largely bound to plasma proteins, about 25% is freely filtered and then virtually completely reabsorbed by the tubules. This conservative process presumably maintains an effective concentration of the drug in or about the tubule cells for a prolonged time <sup>17</sup>.

(c) Salicylate. Historically this was the first drug discovered to have a uricosuric action (See, 1875), while its therapeutic role in gout as an analgesic and anti-phlogistic agent dates back much further to the use of willow bark by Dioscorides in the first century <sup>59</sup>. Like other urate eliminators its site of action is the renal tubule, where it is related in more than one way to urate reabsorption. Bauer and Klemperer observed in 1944 that not only were large doses of salicylate (about 5 G. daily) required for consistent urate elimination, but that smaller doses (1-2 G. daily) raised blood levels of uric acid <sup>77</sup>. Sirote and his associates have studied this phenomenon <sup>15</sup>: they found that urate clearance is depressed by plasma salicylate levels lower than 10 mg./100 ml., is unchanged by moderate levels (10-17 mg./100 ml.) and increased at higher concentrations.

Another puzzling observation is the cancellation of benemid effect by small doses of salicylate. With plasma salicylate levels below 10 mg./100 ml., the uricosuric action of benemid was inhibited, although the administration of benemid during high salicylate dosage had no effect on the latter's augmented urate clearance.

Sirote suggested a balance of two mechanisms involving salicylate: (a) an inhibitory effect of salicylate on urate transport - this would diminish reabsorption and enhance clearance; (b) a removal of glycine from competition with urate for transport, by conjugation of glycine and salicylate - this would facilitate reabsorption. The latter effect appears to predominate at low levels of salicylate. Interference with the action of benemid is

difficult to explain, and is thought to represent a blocking of that compound from its site of action in the tubule - not a very illuminating concept.

(d) Cinchophen. Hueper's <sup>68</sup> detailed review (1948) of this drug and its derivatives has dated prematurely with newer clinical and metabolic advances in the field of gout and the rheumatic disorders. With several other substituted cinchoninic acids, cinchophen displays remarkable uricosuric, antiphlogistic, analgesic, antipyretic and choloretic properties. It is not surprising that some modern workers<sup>20</sup> have been led to seek a stimulating effect on the pituitary-adrenal axis to explain some of these actions. Its renal tubular influence, although conceived by Talbott as being 'mildly toxic', resembles what is known of the foregoing uricosuric drugs in its parallel effect on PSP secretion by frog kidney slices <sup>42</sup>, cinchophen itself having about the same order of activity in this respect as carinamide, while certain related compounds surpass it.

The difficulties of identifying a structural basis common to all compounds with renal tubular affinities are partly illustrated by the irregular, arbitrary pattern within the cinchophen family alone. From reports on 200 derivatives gathered by Hueper, only a few basic structural determinants of uricosuric activity emerge, whereas modifications by 'trivial' substitutions were considerable. Thus, an essential for a uricosuric effect is the presence of a phenyl rest in the 2-position of the quinoline carboxylic (cinchoninic) acid nucleus. In addition to the phenyl group, a second substitution must be present which is most effective when in the 4-position as a carboxyl group. Thereafter all combinations of uricosuric and antiphlogistic efficiency may result from minor changes, e.g., cancellation of uricosuria by an oxy-group in the phenyl radicle; augmentation by halogen in the phenyl group byt cancellation on entering the quinoline ring. The lack of correlation between tubular activity and systemic toxicity is illustrated by neocinchophen, which appears safer to the liver than cinchophen, but is only feebly uricosuric <sup>59</sup>. Beyer demonstrated the same differentiation in the carinamide series<sup>17</sup>

(e) Phenylbutazone. In 1952 this pyrazolidin derivative first received widespread attention for its potency as an anti-rheumatic drug <sup>41</sup>. European workers had used it as a vehicle for aminopyrine in an effective preparation called Irgapyrine <sup>78</sup>, whose special antiphlogistic properties led Kuzell and others to study phenylbutazone alone and establish its therapeutic activity in rheumatoid states and gout <sup>79,80</sup>.

Its uricosuric activity was initially shrouded by Kuzell's observation, as well as that of Kidd and co-workers, <sup>76</sup> that the reductions in plasma urate resulting from its oral or parenteral administration were unaccompanied by increased urinary urate excretion. Their suggestion that intermediate purine metabolism was disturbed by the drug was reminiscent of similar explanations for substances since shown to inhibit renal tubular reabsorption of urate; nor were serial 24-hour urate estimations before and during phenylbutazone dosage checked against urinary creatinine or volume as a guide to the validity of urine collections. Sirote, Yü and Gutman have since clearly demonstrated the uricosuric activity of phenylbutazone at a renal tubular level <sup>106a</sup>.

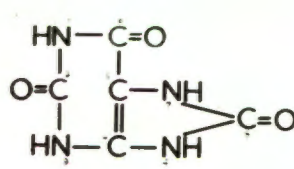
As is the case with benemid, the propensity of phenylbutazone to disturb renal mechanisms is aided by a very slow rate of metabolic transformation in the body (plasma levels persisting for a few days after an adequate dose) <sup>31</sup>. Negligible amounts of the drug are excreted unmetabolized in the urine, so that despite 98% binding to plasma proteins, the relatively small proportion filtered at the glomerulus is apparently wholly reabsorbed by the tubules and enabled to exert its effects in transit. An interesting pharmacological feature is the approach of a limiting plasma concentration as dosage is increased, most subjects achieving plasma levels, on an oral dose of 400 to 600 mg. daily, that are only slightly lower than when 800 mg. or more are given. <sup>80</sup> It is believed <sup>31</sup> that the rate of metabolic transformation of the drug increases greatly at plasma levels higher than the therapeutic zone of 10 to 20 mg. per 100 ml.

The inhibition of tubular reabsorption of urate by phenylbutazone is less than that by comparable doses of benemid <sup>106a</sup>. On the other hand, the reduction in tubular secretion of PAH is equally striking with both substances

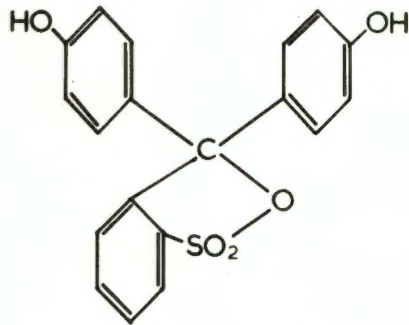
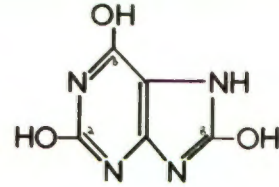
suggesting that the actions of the two drugs on renal transport are not identical. This is further borne out by the considerable retention of sodium, chloride and water during phenylbutazone dosage but not with benemid. Tubular handling of potassium is unaffected. Data on glomerular filtration rate indicate slight depression by phenylbutazone, not only with endogenous creatinine (which would be easily explained as suppression of its tubular component) but during inulin clearance too. The use of benemid together with phenylbutazone by Yü and co-workers<sup>106a</sup> did not suppress the uricosuric effect of either drug.

The resemblance between phenylbutazone and ACTH or cortisone received early comment<sup>79</sup> because of comparable therapeutic activity, similarities in toxicity (reactivation of peptic ulcer) and parallel electrolyte retention with possible oedema. The absence of potassium diuresis, eosinopenia, increased 17-ketosteroid excretion or clinical hyperadrenalism<sup>31</sup> makes it unlikely, however, that the action of phenylbutazone is mediated through a pituitary-adrenal mechanism. The possibility of diminished 17-ketosteroid output resulting from use of the drug, as occurs with benemid, was unfortunately not mentioned in the above study which aimed at finding an excretory rise.

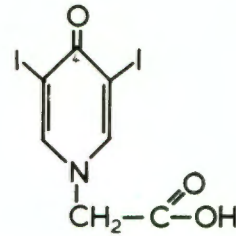
- (f) ACTH and 11-oxysteroids (cortisone, hydrocortisone). With mounting interest one adds to the list of uricosuric substances yet another kind of agent whose striking clinical effect is the suppression of inflammatory response and rheumatic activity. Uricosuria is again a result of altered renal tubular function, changes in which are also reflected in the handling of sodium, chloride, potassium, glucose and certain amino-acids<sup>15,69</sup>. The fact that ACTH and cortisone favour protein catabolism has not accounted alone for enhanced urate excretion, with lowered rather than raised plasma levels and no commensurate rise in other nucleoprotein end-products. During 'average' clinical dosage the uricosuric effect of these compounds is at most moderate. ACTH was not found to influence the activity of benemid<sup>15</sup>.



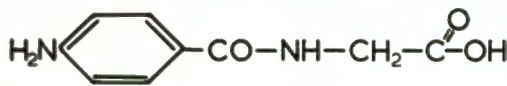
URIC ACID  
2, 6, 8-Trioxypurine



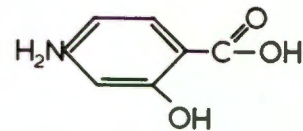
PHENOL RED (PSP)  
Phenolsulphonphthalein



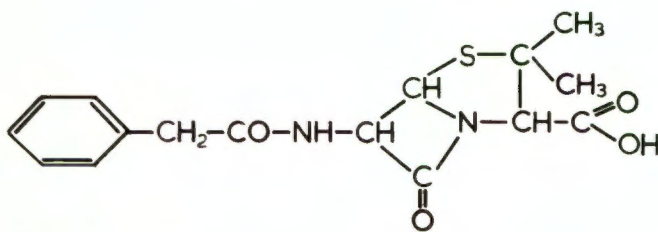
DIODRAST  
3,5-di-iodo-4-pyridone-N-acetic acid



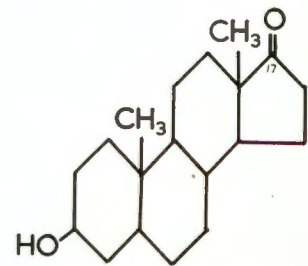
PAH  
*p*-aminohippuric acid



PAS  
*p*-aminosalicylic acid



PENICILLIN-G



ANDROSTERONE  
A 17-ketosteroid

**Fig. 2.** Compounds sharing the same system of renal tubular transport. A transport inhibitor like benemid affects the cellular passage of all.

#### D. PRESENT CONCEPT OF RENAL TUBULAR TRANSPORT MECHANISMS

The processes supplying the energy and guiding the kinetics of tubular reabsorption and secretion are at present far from elucidated. The relation between tubular activity and the pharmacology of uricosuric agents justifies brief consideration of the current concepts of renal transport mechanisms. The biological versatility, moreover, of so many uricosurics in rôles other than renal, such as the antiphlogistic and anti-rheumatic effects of salicylate, cinchophen, phenylbutazone and 11-oxysteroids, and the anticoagulant activity of tromexan, lends special point to an attempted correlation of these diverse effects in terms of a common biochemical mechanism.

1. The active reabsorption of glucose, amino-acids, phosphate, sulphate, creatine, vitamin C and other substances is evidently performed by an independent process for each member <sup>107</sup> which must be attributed to several highly specific cellular mechanisms. On the other hand, in tubular secretion apparently all substances share a common element in one of two transport systems, because in all known instances the loading of the tubules with one substance depressed the tubular secretion of all others in one of two groups. Smith conceives this to be due to competition within the transport system rather than an inhibitory or toxic action, since it is freely reversible.

Most of the compounds secreted by the tubules in man or dog fall into one large group (Fig. 2): Phenol red (PSP), hippuric acid and various derivatives including p-aminohippurate (PAH), other conjugated aromatic acids like cinnamoylglycine and phenaceturic acid, pyridone compounds (typified by diodrast), penicillin, various acetylated sulphonamides, p-aminosalicylate acid (PAS) and, of the naturally occurring compounds in man, probably creatinine in part and 17-ketosteroids <sup>50</sup>.

(The other secretory group is experimentally characterized by N'-methylnicotinamide (NMN), a quaternary ammonium compound which Sperber <sup>107</sup> and Beyer <sup>17a</sup> showed to be distinct from the foregoing substances in its transport through the tubule cells, presumably utilizing a mechanism common to the quaternary bases.)

Agent	Suggested action in cell	Interference with tubular transport mechanism for:									
		URATE	PAH	PSP	DIODRAST	PENICILLIN	PAS	17-KETOS	CREATININE	G. UCOSE	NMN
CINCHOPHEN	Inhibits succinate oxidation	+	+	+						-	
SALICYLATE		+									
CARINAMIDE	Competitive blocking of conjugation	+	+	+	+	+	+		+	-	-
BENEMID		+	+	+	+	+	+	+	(-)	-	-
PHENYLBUTAZONE		+	+						+		
CORTISONE, ACTH		+								+	
DHA	Inhibits succinate oxidation	+	+	+		+				-	+
DNP	Uncouples phosphate energy		+	+	+					-	
PHLORIZIN	Inhibits phosphorylation	-	+	+	+				+	+	
PAH	Compete for transport	(-)	.	+	+	+			+	+	-
PSP		+		.	+						
DIODRAST		+	+	+	.	+			+		
GLUCOSE	Competes for common energy	+								.	
MERCURIALS	Inhibit oxidative -SH enzymes	+	+	+	+					+	
TROMEXAN		+	+	(+)		(±)		(-)	(-)		

Table 1. Functional inter-relationship among certain compounds sharing a common mechanism of renal tubular transport. (Glucose and N'-methyl nicotinamide, while not members of the larger group, are included to show certain overlaps).

Empty squares denote absence of experimental reports; brackets indicate doubtful evidence.

We are immediately faced with the physiological paradox that urate reabsorption is served by the same transport system as the secretion of PSP and its accompanying foreign agents, and is competitively interfered with by members of the latter group and by drugs impairing the transport of those same substances. (See Table 1). In those species whose tubules secrete uric acid (birds, reptiles) this paradox falls away, as it does in the case of the Dalmatian coach hound if the evidence for tubular secretion of urate (supported by the writer's experiments) is accepted. Work on the slight mutual depression of transport maxima of glucose and PAH <sup>17a</sup> offers another instance of two substances, one secreted and the other reabsorbed, competing at some point in the transport system for available energy.

2. Most of the ideas on the biochemistry of tubular transport are derived from the results of experimental inhibition or stimulation of secretory and reabsorptive processes. As a prelude to a proposed scheme of enzymatic cellular transport, Beyer <sup>17a</sup> in an authoritative discussion lists the following types of interference with renal tubular secretion or reabsorption:

(a) Competition between two compounds for transport by a common mechanism. The factors involved here are the quantity of each substance and the affinity of each for the enzymatic process, and their resultant determines the degree to which the enzyme system is 'saturated' with either agent and limits the amount transported per unit time. In this sense there is no true inhibition of cellular function. Examples are the depression of PSP secretion by diodrast, penicillin secretion by PAH, and xylose reabsorption by glucose, all of which are rapidly reversed as plasma levels of the competing agent dwindle.

(b) Depression resulting from competition between two systems for a common source of energy, even though the directions of transport are opposite. The diminished reabsorption of glucose by saturating the functional capacity of the tubules to secrete PAH is thought to be of this type.

(c) Inhibition of cellular respiration by agents acting on oxidative enzymes (oxidases, dehydrogenases) or on the cytochrome system of electron exchange. These agents are frankly toxic to the cell and their effects are often irreversible, e.g., cyanide, mercury, tetrathionate, etc.

(d) Interference with generation of energy-rich phosphate bonds by 2, 4-dinitrophenol and phlorizin, without disturbing

oxidation, explains their inhibition of PSP and other secretory processes, and phlorizin glycosuria represents a reabsorption defect due to inhibited phosphorylation.

(e) Competitive inhibition of a transport mechanism by a compound that is not actively secreted by that system, e.g., benemid. The inhibitor is sufficiently related to a substrate being handled by the enzyme system that it has an affinity for the definitive component of the reaction process, but is itself refractory to the action of the system. Such a compound will inhibit the transport of the susceptible substrate depending on the degree of saturation of the system with the refractory agent, which in turn is determined by their relative concentrations and affinities within the cell. Beyer stresses the 'blocking' nature of this inhibition as being devoid of any essential alteration of the mechanism itself; accordingly, the extent and reversibility of the inhibition depend on the rate at which saturation of the system is attained, its completeness and the time taken for the refractory compound to be metabolized or excreted.

In seeking to localize the intracellular site of benemid interference, its effect has been studied in many experimental enzyme systems. Taggart<sup>114</sup> draws special attention to its inhibition of the reaction whereby benzoate and glycine are conjugated to form hippurate. In view of the fact that this reaction is dependent on the Co-enzyme A system, it is likely that the latter plays an important part in tubular secretory mechanisms (and in the closely related one of urate reabsorption).

Beyer recognizes two more classes of renal transport interference, mainly relating to electrolyte excretion rather than the handling of organic molecules. These are:

(f) Inhibition of ion exchange mechanisms for electrolyte reabsorption, exemplified by the use of mercurial diuretics and carbonic anhydrase inhibitors in altering the excretion of sodium, chloride and water and modifying the pH of the urine.

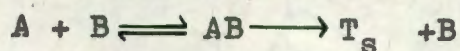
(g) Alteration of the endocrine (e.g., pituitary or adrenal) control of a secretory or reabsorptive function either experimentally or by disease.

The stimulation of tubular transport mechanisms has been studied less extensively; the most revealing data demonstrate

that small organic structures, e.g., acetate, pyruvate, lactate (in descending order of activity) enhance the secretion of PAH and play a leading role in transport reactions.

### 3. Proposed scheme of tubular transport.

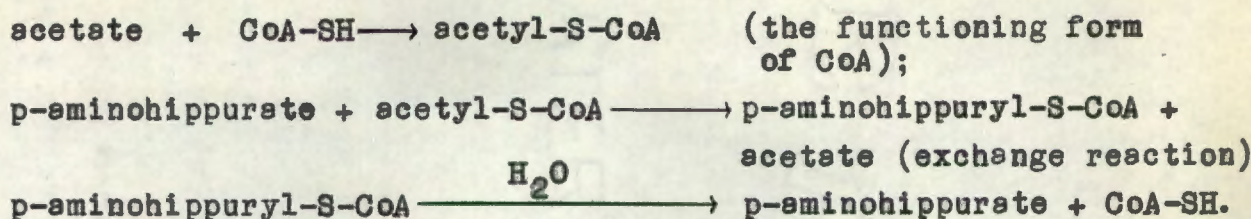
Taggart has proposed the following scheme to correlate the available evidence regarding tubular transport. It is based on Shannon's simple concept <sup>103</sup> which he expressed in the equation



where A is the transported compound at the proximal side of the reaction, B a cellular component, AB the intermediate compound formed reversibly by these two which is prevented from outward diffusion through the cell membrane, and  $T_s$  the transported solute on the distal side of the reaction, the progress of which he regarded as being limited by the breakdown of the intermediary compound. Since active transport implies the movement of A against a chemical potential, free energy is required to be expended in one or both steps of the reaction; this is assumed to be provided by energy-rich phosphate bonds, interference with which impairs transport. Energy from Krebs cycle oxidations must also be implicated, since non-lethal oxidative inhibitors like dehydroacetic acid (DHA) and cinchophen, which inhibit the enzyme succinic dehydrogenase, can suppress tubular secretion of PSP and PAH and urate reabsorption <sup>105</sup>.

Having considered energy requirements, Taggart then nominates the intermediate cellular link in the PAH transport system as Co-enzyme A (CoA), a molecular complex formed from adenosine pyrophosphate, pantothenic acid and beta-mercaptoethylamine <sup>122</sup>. This structure has been found to be a 'spring-board' for the biochemical activity of many smaller-sized organic groups, notably acetate, succinate, benzoate and fatty acids, by forming and unforming ester linkages with them through its -SH group. Recalling the experimental inhibition of glycine-benzoic acid conjugation by benemid, a process dependent on Co-enzyme A, Taggart suggests a correlation between the PAH transport group, their inhibitors and CoA activity. He states that the only structural feature shared by inhibitors of PAH transport, especially those without related respiratory effects, is a carboxyl (-COOH) group. All the compounds which appear to share the same excretory pathway are also carboxylic acids, except PSP. Accordingly it is suggested that the transported substance, by ester condensation between its -COOH and the -SH of CoA, links with the latter to form a mercaptan. At the

distal end the transported compound is released by hydrolysis, e.g.,



A competitive inhibitor is visualised, in this scheme, as using its own carboxyl group to block the mercaptan linkage with CoA, thereby excluding the transport substance. The fact that acetate has been shown to stimulate PAH transport<sup>105</sup> in secretory experiments is applied to the scheme in terms of its activation of CoA.

There are several flaws in this neat hypothesis, of which Taggart himself acknowledges one - failure to account for transport of PSP, which has no -COOH but is a typical member of the transport system. The following criticisms also seem to apply:

(1) The tubular mechanism under consideration is responsible, from all the evidence, for urate reabsorption as well as secretion of various foreign molecules. Uric acid is also devoid of a -COOH group, as are 17-ketosteroids, whose excretion is also blocked by benemid<sup>50</sup>.

(2) Among the inhibitors of the system there are several whose molecule lacks a -COOH group, without any alternative evidence that their effect is due to significant impairment of cellular respiration. Thus, while dehydroacetic acid (DHA) could not be cited in objection because its interference is reasonably ascribed to inhibition of an oxidative enzyme responsible for energy production, there is no positive cause for regarding phenylbutazone or cortisone in similar light. (That such a possibility exists for phenylbutazone is, admittedly, suggested by Kuzell's statement<sup>80</sup> that it depressed the oxygen consumption of rat brain).

(3) If CoA is believed to be the cellular intermediary of transport, this function would be in addition to its already recognized role in vital enzymatic processes such as the Krebs cycle itself. Since the evidence reasonably implicates the Krebs cycle as an energy source for one or more steps of the

transport mechanism, an inhibitor which acted (as suggested for benemid) by blocking CoA in its ferry-boat role would surely be blocking its participation in the energy cycle as well. To show that benemid inhibits PAH transport without having 'related respiratory effects' must contradict the terms of the proposed hypothesis.

(4) The stimulatory activity of acetate on the transport mechanism is only partially accounted for by its conversion of CoA to the functioning acetyl form, even granting CoA its importance as a link. This remark is based on the fact that the addition of acetate will actually antagonize the suppressive effects of carinamide, DHA and 2,4-dinitrophenol (DNP) each of which has been thought to interfere at a different site in the total transport mechanism (Table 1)<sup>105</sup>. One might suggest, therefore, that in overcoming DHA (which inhibits succinate oxidation in the Krebs cycle) the acetate acts by supplying particles to extra succinate formation and saturating the inhibitory capacity of the DHA present. The correction by acetate of DNP suppression is less easily explained, except to infer that the relation between oxidation and phosphate-bond generation (which DNP severs) is also dependent in some way on the vital two-carbon acetate-fragment.

In a system of such complex inter-connections, it is problematic whether the exact pin-pointing of various molecular activities is likely to provide a satisfactory solution. Certain other implications of renal tubular transport mechanisms will be considered in the discussion following the tromexan experiments.

CHAPTER 3.      EXAMPLES OF THE URICOSURIC ACTIVITY  
OF BENEMID

A.    INTRODUCTION

B.    METHODS

1.    Diet
2.    Benemid dosage
3.    Twelve-hour urine collections
4.    Renal clearances of endogenous urate and creatinine
5.    Urate estimation
6.    Creatinine estimation
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C.    RESULTS OF BENEMID ADMINISTRATION

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  - (a)    In absence of renal disease
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CHAPTER 3.      EXAMPLES OF THE URICOSURIC ACTIVITY OF BENEMID

A.    INTRODUCTION

During the study of benemid as a therapeutic agent in the long-term management of gout, the opportunity was also taken of observing its biochemical effects in a small number of non-gouty subjects. Some of the results are shown here to illustrate the action of the drug and to contrast its effects in normals, in varying stages of gout, in certain kinds of renal disease and in other conditions.

## B. METHODS

### 1. Diet.

No detailed restrictions of purine intake were imposed either on the patients cited in this section or on those with gout who took benemid continuously. However, frankly purine-laden foods (liver, kidney, sardines, anchovies, brains and sweetbreads) were omitted routinely to avoid undue fluctuation in urate excretion and to spare gout patients a needless addition to their urate metabolism. It was felt that stricter regulation of diet was unreasonable in the light of evidence that most foods can contribute to urate synthesis, and that an efficient uricosuric drug, whether in acute or prolonged studies, should outweigh any influence exerted by moderate dietary changes on serum and urinary urate levels.

### 2. Benemid dosage.

The drug was administered orally in the form of 0.5 G. tablets, the usual dosage being one tablet thrice daily. In some, the effect was observed of increasing to four tablets daily from an initial daily dose of two. As advised by other workers, all those receiving benemid in the earlier months of the study were also given an alkaline mixture to oppose urate crystallization in acid urine (potassium citrate 5-6 G. daily). This practice was gradually discontinued with increasing doubt as to its usefulness, and because many patients found it neither convenient nor pleasant to take regularly.

### 3. Twelve-hour night urine collections.

To measure changes in total urinary excretion of urate, urine was collected over fixed 12-hour periods from evening till morning, with toluol as preservative. The relative hardship of 24-hour collections, especially for patients followed up after leaving hospital, and the risk of urine loss during bowel actions or through forgetfulness, were thereby reduced. The fact that urate excretion is normally somewhat diminished at night <sup>27</sup> meant that the 12-hour determinations could not be regarded as exactly half the daily urate output, but could still serve as a serial guide to quantitative changes produced by benemid. Furthermore, the physiological error involved in estimating 24-hour excretion on the basis of nocturnal 12-hour collections is probably smaller than the

other potential errors of the whole operation.

Determinations were always made of both urinary urate and creatinine, and considerable attention paid to the serial behaviour of the urate/creatinine ratio rather than to urate output alone, because absolute changes in the latter may be marked by incomplete urine collections, by possible changes in glomerular filtration rate, and by wide variations in urine volume.

#### 4. Renal clearances of endogenous urate and creatinine.

These were always performed under standard conditions, in the morning, at rest, after liberal hydration and a snack breakfast. Urine was collected at carefully timed intervals of about 30 minutes by spontaneous voiding. Patients were instructed in the technique of bladder emptying, and the first collection was usually regarded as a practice one. Those manifestly unable to co-operate or lacking good bladder control were excluded. Nearly all clearance experiments were personally supervised, the few exceptions being managed and timed by a house-physician or trained nurse. To obviate variations in urate clearance at low urine flows <sup>27</sup>, collections of less than 2 ml. per minute - rare with good hydration - were not used. In the absence of intravenous priming infusions (which require successive mid-point blood samples), venous blood was as a rule drawn once (e.g., during the second of three successive collection periods), sometimes more often depending on the duration of the test. Specimens of urine and serum not analyzed on the day of collection were stored at 0-5°C. and dealt with not longer than a day or two later.

#### 5. Urate estimation.

This was performed throughout the work of the thesis by the method of Herman Brown (1945) <sup>32</sup>, as adapted to the analysis of both urine and serum in the laboratory of Prof. G. C. Linder, Cape Town Medical School. The method is based on the blue colour formed between urate and phosphotungstic acid in the presence of cyanide and urea, using a photo-electric colorimeter (Klett-Summerson) to measure the unknown against a standard. The procedure is simple and fairly rapid, gave a 95% recovery of uric acid experimentally in Brown's hands, and is subject to less non-specific enhancement

and interference than many dozens of colorimetric methods used in the previous few decades. These advantages, which make it useful for serial estimations in a large group of patients, outweigh the fact that it lacks the high specificity of the latest, but more involved, enzymatic techniques <sup>21, 72</sup>.

6. Creatinine estimation.

The method followed was that of Bonsnes and Tausky <sup>26</sup> based on the Jaffe alkaline-picrate colour reaction. Variants of this method are in universal use for the determination of so-called endogenous creatinine chromogen, clearances of which are believed to approximate the glomerular filtration rate (as measured by inulin) even more closely than values obtained using an exogenous creatinine technique <sup>29, 87, 112</sup>.

7. Normal standards.

Control figures obtained for serum urate and urate-creatinine clearances are presented more fully in Section III together with the results in the gout series. Relevant standards may be mentioned here:

- (a) Serum urate . . . . 6 mg./100 ml. (approximate upper limit of normal);
- (b) Serum creatinine . . . 0.6 to 1.1 mg./100 ml.;
- (c) Glomerular filtration rate (endogenous creatinine clearance) . . . . . 127 and 117 ml./min. in men and women respectively, calculated per body area of 1.73 m<sup>2</sup>. From 50 years of age onwards, allowance is made for 'physiological' diminution of glomerular filtration <sup>107</sup>.
- (d) 24-hour urinary urate excretion in normal subjects on a low intake of purine is of the order of 400 mg., higher figures occurring i.e. with greater consumption, with increased nitrogen catabolism (fever, starvation), with greater nucleoprotein turnover (red or white marrow activity) and to a small but significant degree in most gout subjects without frank renal impairment <sup>59</sup>.
- (e) Normal urate clearance is of the order of 10 ml./min., <sup>59</sup> giving a urate/creatinine clearance ratio of about 0.1.

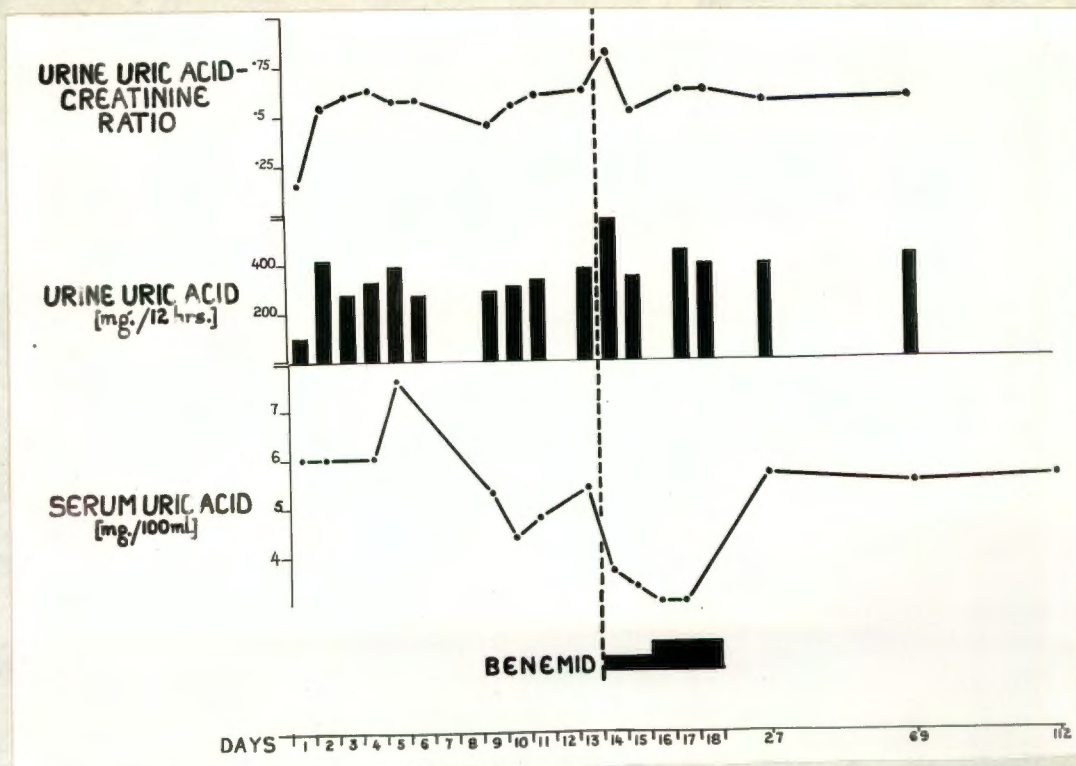


Fig. 3. Changes in urinary excretion and serum concentration of uric acid, resulting from administration of benemid (1-2 G. daily) to a patient with early gout. (Case 61.)

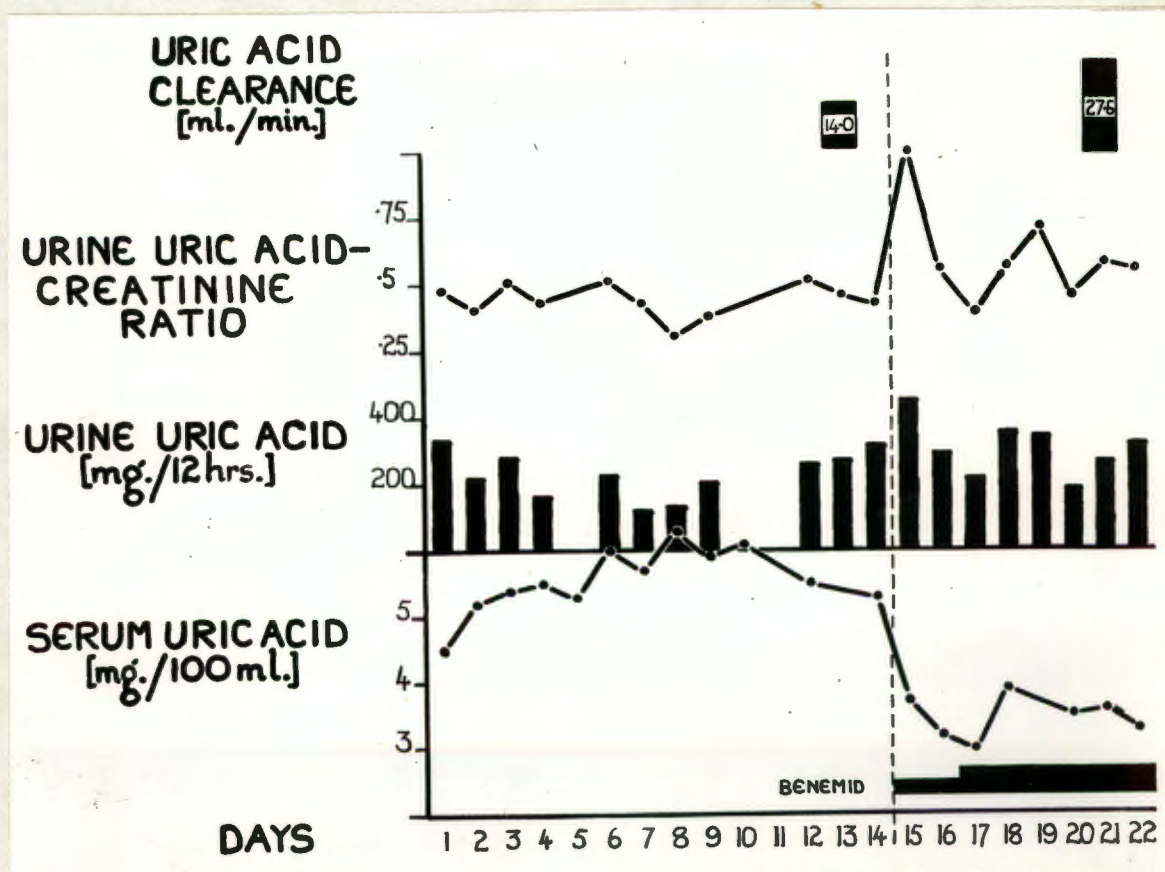


Fig. 4. Effects of benemid administration (1-2 G. daily) in a patient with lymphocytic leukaemia. As in case 61 above, urate diuresis is maximal initially.

## C. RESULTS

Table 2 and Figs. 3-7 provide eight individual illustrations of benemid activity in different clinical conditions. Their purpose is to demonstrate the principles of uricosuric action and the main factors influencing it. As no statistical compilation is intended in this chapter, data in other patients have not been included which would not have amplified a particular item further.

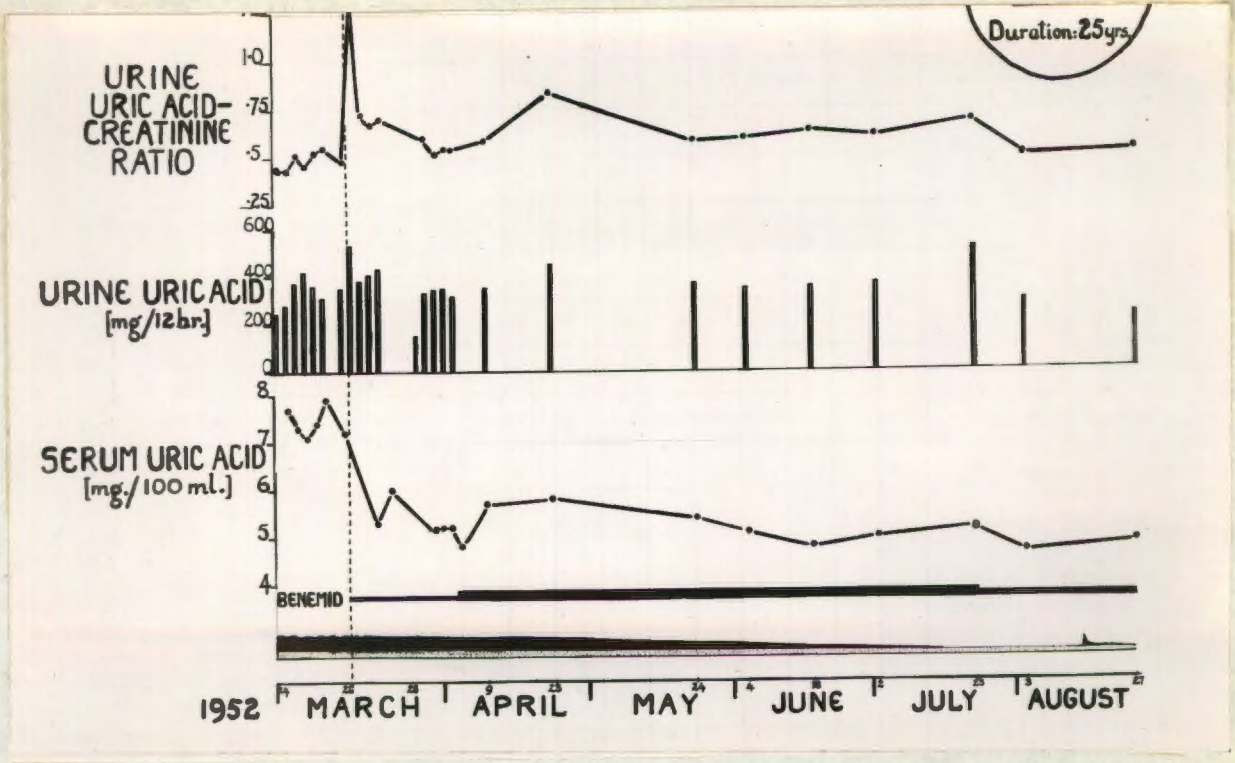
### 1. Serum urate.

Daily values were determined for each of the subjects in Table 2. Every study period was divided equally into control and benemid phases, and the average value for each phase used in calculations. In every instance the concentration of serum urate fell at the first analysis (24 hours) after starting the drug. In acute experiments involving a diurnal series of determinations, the effect of orally ingested benemid was seen as soon as one hour later. The degree of lowering of serum urate varies considerably, being typically of the order of 40-50% in normal subjects and those with 'uncomplicated' gout, and least in those with severe renal disease at the stage of nitrogen retention. As illustrated in Table 2 by case 4 (advanced gout with many large tophi), the effect of benemid in lowering serum urate may be largely offset by the presence of an excessive 'miscible metabolic pool' which promptly replenishes excreted urate.

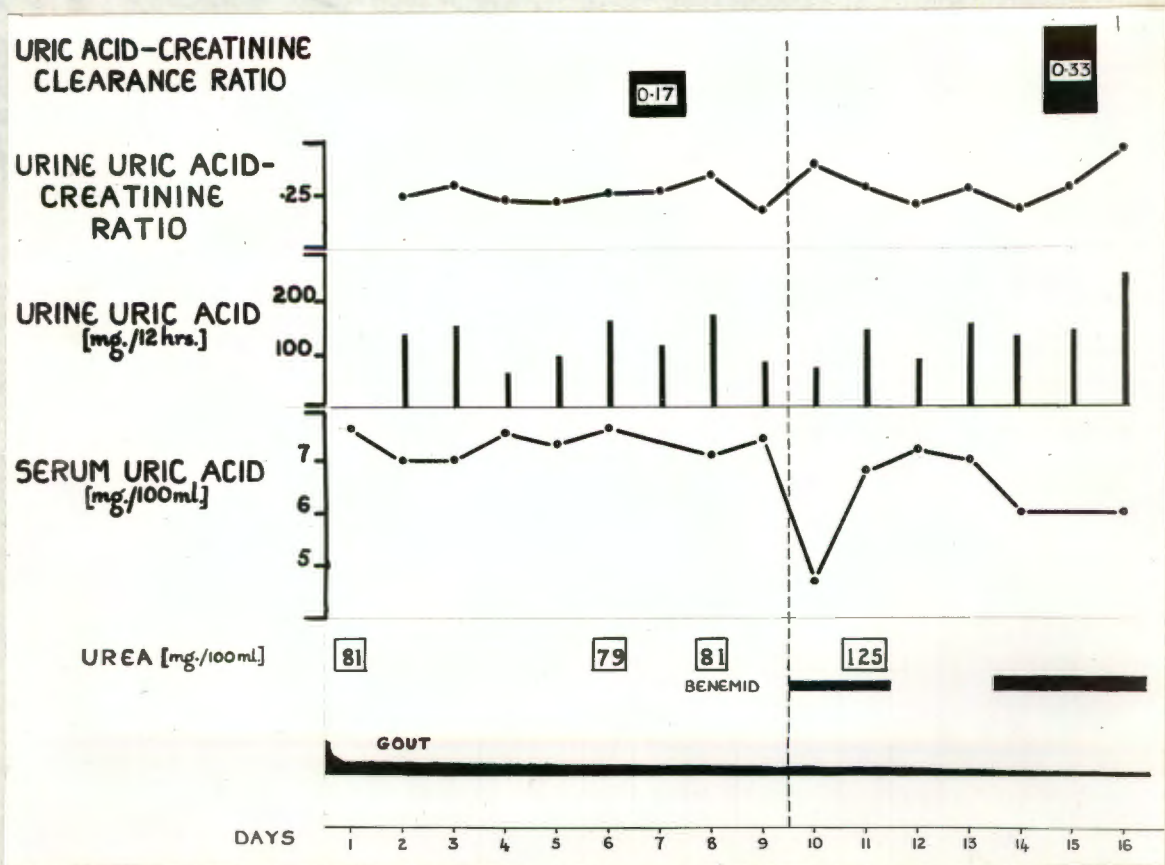
Not only during short 4-7 day studies like these, but in others taking benemid regularly for many months, the serum urate is kept with fair constancy at its new low level. (Fig. 5). After stopping the drug previous levels are regained in 2 days to a week, those with the smallest 'pool' taking longest to do so. (Fig. 7).

### 2. Urate clearance.

Short-period clearance tests were carried out on one of the control days (usually immediately before benemid was begun) and on one of the drug days. No case failed to show an increased clearance of urate and a rise in the ratio of urate to creatinine clearance. Specially noteworthy are the following observations:



**Fig. 5.** Benemid administration (1-2 G. daily) for several months to patient with chronic tophaceous gout (case 7). Serum urate levels remain consistently normal, and quantity excreted stays higher than control figures for many weeks while "stores" are depleted.



**Fig. 6.** Unimpressive, though definite, uricosuric response to benemid by gout patient with progressive renal failure (case 28). The doubling of urate/creatinine clearance ratio mainly reflects diminished glomerular filtration.

(a) In the absence of renal failure, the urate clearance is more or less doubled, and since benemid produces no significant change in glomerular filtration rate, the urate/creatinine clearance ratio is increased by about the same amount.

(b) The presence of even severe renal disease with uraemia is still compatible with some uricosuric effect, as demonstrated by case 28 (Table 2 and Fig. 6) and subject C. F. (Table 2), and observed in several gout patients with renal disease who took benemid therapeutically. This carried practical implications in the long-term management of gout, where it may be important that significant amounts of urate can be drained from those with advanced joint disease in whom some grade of kidney lesion is common.

At a late stage in any nephritis, when virtually the whole nephron has become involved, it might seem surprising that the tubular function of reabsorbing urate is sufficiently preserved to permit of its modification by benemid. For example, the clearance of urate is relatively well maintained in progressive renal disease with azotaemia, as this study and others before<sup>38, 107</sup> have regularly shown. Presumably this is an expression of impaired urate reabsorption by failing tubules, so that even the reduced urate load associated with a falling glomerular filtration rate is beyond the capacity. That such tubules can respond to the action of benemid by further impairment of urate reabsorption, suggests a survival of tubular reserves until a very late stage.

One other item of laboratory interest emerges from the foregoing observations: if, in the total azotaemia of renal failure, the reduction of urate clearance is relatively less than for creatinine, it is unlikely (as suggested by earlier workers) that significant hyperuricaemia will precede the retention of other nitrogenous products as an early chemical sign. We have been struck by the way that serum urate levels, even in gout patients with previous hyperuricaemia, have lagged behind urea and creatinine in their rate of increase in advancing renal failure.

(c) The results of benemid administration to patients with 'primary' renal tubular disorders were interesting, especially

in view of the findings of Sirota, Yü and Gutman<sup>106</sup> in one similar case. They reported a patient with marked glomerulo-tubular imbalance of the Fanconi type, in whom glomerular filtration was abnormally low, and, in addition, tubular constants were strikingly diminished and glycosuria, amino-aciduria and hyper-phosphaturia were present. Urate clearance was over 25 ml./min., virtually equal to glomerular filtration, and they inferred that tubular reabsorption of urate was in abeyance, explaining also a reduced plasma urate of 2.3 - 2.8 mg./100 ml. These workers found this patient to be the only one in their experience who failed to show enhanced urate clearance on administering benemid, an observation explicable by the absence of a normal reabsorptive process for the drug to act on.

In Table 2, subject A. E. is one of two child siblings suffering from a similar condition of multiple tubular defect and other congenital abnormalities, who have been reported by Jackson and Linder<sup>70</sup>. It may be seen that an unequivocal uricosuric effect was produced by the administration of benemid for six days, the average serum urate falling by 30%, the urate clearance rising, and the total amount of excreted urate increasing by a third of the mean daily control value. The difference in uricosuric response between this patient and that of Sirota and colleagues seems to lie in the normal tubular reabsorption of urate in ours (clearance 9.2 ml./min., daily output not high, and serum levels acceptable for a young child). The stage is thus correctly set for the action of benemid, and the margin of latitude within the Fanconi type of disorder (stressed by Jackson and Linder) further illustrated. This patient's brother, in whom evidence of proximal tubule defect was much greater, gave entirely similar results.

A comparable defect of tubular reabsorptive processes is now known to exist in hepato-lenticular degeneration<sup>6</sup>. Subject D. W. was given benemid for one day and urate clearance compared before and after. It may be inferred (Table 2) that, in addition to mild and inconstant proteinuria, glycosuria and amino-aciduria, and his disturbance of copper metabolism manifesting itself as marked hypercupruria, this patient has moderately defective tubular reabsorption of urate, with sufficient normal reserve to respond to the interfering action of benemid. Thus an abnormally high urate clearance is further increased, and a low serum urate of 2.1 reduced to 1.7 mg./ 100 ml.

The possibility that such variations in the degree of benemid responsiveness might constitute a diagnostic approach to the severity of the lesion in an individual case is not strongly suggested by the foregoing data, among which the direct evidence of particular disturbances seems more informative.

### 3. Daily urate excretion.

The values recorded are based on the serial 12-hour night collections whose urate content has been doubled in approximation of the true 24-hour output. To reduce to a minimum any errors due to loss of specimens or variations in urine flow, each subject's urate excretion has been corrected to a constant 24-hour creatinine output (for each one, his average creatinine figure for the whole study period).

The results are the counterpart of those for serum urate: the quantity of urate excreted under the influence of benemid is dependent on the absence of severe renal impairment and on the size of the available urate reserves. The significance of these figures, however, is much wider than suggested by the latter conclusion. They serve to show, in a simple way, some of the implications of the recent concept of a miscible urate pool, and the concrete benefits theoretically to be derived from effective uricosuric therapy in gout:

(a) Normal subject. The excess urate output during the six days on benemid measures 6 x 120 mg., the mean daily excretion having risen from 550 to 670 mg. Mason has recalled that it is possible to calculate (as Graham did in 1920) the quantity of urate lost from the plasma if one is able to follow the changing level of its concentration during the uricosuric period. If it is assumed that urate is distributed throughout the extra-cellular fluid at the same concentration, the following would be the theoretical urate loss from the body in subject R. S. M. (weight 75 Kg; extra-cellular fluid regarded as 0.2 body weight):

Body urate before benemid	(5.7 mg./100 ml.)	=	860 mg.
" " after	" (2.9 " "	)	= 435 mg.
Calculated loss of urate from body		=	425 mg.

Since the observed loss in the urine amounts to 720 mg. for the period during which the serum urate averaged

Subject	Length of study (days)	Serum urate (mg./100 ml.)			Observed mean daily urate excretion (mg./24 hrs.)			Creatinine clearance (ml./min.)		Urate clearance (ml./min.)		Urate/creatinine clearance ratio		
		Control	Benemid	% fall	Control	Benemid	% rise	Control	Benemid	Control	Benemid	Control	Benemid	% rise
R.S.M. (Normal)	12	5.7	2.9	49	550	670	22	129	155	10.4	22.2	0.08	0.16	103
Case 61 (Early gout)	8	5.2	3.3	37	714	820	15	74.8	84.8	10.1	20.1	0.14	0.24	72
Case 4 (Advanced gout)	8	7.3	6.4	12	694	1024	48	103	52.1	9.1	13.9	0.09	0.27	200
Case 28 (Gout and renal failure)	12	7.5	6.6	9	342	300	22	35.2	24.2	5.9	8.0	0.17	0.55	94
G.F. (Chronic nephritis)	12	4.2	3.9	7	222	244	10	29.7	34.2	6.8	8.2	0.25	0.26	13
A.S. (Fanconi tubule-defect)	12	2.5	1.6	30	248	355	34	24.5	46.4	9.2	22.5	0.38	0.48	26
D.W. (Hepato-lenticular degeneration)	-	2.1	1.7	19	-	-	-	122	115	30.4	40.7	0.25	0.56	44
R.T. (Lymphocytic leukaemia)	14	5.8	3.6	38	472	656	39	90.2	98.4	14.0	27.6	0.16	0.28	77

Table 2. Summary of effects of benemid administration in 8 different conditions. (Discussion in text).

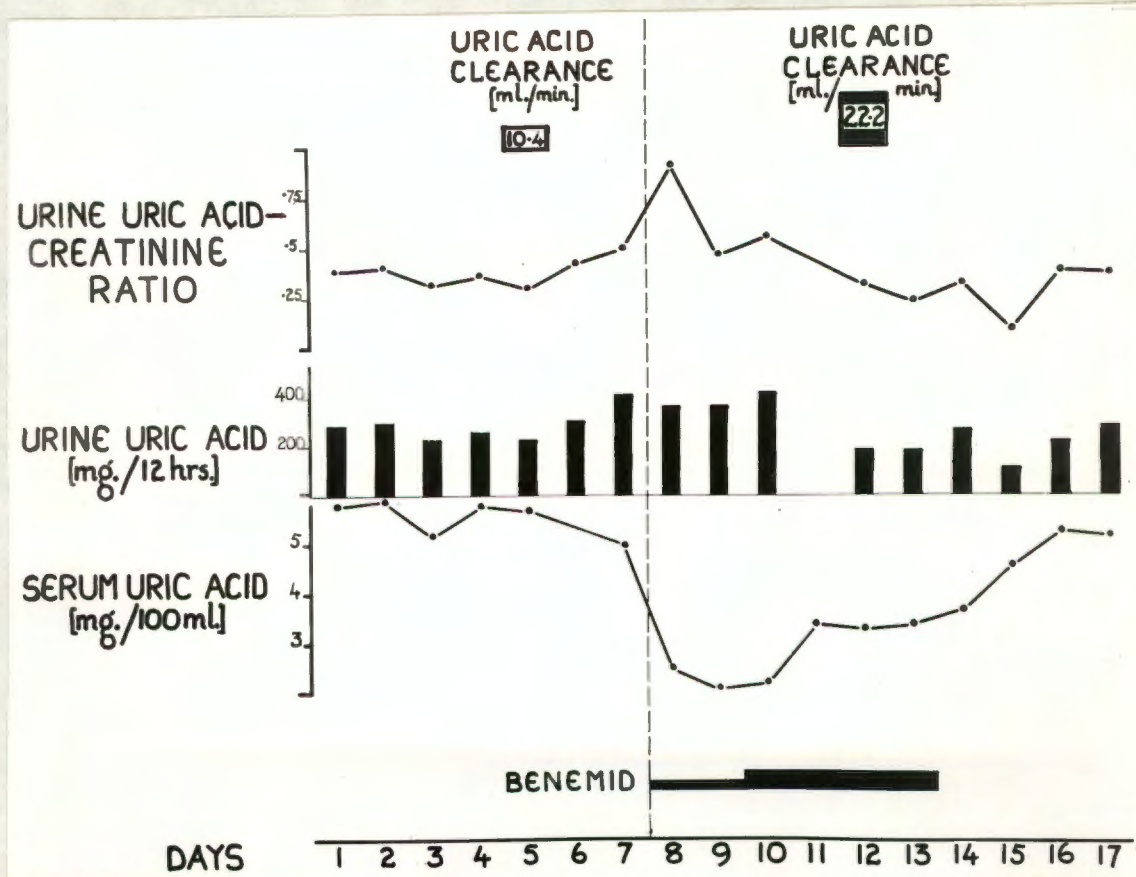


Fig. 7. Marked but short-lasting uricosuric effect in normal subject receiving benemid (1-2 G. daily). Urate excretion dwindles in a few days while still on the drug, cessation of which is followed by a temporarily sub-normal output.

2.9 mg./100 ml., there are roughly 300 mg. which have come from somewhere other than the extra-cellular fluid. While this discrepancy might readily be ascribed to the technical errors and false assumptions underlying the calculation, the same manoeuvres applied to case 4 yield very different results.

(b) Advanced tophaceous gout. In case 4 (Table 2) a rather high resting output is strikingly augmented during benemid dosage, the excess amounting to 1,320 mg. in 4 days. Far from showing a commensurate fall in serum urate, however, the average only changes from 7.3 to 6.4 mg./100 ml., the difference accounting for a theoretical loss of 140 mg. A source for a further 1,180 mg. of urate drained by benemid has to be explained. Not even the assumption that body urate is equally distributed throughout the total body fluids <sup>55</sup> (which would magnify the theoretical loss to 480 mg.) meets the discrepancy in this patient. It is but one step further to postulate that urate in the solid phase as tophi contributes to the metabolic pool. It will be recalled that recent isotope dilution techniques <sup>10, 52</sup>, have led to the same conclusion, which carries the implication that at least part of the tophaceous deposits in established gout are susceptible to mobilization. Gout subjects without overt tophi also have a urate pool greater than normal, which can be depleted even more easily by the use of uricosuric agents. It is probably on such a basis that, while maintaining lowered serum levels for many weeks or months, a gout patient taking benemid gradually excretes less urate in so doing, until returning to the pre-benemid daily output. On withdrawing the augmenting effect of benemid, the daily excretion tends to fall to subnormal levels for a temporary period while the pool reconstitutes. This sequence of changes occurs most rapidly in a normal subject (Fig. 7) where a few days' dosage is enough to show commencing return of urate output to control figures, and a temporary subnormal depression on stopping.

CHAPTER 4.      TROMEXAN, A POTENT URICOSURIC AGENT

A.      DISCOVERY

B.      CONFIRMATION OF URICOSURIC ACTIVITY

1.      Men

- (a)      Effect of a single oral dose of tromexan on the level of serum urate
- (b)      Effect of tromexan on urate clearance and on urate/creatinine clearance ratio
- (c)      Influence of renal disease on the uricosuric effect of tromexan
- (d)      Effect of simultaneous benemid and tromexan administration on urate clearance

2.      Rat

- (a)      Procedure
- (b)      Results
  - (i)      Serum urate level
  - (ii)     Urinary urate concentration
  - (iii)    Secondary effect of tromexan on urate metabolism

3.      Cat

4.      Dalmatian coach hound and mongrel dog

- (a)      Background
- (b)      Experimental procedure
- (c)      Results
  - (i)      Mongrel dog
  - (ii)     Dalmatian coach hound

C.      EFFECT ON OTHER RENAL TUBULAR TRANSPORT FUNCTIONS

- 1.      Para-aminohippurate (PAH)
- 2.      Penicillin
- 3.      Phenolsulphonphthalein (PSP)
- 4.      17-Ketosteroids

## CHAPTER 4. TROMEXAN, A POTENT URICOSURIC AGENT

### A. DISCOVERY OF THE URICOSURIC ACTION OF TROMEXAN

Ethyl biscoumacetate, or tromexan (Fig. 1), is a synthetic anticoagulant drug introduced in the last five years for the clinical management of thrombo-embolic disease. Compared with the closely related dicoumarol, it has the advantages of speedier increase in the prothrombin time and of smaller delay in returning to normal on stopping the drug. A typical effective single oral dose in man is 1,500 mg., making it about five times less potent than dicoumarol<sup>130</sup>.

The uricosuric properties of tromexan were first noticed under the following circumstances;

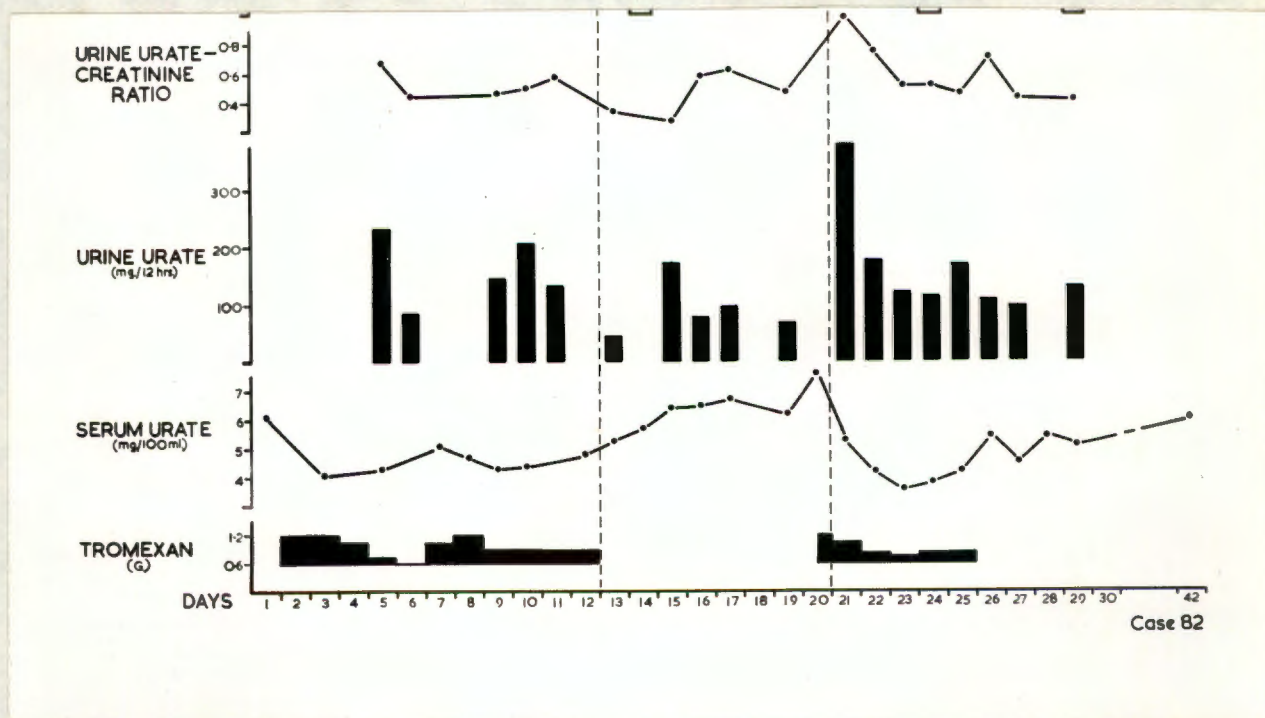
A gout patient, case 82 of the series, was admitted to hospital for clinical assessment. In addition to the recent onset of episodic arthritis which responded to colchicine and with which there was hyperuricaemia, he had symptomless auricular fibrillation, pyramidal tract disturbances, and a firm, moderately enlarged liver. He was 58 years old and an inveterate alcoholic.

Serological reactions for syphilis were negative in both blood and CSF, air encephalography showed diffuse cortical atrophy, and no additional evidence, clinical or cardiographic, of heart disease was found. He was given a course of quinidine to correct the auricular fibrillation, and as it was presumably of long standing, anticoagulant measures were taken in case of thrombo-embolism.

After a day or two on quinidine and tromexan, (dosage of the latter being guided by daily prothrombin estimations), it was noticed that he was no longer hyperuricaemic. When the drugs were discontinued because of failure to convert the arrhythmia, the serum urate, which was being followed in case of future uricosuric therapy, rose to its former level. Simultaneously, total urate excretion and the ratio of urate to creatinine output dropped.

This coincidence of events prompted renewal of tromexan administration alone. The metabolic results (Fig. 8) were indistinguishable from those which a potent uricosuric agent like benemid might have produced. After another vein

attempt to correct the auricular fibrillation, and unaware of the excitement he had aroused, the patient was discharged.



**Fig. 8.** Changes in serum urate, urine urate, and urinary excretion ratio of urate/creatinine, during and after continuous tromexan administration to a gout patient.

B.      CONFIRMATION OF THE URICOSURIC ACTIVITY OF TROMEXAN

1.    MAN

(a)    The effect of a single oral dose of tromexan on the level of serum urate.

Four gout patients, three patients with coronary disease, in whom there was no overt cardiac or renal failure, one orthopaedic patient in good general health, and one normal subject were each given 1,200 or 1,500 mg. of tromexan in one oral dose. Serum urate was measured before the drug and one or more times in the succeeding 24 hours. The results are illustrated in Fig. 9, using the lowest value of the post-tromexan period when more

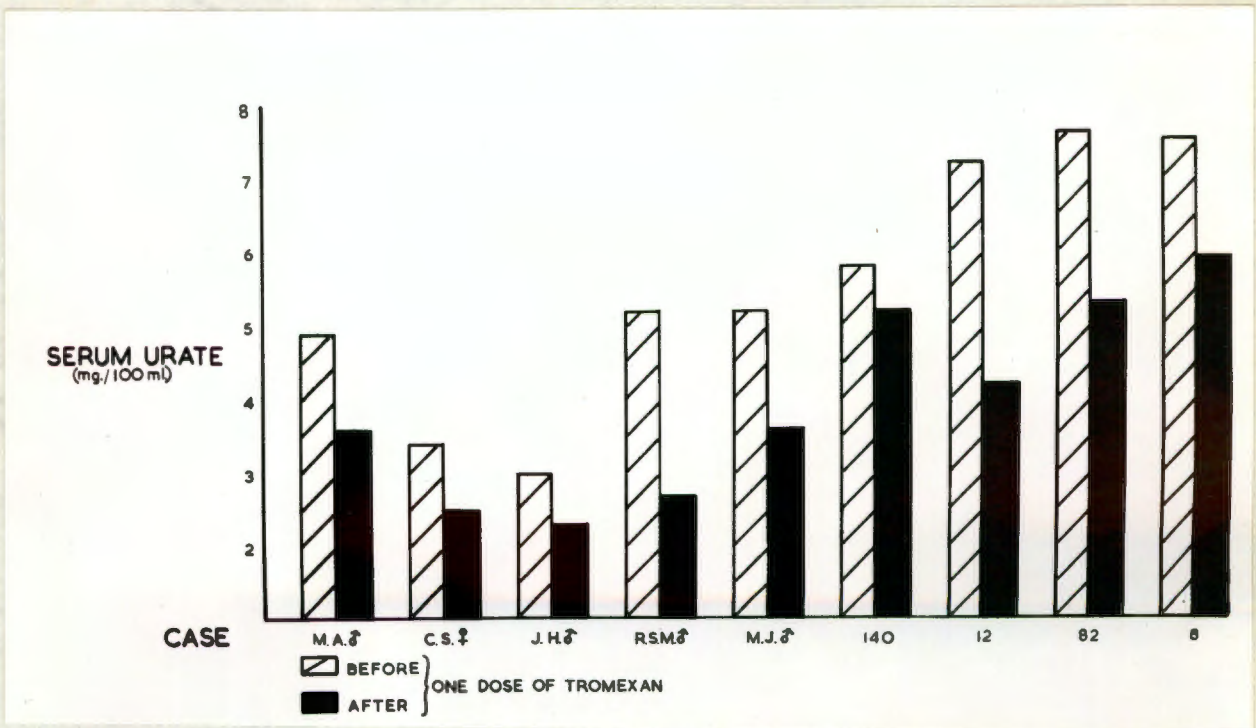


Fig. 9.      Effect of a single oral dose of tromexan (1,200-1,500 mg.) on serum urate concentration in 4 gouty and 5 non-gouty persons.

than one determination was made. (In addition, prothrombin time was measured before and after tromexan by the one-stage method of Quick).

In every instance there was an impressive fall in the serum urate concentration. This ranged in degree from 46% in the normal subject to 12% in one of the gout patients, a woman with severe hypertension and slight renal functional impairment. Case 8, suffering from tophaceous gout and severe renal disease, responded with a 22% fall.

The earliest clear-cut reduction occurred 1-2 hours after taking the tromexan tablets, and the maximum change after 5 hours in two subjects observed at frequent intervals. In the latter there was no lengthening of the prothrombin times until the following day.

(b) The effect of tromexan on urate clearance and on the clearance ratio of urate/creatinine.

Fig. 10 shows the change produced in the urate/creatinine clearance ratio of four gout patients and one normal.

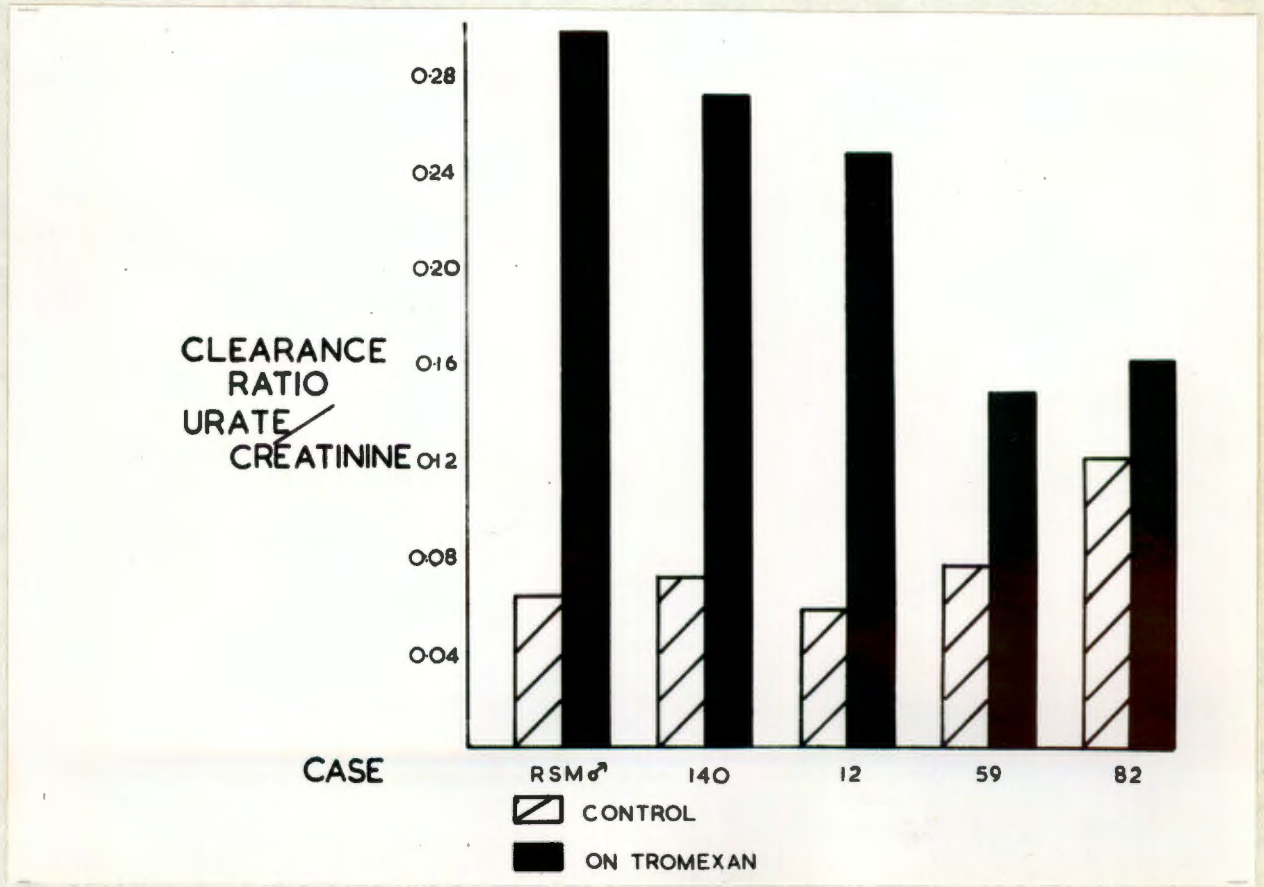


Fig. 10. Effect of tromexan on urate/creatinine clearance ratio in 4 gout patients and one normal subject.

In case 82, the clearance tests were done a week apart, the first soon after ending his initial course of tromexan and the second on resuming dosage. Each of the other subjects had clearances done for several successive periods (as described in Chapter 3.) immediately before and after taking one oral dose of tromexan. The smallest dose was 1,200 mg. (case 140) and the largest 1,800 mg. (subject R. S. M.). The bars in Fig. 10 represent the averages of the pre- and post-tromexan clearance values. The rise in urate clearance, and hence U/C ratio, is quite striking, the latter increasing by as much as 370%. No significant changes took place in creatinine clearance.

Table 3 shows in detail the individual results in R. S. M. and case 12, who were able to provide many collections of urine and blood in a diurnal series of clearances. In both, the following observations are noteworthy:

- (i) The first steep rise in urate clearance takes place during the collection period ending before the 2-hour post-tromexan mark. This denotes a lag of one to two hours after ingestion before uricosuric effect is exerted, which <sup>30</sup> is the time known to be taken for the absorption of tromexan .

Subject	Time (min.)	Urine flow (ml./min.)	Creatinine		Urate		Urate/creatinine clearance ratio	Prothrombin index (%)
			Serum concn. (mg./100 ml.)	Clearance (ml./min.)	Serum concn. (mg./100 ml.)	Clearance (ml./min.)		
(a) R.S.M. Tromexan: 1.5 G. ingested at + 7 mins. Oral hydration throughout	-172	2.45	1.26	104	5.15	8.20	0.078	
	-88	10.00	1.16	143	5.00	7.98	0.085	100
	-58	16.80	1.16	136	4.35	7.76	0.087	100
	0-39	10.65	1.11	117	4.26	9.26	0.079	
	40-118	1.48	1.00	128	4.30	37.5	0.293	
	119-234	1.00	1.20	104	4.32	35.2	0.339	100
	235-308	4.26	1.11	141	2.83	50.4	0.358	100
	309-367	5.18	1.20	101	2.72	34.0	0.337	
	368-418	2.27	1.20	109	2.72	40.2	0.369	
	(b) Case 12. Tromexan: 1.5 G. ingested at + 4 mins. Oral hydration throughout	-106	8.30	0.91	131	7.20	7.08	0.064
-76		7.10	0.88	126	7.40	8.80	0.070	100
-35		11.10	0.95	131	6.95	6.65	0.081	
0-39		11.30	0.88	157	6.20	8.90	0.057	
40-78		3.85	0.88	137	6.20	11.40	0.088	
79-114		10.40	0.81	162	6.20	35.0	0.216	
115-148		12.50	0.75	178	5.60	46.0	0.258	
149-184		8.55	0.75	140	5.60	29.0	0.207	100
185-221		8.65	0.80	140	5.00	26.3	0.188	
222-255		14.00	0.90	142	4.50	76.2	0.538	
256-299	12.30	1.02	118	4.15	66.0	0.560		
300-344	3.78	1.02	108	4.15	19.2	0.178		

Table 3. Effect of one oral dose of tromexan on urate clearance and urate/creatinine clearance ratio serially determined in one normal and one gout subject.

(ii) The greatest increase, attained in any single period in the urate/creatinine clearance ratio, is 480% (0.369 from 0.064) and 800% (0.560 from 0.058) respectively, considerably more than the average increase for each depicted in Fig. 10.

(iii) A significant rise in urate clearance precedes the first distinct fall in serum urate, supporting a renal site of uricosuric action.

(iv) Early slight loss of serum urate unassociated with a clearance rise, is detectable apparently as a result of sheer copious diuresis.

(v) Prothrombin activity, expressed as Prothrombin Index (Control prothrombin time/Subject's prothrombin time, x 100), stayed at 100% in both cases when urate clearance had already greatly increased. In this and other experiments, the impairment of prothrombin after one dose of tromexan was first detected at a time when serum urate was already returning to normal, usually on the day after the drug. This conforms to the recognized lag in the anticoagulant effect of tromexan in clinical states 130.

(c) The influence of renal disease on the uricosuric effect of tromexan.

Two of the patients studied, cases 82 and 8, had significant renal functional impairment according to criteria of clearances and azotaemia stated elsewhere. One of them (case 8) had severe chronic kidney disease with levels of serum urea at times exceeding 100 mg./100 ml. His metabolic responses to tromexan, given in divided daily doses for ten days, are illustrated in Fig. 11. Several weeks later a comparable record was obtained on starting benemid therapy, and is shown in the same chart for comparison.

Falling serum urate and rising urinary excretion were again associated with tromexan administration. Neither the serum concentration nor the urinary loss ran parallel with the daily values for the prothrombin index which varied independently from the somewhat fluctuating urate figures. Clearance ratios, determined during the control and tromexan periods, were unhelpful in clinching the uricosuric demonstration; reference to the chart suggests the excuse that for the second clearance test the serum urate level - denominator in the clearance formula had temporarily risen.

The pattern of response to benemid in this case is more impressive, but one would hesitate to draw conclusions as to relative effectiveness: the two drugs were separated by a considerable period during which a change in renal tubular function may have occurred, and the need for caution and daily dose-revision in the extended use of tromexan is not shared by benemid, which was taken more evenly.

The observations on both cases suggest that tromexan, whose uricosuric action as demonstrated thus far is apparently renal tubular in site, is only partially impeded in its effect by the presence of renal disease.

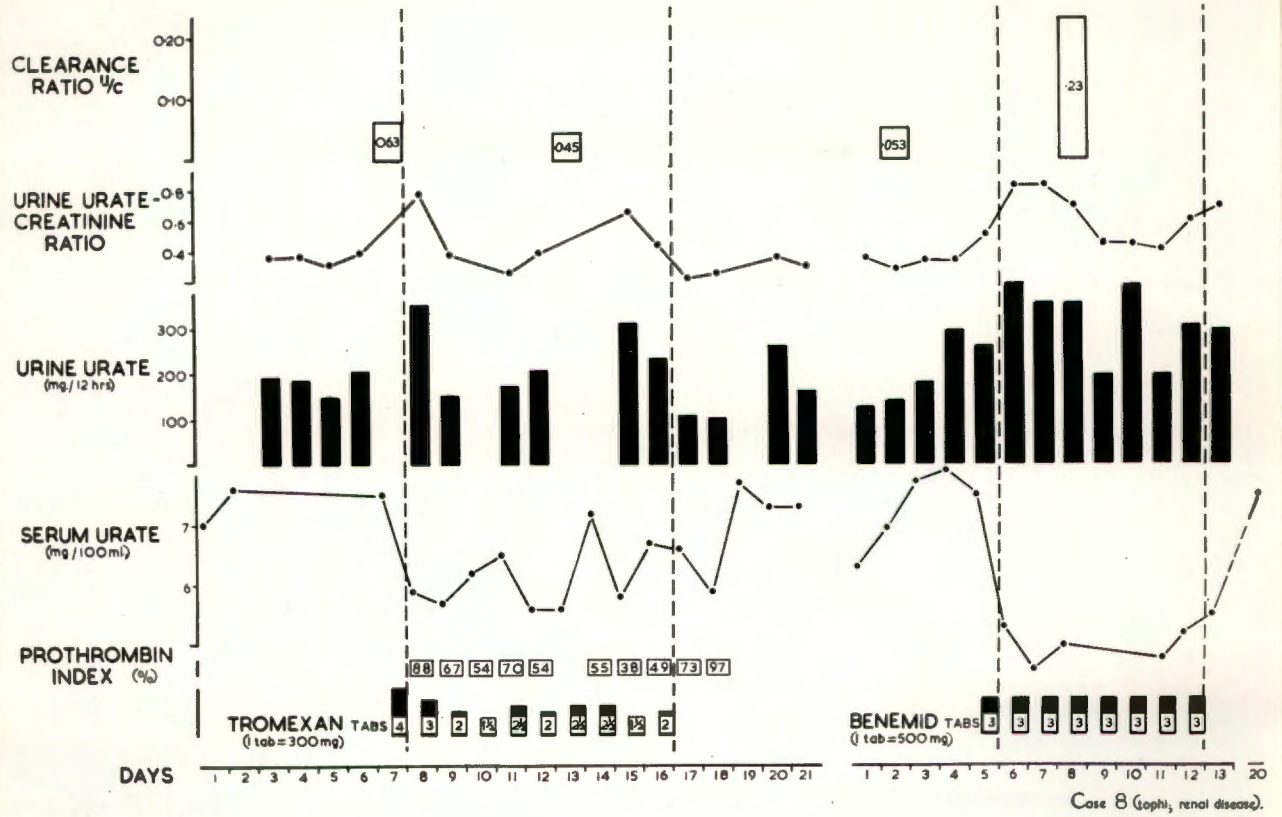


Fig. 11. Changes in urate excretion and serum urate levels during administration of tromexan - and subsequently benemid - to a gout patient with chronic renal failure.

(d) The effect of simultaneous benemid and tromexan administration on urate clearance.

One experiment was conducted on a normal subject (Fig. 12).

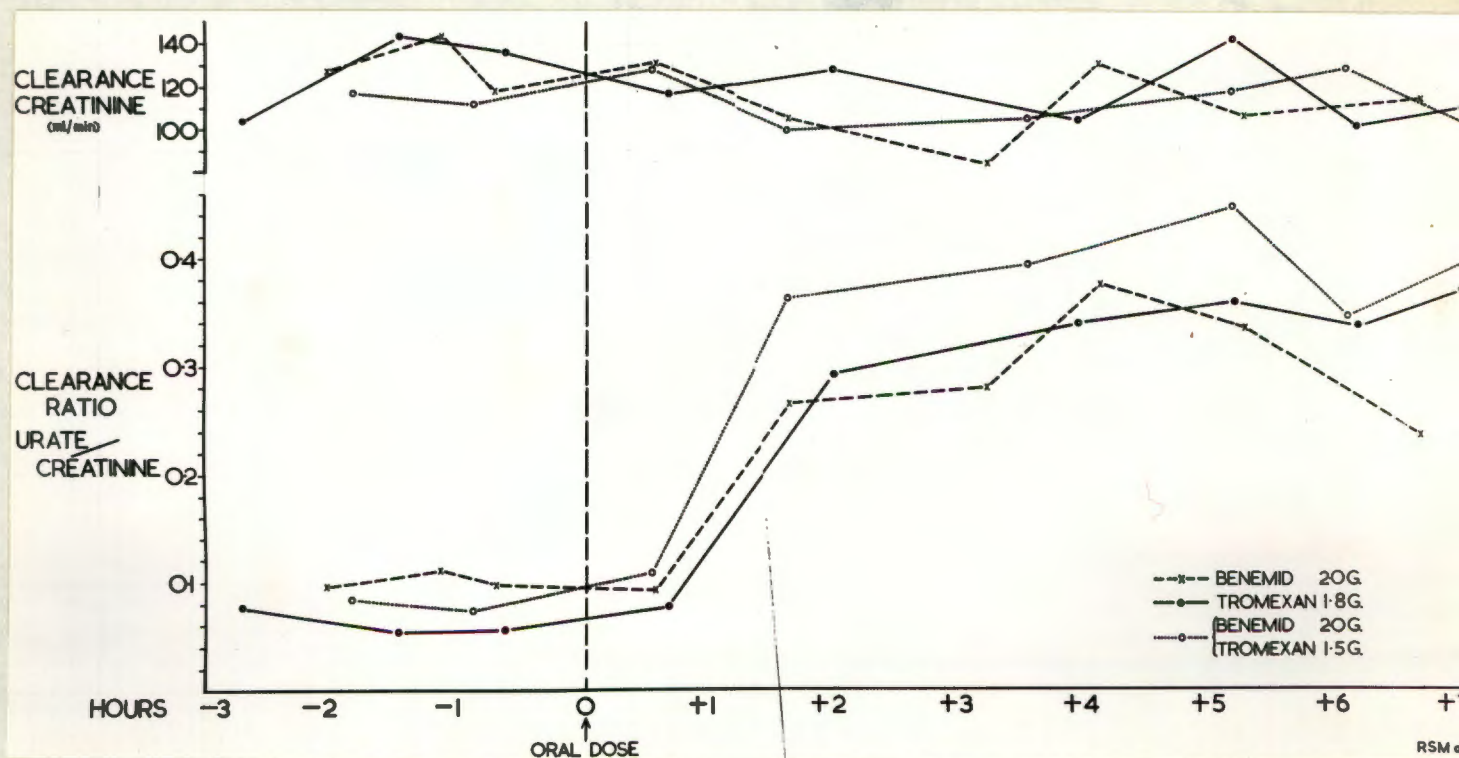


Fig. 12. Comparison of uricosuric effects of benemid and tromexan given singly and together to a normal person: The urate/creatinine clearance ratio increased  $3\frac{1}{2}$ -fold on benemid,  $5\frac{1}{2}$ -fold on tromexan, and 5-fold on the combined dosage.

A diurnal series of clearances was carried out in each of three days, separated from each other by five-day intervals to ensure elimination of drugs and restoration of balanced urate metabolism.

Each series of clearances tested the uricosuric effect of one dose of benemid (2.0 G.), one dose of tromexan (1.8 G.), and a combined dose of benemid and tromexan, respectively. On each occasion three control periods - for the combined dose only two - were followed by ingestion of the tablets on an almost empty stomach. Spaced collections of urine and blood were continued thereafter for seven hours, the subject maintaining oral hydration all the while. The relationships between urate and creatinine clearances were then plotted and compared:

(i) Creatinine clearance. Neither the single drugs nor their combination significantly altered glomerular filtration rate as measured by creatinine clearance.

(ii) Urate/creatinine clearance ratio. A steep rise took place every time at an interval of 1-2 hours after ingestion.

While not drawing firm conclusions about relative

potencies, study of the graph shows that in this experiment, the least marked and least sustained uricosuria resulted from the administration of 2.0 G. of benemid alone, with a peak clearance ratio  $3\frac{1}{2}$  times greater than the mean control. Tromexan alone (1.8 G.) yielded a peak ratio  $5\frac{1}{2}$  times greater than its control and the effect was undiminished at 7 hours.

The two drugs together resulted in a peak 5 times greater than the control, and uricosuria was still sustained 7 hours after their ingestion. The combined dose consisted of 2.0 G. of benemid and 1.5 G. of tromexan. Their effect is in keeping with the inference that tromexan enhanced the action of the benemid (five-fold increase compared with three-and-a-half by benemid alone); and that the slight difference in effect between 1.8 and 1.5 G. of tromexan could not be compensated by the use of benemid with the smaller dose of tromexan.

(iii) Tentative comparison between uricosuric potencies of two drugs. Ideally this point should have been elucidated by determination of the respective minimum effective doses needed to produce a certain uricosuric effect. It is regrettable that this and many other relevant problems could not, to date, be tackled. From the foregoing, it is perhaps reasonable to suggest that, weight for weight, if tromexan is not actually more efficient than benemid in short-term studies at this order of dosage, it is at least comparable to it. That in itself points to tromexan being, molecule for molecule, a better uricosuric agent under these conditions, since the molecular weights of the two drugs are benemid 285 and tromexan 408; thus any given dose of tromexan contains only  $7/10$  of the number of active molecules present in an equal weight of benemid.

## 2. RAT

Renal physiologists have raised the rat to a position of considerable eminence in experimental work, on the combined grounds of similarity to man and ready availability. It was decided to investigate the effect of tromexan on urate excretion in this species.

The chief end-product of purine metabolism in mammals other than primates and the Dalmatian coach hound is allantoin. This is derived from its parent uric acid by the action of uricase, an enzyme found mainly in the liver and in smaller amounts in the kidney. Uric acid in the blood and urine of most mammals exists, therefore, by virtue of not yet having undergone complete uricolysis, and its concentration in both is accordingly low. On this reduced scale, however, its renal excretion appears to follow a pattern of filtration and partial reabsorption essentially similar to man.

### (a) Procedure

Two groups of rats were used, the first receiving benemid and the second tromexan in two separate experiments.

The rats were all healthy, adult, male albinos, weighing about 200 G., on a previously constant balanced laboratory diet. On the night before the experiment they were deprived of food to facilitate the administration of water for hydration and to reduce the passage of faeces which might contaminate urine specimens.

Each series consisted of 14 rats paired off in seven special rat-metabolism cages.\* These enabled urine to trickle through a wide funnel on to a pear-shaped glass bulb and into a collecting flask: faeces were deflected off the sides of the bulb on to the bench.

The rats were hydrated with 10% body weight of water by intra-oesophageal injection through a cannula. Hourly urine collections were made by pooling the yield from all cages; blood samples were obtained by stunning one pair of rats each hour and pooling the blood after carotid section.

The drug was administered after two control collections of blood and urine. In Series I the remaining rats were each given benemid, 50 mg./Kg. in aqueous suspension by oral cannula; in Series II they received tromexan

\* (The cages were devised by Dr. N. Sapeika and Mr. W. Bates of the Pharmacology Department, to whom I am indebted for assistance in the rat experiments).

Experiment	Time (hours)	Urine volume (pooled) (ml.)	No. of rats contrib- uting	Creatinine concentration		Urate concentration		Urine urate/ creatinine ratio	Serum urate/ creatinine ratio		
				Urine (mg./100 ml.)	Serum	Urine	Serum				
(a) <u>Rat Series I.</u> Benemid: 50 mg./Kg. by stomach tube at 0 hours. Oral hydration	-2	15	14	20.5	0.67	8.7	2.92	0.43	0.36	4.35	3.70
	-1	47	12	16.9	0.79	4.4	2.46	0.28			
	0-1	10	10	12.8	0.85	5.6	1.95	0.44	0.68	2.36	2.58
	1-2	5	8	18.2	0.90	8.0	2.27	0.44			
	2-3	5	6	19.8	1.08	17.6	2.26	0.88			
	3-4	6	4	17.7	0.66	12.8	1.85	0.72			
4-5	3	2	22.4	1.08	18.1	2.29	0.81	2.12			
(b) <u>Rat Series II.</u> Tromexan: 300 mg./Kg. at 0 hours. Oral hydration	-2	29	14	18.7	0.98	10.2	3.04	0.55	0.47	3.10	2.90
	-1	22	14	14.6	1.03	5.7	2.77	0.39			
	0-1	17	12	12.7	-	6.4	-	0.51	1.04	-	2.11
	1-2	8	12	22.7	0.80	19.8	1.69	0.88			
	2-3	6	10	31.4	0.79	39.5	1.83	1.26			
	3-4	13	8	19.9	0.71	25.0	2.72	1.26			
	4-5	8	6	15.1	0.79	15.3	2.70	1.02	3.00	3.41	
	22-23	17	3	9.6	0.95	6.8	4.04	0.71	0.98	4.25	3.90
	28-29	4	1	26.2	0.95	24.6	3.37	0.94			

(The underlined figures represent mean values of bracketed periods)

Table 4. Effect of (a) benemid and (b) tromexan on urate excretion in rats. In each case the ratio of urate/creatinine concentration rises in urine and falls in serum.

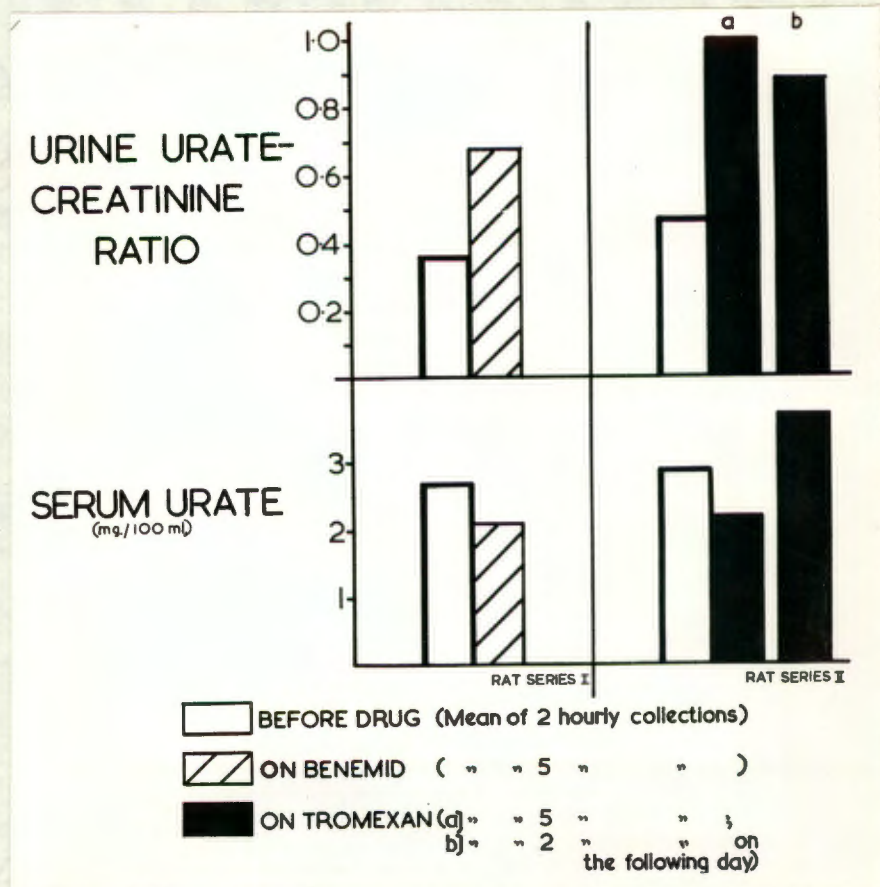


Fig. 13. Uricosuric effect of benemid and tromexan in rats. (Columns represent average values for experimental periods tabulated above). Secondary changes after tromexan (b) are discussed in text.

300 mg./Kg.

Urate and creatinine concentrations were determined in the hourly samples of serum and urine (Table 4), and their averages before and after the drugs compared (Fig. 13). In Series II, two collections were also obtained on the day after tromexan administration, by omitting one of the earlier bleedings and giving the drug to an extra two rats.

(b) Results

(i) Serum urate. Benemid and tromexan were each followed by a moderate reduction of the mean level in the 5 hours following ingestion. During that time, the greatest single fall for benemid was 31% and for tromexan (in a much larger dose) 41%.

(ii) Urinary urate concentration was approximately doubled after the administration of each drug. Lest this merely reflected the passage of less dilute urine, the figures are compared with the corresponding creatinine concentrations (Table 4 and Fig. 13). The urate/creatinine ratio in each series is seen to have doubled as well.

(iii) Secondary effect of tromexan on urate metabolism. A speculative point arises from studying the serum and urine figures for the second day after tromexan. It is seen that, while the urinary urate/creatinine ratio is still considerably higher than the previous day's control figure, the serum urate has risen not only above its initially reduced level, but well above the original control. The following explanation suggests itself:

- (a) Renal damage in most mammals is associated with retention of allantoin,<sup>35</sup> not urate as in man. The small amount of uric acid normally excreted by the kidney is, in azotemic mammals, oxidized in the liver to allantoin, which rises still further.
- (b) On the other hand, uric acid accumulates in most mammals if, experimentally or pathologically, the liver is unable to convert it as usual to allantoin. Serum levels and urinary excretion of uric acid rise as allantoin production dwindles.
- (c) Tromexan is believed to interfere with the clotting mechanism by disturbing hepatic production of factors in the prothrombin complex<sup>122a</sup>. The dose given to these rats was very large and may have disturbed other liver functions such as uricolysis, giving rise to the observed second day situation which

fits hepatic insufficiency. While haemorrhage and jaundice were not present to support this suggestion, the killing of the rats may have forestalled their imminent appearance.

- (d) The initial lowering of serum urate in the early hours after tromexan is explicable by renal tubular uricosuria. The presumed hepatic action of tromexan, in lengthening prothrombin time, is known to appear after considerable delay, and if the secondary urate changes under discussion are due to liver disturbance, their similar delay would be understandable.

The premises underlying the above remarks might have been strengthened had the observations affected a larger number of rats, included 2nd-day estimations on the benemid series too, and also tested prothrombin activity and other liver functions. Not having anticipated the results, these requirements were not fulfilled, and in seeking to amplify the prime observation that tromexan is uricosuric, the secondary problem has not yet been re-opened.

### 3. CAT

After the rat experiments outlined above, the need was felt for a more refined technique (including clearance determinations which were not considered justified on the rat results) permitting also the survival of the animal.

Pending the procuring of suitable dogs, it was thought that this need might be filled by cats, and Table 5 shows the results of administering a known uricosuric agent - benemid - and tromexan to each of two cats respectively.

It was found necessary, after anaesthetizing the animals with pentobarbital sodium to collect urine accurately by cystotomy and blood by carotid exposure and tapping. In addition, the rate of diuresis, while less sluggish in the tromexan experiment than with benemid, was unsatisfactory for reliable clearance determinations. For these reasons the study was not further pursued, and the results obtained are

presented in the table for their limited interest in supporting the uricosuric action of tromexan. Correction of clearances to 100 G. of body weight has been omitted in this comparison of serial values.

Experiment	Time	Urine flow	Creatinine clearance	Urate clearance	Urate/creatinine clearance ratio	Prothrombin index
	(min.)	(ml./min.)	(ml./min.)	(ml./min.)		(%)
(a) <u>Cat I</u> , 2.8 Kg. Benemid: 300 mg./Kg. at + 4 mins. Oral and intra- venous hydration. (Experiment technically unsatisfactory)	-140	0.07	6.60	0.87	0.132	
	-80	0.10	7.29	0.82	0.112	
	0-65	0.12	7.48	1.10	0.148	
	66-145	0.07	6.72	0.76	0.113	
(b) <u>Cat II</u> , 2.4 Kg. Tromexan: 150 mg./Kg. by stomach tube at + 3 mins. Oral and intra- venous hydration.	-136	0.15	4.58	1.45	0.318	
	-50	0.20	4.49	1.20	0.267	100
	0-61	0.27	4.90	1.45	0.296	
	62-111	0.42	5.50	1.41	0.267	85
	112-172	0.24	4.20	1.53	0.365	80
	173-239	0.14	3.44	1.62	0.472	
	240-392	0.20	4.09	1.73	0.424	63

Table 5. Effect of oral administration of (a) benemid, and (b) tromexan on renal clearances of urate and endogenous creatinine in two cats.

The figures are in keeping with a rise of urate clearance after administration of tromexan. Prothrombin activity was relatively soon impaired, the index being certainly reduced between 4 and 7 hours after ingestion of the drug.

#### 4. DALMATIAN COACH HOUND AND MONGREL DOG

##### (a) Background

In a lecture to the Harvey Society of New York in 1916<sup>11</sup>, Stanley Benedict reported an observation which classed the Dalmatian coach hound as an enigma of nature. Having 'encountered' a member of this breed in his laboratory, he found its urine to contain large quantities of uric acid at all times. Since then confirmation of this phenomenon has come from several workers,<sup>47, 126</sup> including one named H. G. Wells<sup>123</sup> but to date, apart from recognizing its genetic correlation with spottedness and a few of the physiological mechanisms involved, the mystery of this mammal's unique purine metabolism has not been solved.

The pattern of urate abnormality in the Dalmatian is as follows :

- (1) The urine contains large amounts of urate and relatively small amounts of allantoin.
- (2) The urinary urate excretion of the Dalmatian is several times that of man per unit body weight.
- (3) This large urate excretion is accomplished at a much lower plasma urate level than that of man; that is, the renal clearance of urate is very high.
- (4) The high clearance is due to a renal tubular anomaly, of failure to reabsorb urate from the glomerular filtrate. Urate is therefore lost from the body that would have been converted to allantoin, the production and excretion of which are therefore low.
- (5) Uricase is adequately present in Dalmatian liver and does enable allantoin to be formed from the depleted urate of the plasma; it may be, however, that there is actually slight impairment of hepatic uricolysis as well to explain the low allantoin output<sup>47</sup>.
- (6) Tubular secretion of urate. Controversial reports have been published on the possibility that the high urate clearance of the Dalmatian is due not only to absent tubular reabsorption, but to active tubular secretion. The answer, which lies in the comparison of simultaneous urate clearance and glomerular filtration rate, has been

clouded by conflicting results. Thus Friedman and Byers<sup>47</sup>, using a colorimetric urate method, and allantoin clearance as the index of GFR, showed that urate was neither reabsorbed nor secreted by the tubules; in Wolfson's hands<sup>126</sup>, the urate clearance exceeded GFR, and Beyer and co-workers<sup>17</sup> agree with him that the tubular mechanism for urate in the Dalmatian is not in abeyance but is reversed, active secretion contributing to renal clearance of the compound.

(7) Response to uricosuric agents by the Dalmatian.

It is to be expected and has, in fact, recently been shown<sup>17, 95</sup>, that uricosuric drugs acting by impairment of urate reabsorption are ineffective in the Dalmatian where this process is absent. In first reporting the renal effects of benemid, Beyer and his colleagues further observed that the urate/creatinine clearance ratio (greater than 1.0 at the start) was not only unchanged but reduced by benemid, while plasma urate rose slightly. This was regarded as confirmatory evidence of tubular secretion of urate in the Dalmatian.

(b) Experimental Procedure

It is apparent from the foregoing that in the Dalmatian coach hound we have an 'elegant' indicator of the exact site of action of a uricosuric agent. Since urate excretion in this animal differs from that in other dogs and man only by its renal tubular transport, the production of opposite results with a test agent pin-points the mechanism of the drug to the tubule cell.

The experiments described below confirm that

- (1) tromexan is a drug with definite uricosuric activity;
- (2) the renal mechanism for urate excretion in the Dalmatian coach hound involves active tubular secretion.

Subjects. The mongrel was a well-built, adult female, weighing 18 Kg. The Dalmatian was a young 16 Kg. male of pure lineage and engaging disposition (Fig. 14).



Fig. 14. Zog, the writer's Dalmatian, on completion of his research duties.

Both were kept on a normal balanced diet including meat, but were deprived of solid food for 15 hours before each experiment.

Anaesthetic. Light anaesthesia was maintained with pentobarbital sodium, 20 mg./Kg. intra-peritoneally followed at judicious intervals by small additions to the intravenous infusion.

Hydration. Free water was allowed before the tests and the dogs were given half a litre by stomach tube during the 1-2 hours before clearance collections began. To ensure adequate diuresis and provide a route of drug administration, 0.6% saline solution was given by venoclysis at a fairly constant rate of 2 ml./min. throughout the procedure. Limb veins were entered percutaneously with a 20-gauge short-bevel Luer-Lok needle attached to an infusion set.

Urate and creatinine clearances. These were determined in both dogs from the endogenous chromogens. While analytical quantities would have been enhanced by priming the animals with both test substances, the advantages of avoiding the exogenous technique were simplicity, greater freedom in the duration of clearance periods and in timing the mid-point blood samples, greater freedom in the rate of flow of the intravenous infusion, and absence of possible reactions to injected alkaline solutions of urate. Moreover, the validity of endogenous creatinine clearance as an index of glomerular filtration in the dog has been established.<sup>65</sup>

Urine collections were made at carefully timed intervals varying from 20-30 minutes (usually) to 1½ hours when urine flow slackened. The bladder was emptied through an in-dwelling

catheter with the aid of supra-pubic pressure and air displacement.

Blood samples for analysis of serum urate, serum creatinine and plasma prothrombin index were obtained at intervals throughout the test by direct puncture of limb veins other than the infused one.

Administration of test agents. While seeking to establish the action of tromexan, it was decided to measure the changes produced in each dog by the prior administration of the known uricosuric agent benemid, thereby checking the reliability of the experimental procedure, and providing a comparison for tromexan.

Intervals of at least a week separated successive series of clearance determinations in each dog, to ensure elimination of drugs and restoration of possibly disturbed renal function and purine metabolism.

It was obviously desirable to administer both substances parenterally when seeking changes in a short-term clearance experiment. Solutions of benemid and tromexan (both weak acids) were prepared for intravenous injection by extraction from the crushed tablets with equivalent proportions of warm dilute NaOH and separating the dissolved sodium salt from the suspension by filtration. The pH of the filtrate was adjusted to neutrality, short of precipitating either drug as the insoluble free acid. Prior to use, the solution (containing 1,000 mg. of the drug in 20 ml.) was sterilized through a Seitz filter and then administered, after several control collections, by rapid injection of half the chosen dose and infusion of the remainder at the drip rate. The mongrel dog received 60 mg./Kg. of benemid in the first experiment and 45 mg./Kg of tromexan in the second. In the absence of mishap with the mongrel, the Dalmatian was given twice the amount of each drug, to facilitate detection of a possibly lowered urate/creatinine clearance ratio.

(c) Results

(1) Mongrel dog. (Table 6). During both series of clearances excellent diuresis was maintained, and the glomerular filtration rate remained constant on each occasion. It may be seen that the absolute values of both creatinine and urate clearance are liable to be different on different days, though on any one day the figures are fairly stable.

Mongrel dog, 18 Kg. Oral and intravenous hydration					
Experiment	Time	Urine flow	Creatinine clearance	Urate clearance	Urate/creatinine clearance ratio
	(min.)	(ml./min.)	(ml./min.)	(ml./min.)	(x 100)
(a) Control periods.	-157	0.40	20.8	1.73	8.3
	-97	1.54	35.8	1.76	4.9
	-67	3.29	41.8	2.50	6.0
	-39	3.50	39.4	2.28	5.8
	-19	3.90	41.1	3.28	7.9
<u>Benemid</u> 60 mg./Kg. intravenously, from +6 to +180 mins.	0-25	2.56	40.1	3.08	7.7
	26-52	1.60	36.8	4.05	11.0
	53-131	1.40	36.1	4.70	13.0
	132-177	1.24	33.4	4.12	12.4
	178-227	1.65	38.6	4.92	12.8
(b) Control periods.	-130	1.48	25.7	5.52	21.6
	-59	2.58	25.5	6.65	26.1
	-35	2.53	24.0	5.62	23.4
	-20	2.20	22.3	6.32	28.3 (Pr.I.100%)
	<u>Tromexan</u> 45 mg./Kg. intravenously, from +9 to +180 mins.	0-19	3.58	29.7	6.24
20-40		3.38	24.0	6.97	29.0
41-92		2.97	22.7	7.00	30.8
93-116		4.88	28.9	10.01	34.9
117-171		3.00	23.6	9.60	40.6 (Pr.I.60%)

Table 6. Effect of intravenous administration of (a) benemid and (b) tromexan on renal clearances of urate and endogenous creatinine in the mongrel dog.

The explanation lies in the very low serum levels of endogenous urate and creatinine (both of the order of 0.5 mg./100 ml.) which, being the denominator in the clearance formula, are able by a small change to influence the result widely. The ratio of the two clearances may cover an even wider range if the serum levels both change slightly from one set of clearances to the next. For this reason, comparison of clearance ratios is only valid during serial determinations in any one experiment; and to ensure the reasonable truth of this statement, all clearances in each series are calculated on the mean level for serum urate and creatinine for that day, thereby eliminating technical errors at low concentrations.

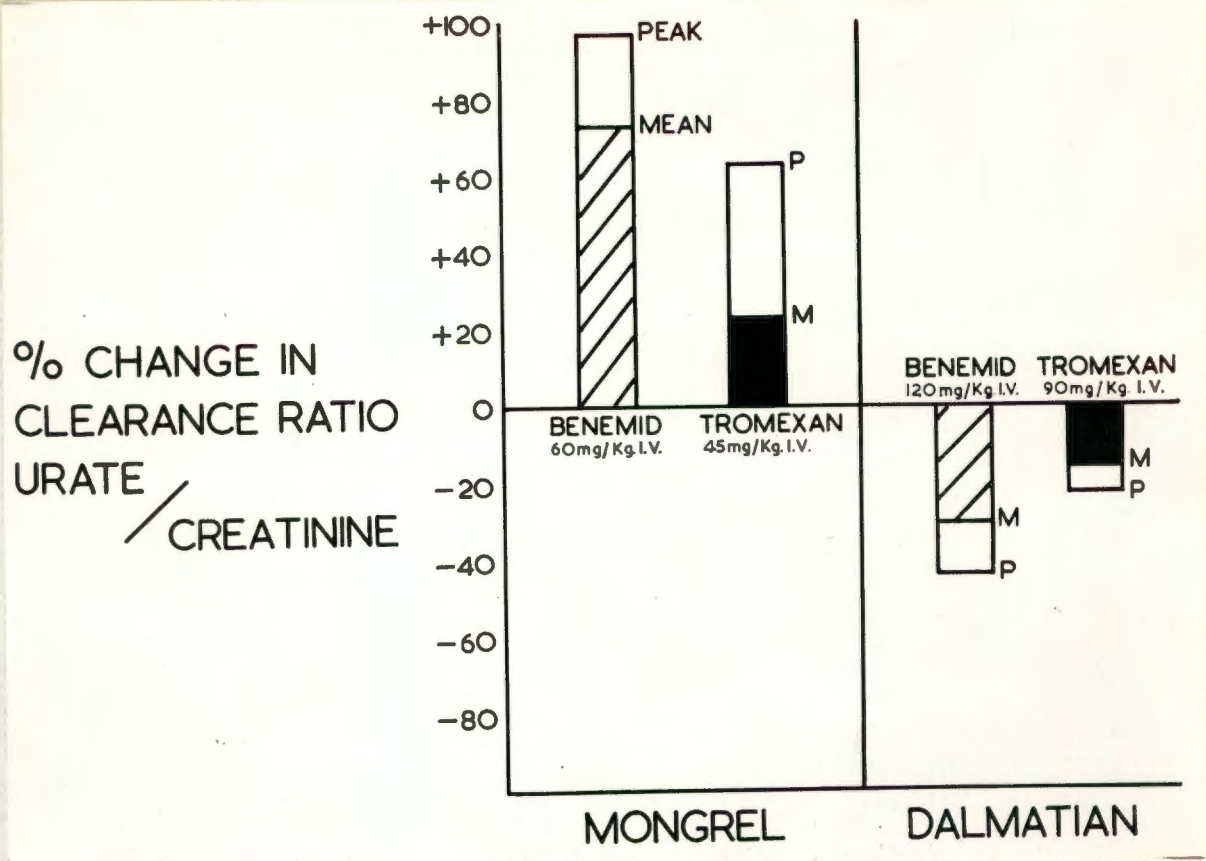


Fig. 15. Diagram summarizing the effects of benemid and tromexan on urate clearance in the mongrel dog and Dalmatian coach hound.

(The mean and peak figures refer to the clearance ratios in Tables 6 and 7, percentage changes being based on the averages for the respective control periods).

The injection of benemid was associated with a striking uricosuric response. Compared with the average control figures the urate/creatinine clearance ratio rose by a maximum of 97% and a mean of 73% (Fig. 15).

When tromexan was given, urate/creatinine clearance underwent a maximum and mean increase of 63% and 26% respectively. (Statistical analysis of these results according to difference of means, using 'student  $t$ ' distribution shows them to be highly significant at a 1% level.)

For both agents, the increased urate clearance became apparent a few minutes after their intravenous administration, contrasting with the rather longer lag period after oral dosage in man and rat. Prothrombin impairment by tromexan was again a later event, occurring between the 2nd and 3rd hours.

(ii) Dalmatian coach hound. (Table 7). Urine volumes were well maintained throughout the clearances, with one interesting exception.

Dalmatian dog, 16 Kg. Oral and intravenous hydration						
Experiment	Time	Urine flow	Creatinine clearance	Urate clearance	Urate/creatinine clearance ratio	
	(min.)	(ml./min.)	(ml./min.)	(ml./min.)		
(a) Control periods.	-190	0.24	34.0	47.0	1.38	
	-98	2.08	41.6	64.5	1.55	
	-72	3.29	35.5	60.9	1.71	
	-51	2.96	24.3	46.7	1.92	
	-27	3.23	30.0	55.7	1.86	
	<u>Benemid</u> 120 mg./Kg. intravenously, from +4 to +95 mins.	0-22	3.10	25.3	41.6	1.64
		23-59	1.36	30.0	32.3	1.08
		60-131	0.39	31.6	36.3	1.15
		132-157	1.46	38.0	38.8	1.02
		158-185	2.45	44.8	41.8	0.94
		(b) Control periods.	-355	1.30	47.3	63.3
	-255		1.12	46.4	53.2	1.16
	-221		1.42	46.5	45.4	0.98
	-195		1.98	49.2	54.0	1.10
-154	4.57		52.0	62.4	1.20	
-93	2.34		50.0	48.3	0.97 (Pr. I. 100%)	
-28	3.11		46.4	49.5	1.07	
<u>Tromexan</u> 90 mg./Kg. intravenously, from +1 to + 60 mins.	0-30		3.23	48.2	42.6	0.88
	31-67		1.36	45.7	45.2	0.99
	68-129		1.21	41.4	35.7	0.86
	130-160		2.48	42.7	40.2	0.94
	161-193		3.05	43.4	37.5	0.86
	194-226		1.61	40.1	41.4	1.03
	227-281		1.42	44.5	46.9	1.05 (Pr. I. 100%)

Table 7. Effect of intravenous administration of (a) benemid, and (b) tromexan on renal clearances of urate and endogenous creatinine in the Dalmatian coach hound.

In the first collection period after injecting benemid or tromexan, diuresis diminished considerably despite constant hypotonic infusion. There was no accompanying reduction in glomerular filtration rate. The phenomenon seemed related to the temporary correction by the drugs of the animal's 'urate diabetes'; but against this explanation is the recovery of urine flow while urate clearance was still depressed, and the disproportion in their respective reductions. Alternatively, it represented a reaction to the injection of a foreign substance, or was coincidental.

Mechanism of urate clearance: The first conclusion suggested by both series of results is that the normal urate/creatinine

clearance ratio of the Dalmatian is substantially greater than 1.0, and that urate is therefore eliminated by active tubular secretion in addition to glomerular filtration. This is in agreement with the reports of Wolfson and Beyer's teams cited above. It must be pointed out, however, that the calculation of absolute clearance values - and hence their ratios - is subject to the error discussed under the mongrel results, at low serum concentrations. Just as the clearance ratio was calculated to have a mean control value of 1.68 on the first occasion, and of 1.12 on the second, so might it have been 1.9 or 1.0 at other times. The last figure would be evidence against tubular secretion of urate. The situation is relieved, however, by the positive action of the transport-inhibitor benemid in reducing the calculated figure for urate/creatinine clearance, thus providing independent evidence of a tubular secretory mechanism.

Action of tromexan: The results confirm the action of tromexan as an inhibitor of renal tubular transport of urate. The urate/creatinine clearance ratio fell from a mean control figure of 1.12 to 0.94, a 16% reduction. The maximum single reduction was 23%. After benemid (in larger dosage on a different day) the reductions were 30% and 44% respectively (Fig. 15). Analysis of results for each experiment, using 'student t' distribution, shows that with the number of determinations involved the reductions are statistically significant. (The modest percentage changes should be viewed in the light of their negative direction and the total amount of urate which they represent in this animal).

No reduction of prothrombin index occurred during the experiment.

C. EFFECT OF TROMEXAN ON OTHER RENAL TUBULAR  
TRANSPORT FUNCTIONS

Having established the activity of tromexan as a uricosuric agent, it was desirable to test its inhibition of other members of the 'PAH-family' of tubular transport substances (Table 1, chapter 2). It will be recalled that the passage of several organic compounds across the renal tubule cell is achieved by one mechanism which is also responsible for the reabsorption of urate; and that uricosuric agents like carinamide, benemid, cinchophen and phenylbutazone affect the transport of some or all of those compounds in addition to blocking urate reabsorption.

1. Para-aminohippurate (PAH)

This substance, used by renal physiologists and clinicians as a measure of renal plasma flow and tubular function, is the prototype of the transport-group under discussion. Its passage through the tubule cell is best gauged by determining the  $T_m$  (maximum tubular secretory capacity) for the compound, and Fig. 16 illustrates the effect of a single oral dose of tromexan on  $T_{mPAH}$  in one normal subject.

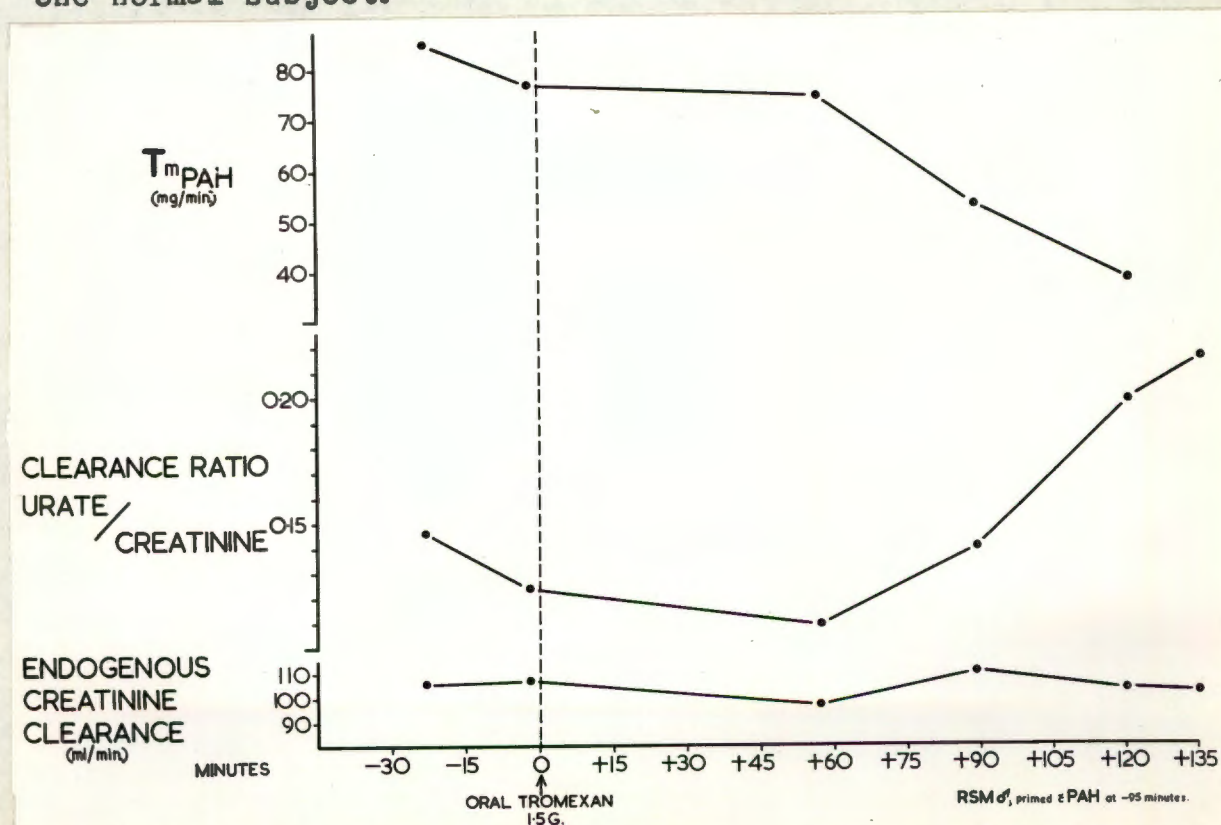


Fig. 16. Simultaneous interference by tromexan with renal tubular reabsorption of urate and secretion of PAH.

(a) Method\*

After liberal oral hydration, the subject was primed with PAH (50 ml. of 20% solution) intravenously and a sustaining infusion of 15% PAH run in at constant rate for the rest of the experiment. An hour was allowed for equilibration and then two control collections of blood and urine taken for estimation of urate and creatinine clearances and  $T_{mPAH}$  values. PAH in serum and urine was determined by the method of Goldring and Chasis<sup>107</sup> and the  $T_m$  calculated according to Homer Smith.

Tromexan 1,500 mg. was ingested on an empty stomach and carefully timed collections of urine and mid-point blood samples continued for another two hours. The subject's technique of voiding was flawless and a tremendous diuresis minimized clearance errors. The 1st urine specimen after the drug was accidentally lost.

(b) Results

(i)  $T_{mPAH}$  underwent progressive reduction after an interval of 1-1½ hours following the administration of tromexan. This fall was associated with a synchronous rise of urate clearance and of urate/creatinine clearance ratio (Fig. 16). Demonstration of the duration and final depth of the fall in PAH transport was prevented by premature termination of the experiment; but the results offer fair evidence that tromexan resembles the established uricosuric agents in interfering with a mechanism serving the transport of more than one tubule passenger.

(ii) An incidental observation is worth commenting on as it affects previously mentioned results produced by Talbott<sup>115</sup>. In contributing to the list of substances increasing urate clearance, he remarked on the absence of effect of certain compounds including PAH. A priori one would expect PAH to impair urate transport (i.e., increase its clearance) by competing with it for the same transport mechanism. Oddly enough,

\* I am indebted to Dr. E. Dowdle for assistance with the clearance procedure and to Dr. L. Eales and Mr. T. Turner for the PAH estimations.

while this has been demonstrated for PSP and urate, and diodrast and urate (Table 1) and should be true for PAH and urate, an experiment to prove it has not been reported other than Talbott's negatory one.

In Fig. 16 urate and creatinine clearances were determined at a time when the renal tubules were being saturated with respect to PAH secretion. This would explain the somewhat low values of endogenous creatinine clearance throughout the experiment, as PAH has been shown to block the tubule-secreted fraction of this substance in man (Table 1). The control values for urate clearance in this experiment average 14.2 ml./min., substantially more than the figure of 10 ml./min. for this subject at other times. A two-fold cause therefore exists for the rather high clearance ratio (0.135) in Fig. 16 before tromexan.

It is felt that the initially high urate clearance in this experiment is reasonably explained by a competitive action of PAH on urate transport, impairing its tubular reabsorption.

## 2. Penicillin

This antibiotic is an integral member of the group of tubular transport passengers to which uric acid belongs. Table 8 presents the results of administering tromexan together with penicillin, on the serum levels of the latter after a standard intra-muscular injection.

### (a) Procedure

Two normal male subjects and one gout patient were each given, on two occasions, an intra-muscular injection of 1,000,000 units of crystalline sodium penicillin-G. Precautions were taken to keep the technique and site of administration constant, and not less than four days were allowed to elapse between injections in each case.

Tromexan was given to each subject in association with the second penicillin injection: R.S.M. received 300 mg. 6-hourly on the preceding day and on the morning of the injection; M.J. and case 12 received 300 mg. in the preceding night, 600 mg.

shortly before the penicillin and 600 mg. one hour after its injection. The aim in the latter two instances was to ensure maximum levels of circulating tromexan at the time of penicillin introduction. Two subjects were kept at bed rest, but R. S. M. maintained restricted activity.

Blood was taken immediately before each penicillin injection and at hours 1, 3 and 6 thereafter, and serum penicillin assays performed by a plate-culture method, measuring inhibition of a micrococcus albus.\*

SUBJECT	TIME hours	PENICILLIN ALONE			PENICILLIN+TROMEXAN		
		Penicillin units/ml.	Ser. urate mg/100ml.	P.I. %	Penicillin units/ml.	Ser. urate mg/100ml.	P.I. %
R.S.M.	0	0	6.0		0		
	1	10.00	6.2		8.50		
	3	0.71	5.8		0.55		70
	6	0.47	5.8		0.44		
M.J.	0	0	5.4	100	0	5.2	100
	1	6.50			7.00		
	3	<u>0.40</u>			<u>1.60</u>	4.2	
	6	0	5.7		0	3.6	
	(30)				3.9		70
CASE No. 12	0	0	6.6	100	0	6.6	80
	1	4.00			4.00		
	3	<u>0.30</u>			<u>0.80</u>		
	6	0.16	8.8		0.30	4.4	
	(30)				5.7		25

Table 8. Serum levels of penicillin after intramuscular injection of 1 million units, before and during tromexan administration in 3 persons. There is suspicion of slight penicillin retention at the 3rd hour in subject M. J. and case 12 on tromexan.

\* I am grateful to Dr. A. Kipps and Mr. S. Moore of the Bacteriology Department for the penicillin assays.

(b) Results

Nothing can be inferred from the figures on subject R.S.M., possibly because the dosage schedule of tromexan was so spread out relative to its metabolic break-down in the body <sup>30</sup> that an effective amount was lacking at the time of the injection.

The results in subject M. J. and case 12 constitute so few data that no valid conclusion can be drawn, but the following may be remarked on:

- (i) The pattern of serum levels of penicillin administered under standard conditions to the same person at different times, is fairly constant.
- (ii) In both subjects, the level of serum penicillin at the 1st hour was the same with tromexan as without it. This level is probably governed by the absorptive process.
- (iii) In both subjects, little or no penicillin was retained at the 6th hour, with and without tromexan. Serum levels at this stage are governed by renal excretion, which appears, therefore, not to have been greatly delayed.
- (iv) In both subjects, the 3rd-hour serum penicillin level was a little higher when tromexan had been given. Many more such determinations would have to be made before deciding the significance of these figures, and the whole question more satisfactorily answered by doing renal clearances of penicillin. There are grounds for suspecting, however, that at the 3rd hour, when penicillin excretion is proceeding and when tromexan is almost certainly in circulation, any differences in serum level may prove to be due to impaired tubular secretion of penicillin by tromexan.

### 3. Phenolsulphonphthalein (PSP)

The opportunity was lacking for according any but the briefest attention to the effect of tromexan on tubular secretion of PSP:

#### (a) Method

One normal subject in a state of liberal hydration was given 6.0 mg. of PSP intravenously on two successive mornings. During the five hours prior to the second injection, 1,500 mg. of tromexan were ingested.

The quantity of PSP excreted in the urine 15 and 60 minutes after each injection was determined colorimetrically.\* Urate and creatinine clearances were estimated during the second hour.

#### (b) Results

	<u>PSP in urine</u>	
	Control	Tromexan
At 15 minutes	2.4 mg.	1.3 mg.
At 60 "	4.8 mg.	3.5 mg.

Clearances done in the second hour yielded a urate/creatinine clearance ratio of 0.073 on the first day and 0.27 after tromexan.

#### (c) Conclusion

In this experiment, the uricosuric activity of tromexan appeared to be associated with delay in the renal excretion of PSP, probably by slowing the rate of its tubular secretion.

### 4. 17-Ketosteroids

The highly interesting property of decreasing urinary 17-ketosteroid excretion, which has been reported for benemid<sup>50</sup> and ascribed to impairment of a tubular secretory mechanism, has aroused remarkably little comment in later publications. It joins a long list of worth-while problems needing to be tackled in the light of the renal activities of tromexan. Whether or not compounds like cerinamide or phenylbutazone share the effect of benemid on 17-ketosteroid transport is unknown, although the lack of reported data, at least on cerinamide,

\* Mr. E. Duncan of the Chemical Pathology department kindly did the PSP analysis.

suggests that benemid may be alone in blocking their tubular secretion. All that can further be said is that the spaced ingestion of 2.0 G. of benemid during 24 hours by one normal subject was associated with a fall in 17-ketosteroid output from 17.4 to 8.6 mg./24 hours; but during administration of 1.8 G. of tromexan a few days later, the urinary output of 17-ketosteroids was not diminished.

CHAPTER 5.      IMPLICATIONS OF THE URICOSURIC ACTION OF TROMEXAN

A.      STRUCTURAL BASIS OF ACTIVITY

1.      The two-fold influence of molecular structure on pharmacological activity
2.      Anticoagulant activity
3.      Uricosuric activity

B.      BIOLOGICAL RELATIONSHIP OF URICOSURIC, ANTICOAGULANT AND ANTI-RHEUMATIC MECHANISMS

1.      Relation between uricosuric and anticoagulant mechanisms
2.      Relation between uricosuric and anti-rheumatic activity
3.      Relation between anticoagulant and anti-rheumatic activity
4.      Conclusion

C.      THERAPEUTIC IMPLICATIONS

CHAPTER 5.    IMPLICATIONS OF THE URICOSURIC ACTIVITY OF  
TROMEXAN

A.    STRUCTURAL BASIS OF ACTIVITY

The discovery that a chemical compound can modify a biological process is likely to be of at least some academic interest. Where a new inhibitor of renal tubular function is the compound concerned, the chance that it may identify key groups determining cellular transport makes its advent more welcome.

One might have suspected, however, from the biochemical review in Chapter 2, that the addition of another uricosuric agent to a group among which there were so few discernible chemical similarities, might only add to the problem of explaining their renal tubular effects in terms of molecular structure. The difficulties of such an attempted correlation will be briefly presented and a few possibilities discussed.

(1)    The two-fold influence of molecular structure on pharmacological activity

Whether or not a compound will exert its specific effect after being introduced to the body depends to a large extent on its distribution and ability to reach its target. As an example one recalls the particular suitability of benemid as a renal tubular drug by virtue of its long survival in the circulation and its special localization during that time in and about the tubule cells. These 'navigational' properties of the molecule lie in its alkyl side-chain, on the directional effects of which depend the cellular activities of the remaining portion.

In the case of tromexen, evidence has been presented suggesting that during its period of systemic circulation the drug is capable of exerting a uricosuric effect comparable to that of benemid. From studies of its anticoagulant properties <sup>30</sup>, it is known to be rapidly absorbed from the gastro-intestinal tract, reaching peak levels in the blood in from one to six hours after ingestion. The metabolic breakdown of tromexen proceeds rapidly, averaging 25% per hour.

and after a single dose it has disappeared from the body before the prothrombin effect becomes evident. This behaviour is in keeping with the observations made by the writer regarding the rapid onset of its uricosuric action after an oral dose, and also implies an inferiority to benemid in terms of duration of tubular interference, benemid being known to survive 48 hours in the blood stream. Brodie's work<sup>30</sup>, which showed that hardly any tromexan was excreted in the urine, offers an interesting comparison with benemid and may point to a similar explanation of their renal tubular affinities. Benemid is also excreted slowly and only partially in the urine<sup>17</sup>, apparently because of constant tubular reabsorption from the glomerular filtrate. Further work on tromexan may reveal a similar mechanism underlying its intimacy with tubular function during the period it survives in circulation.

On the other hand, the fact that benemid fails, as far as is known, to display any striking anticoagulant action need not imply that the molecule of tromexan is equipped for two specific activities and that of benemid only for one. Both pharmacological actions (uricosuric and anticoagulant) might depend on the same chemical feature, but the molecular properties which direct tromexan to its site of anticoagulant action (probably the liver cells) may be lacking from the structure of benemid.

Bearing in mind, therefore, that the biological actions of a substance may depend on its structure in at least two ways, (in addition to such other considerations as solubility, toxicity to the organisms and route of entry), the chemical similarities among this group may be sought further.

## (2) Anticoagulant activity

In 1944 Overman, Link and their colleagues<sup>97</sup> reported the anticoagulant properties of 106 compounds related to 4-hydroxycoumarin. The minimum structural requirements for activity were an intact 4-hydroxycoumarin residue substituted in the 3-position by a carbon residue or hydrogen atom. The most potent compound tested was dicoumarol (Fig. 17), and in general the highest activity was shown by the bis-4-hydroxycoumarin molecule, or a 4-hydroxycoumarin with the 3-substituent containing a keto group in position 1,5 relative to the 4-hydroxyl.

Tempering with the latter structures by inactivating the enolic hydroxyl group, or freeing the lactone oxygen from its ring, reduced or abolished anticoagulant activity. Changes ostensibly less fundamental, however, altered the activity in a way which emphasises the difficulty of such attempted correlations: Link's team found that a carboxyl substitution on the methylene bridge of dicoumarol (resulting in the unesterified form of tromexan) abolished anticoagulant properties while increasing solubility. The return of activity by esterifying the free acid was discovered by later workers (Fig. 17).

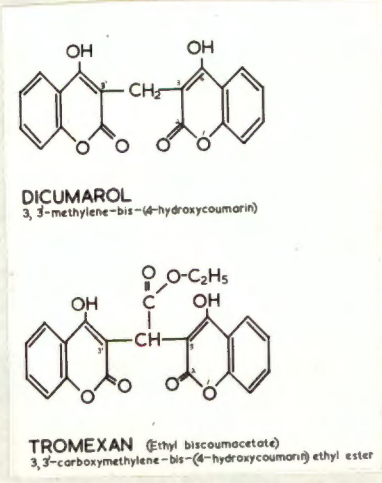


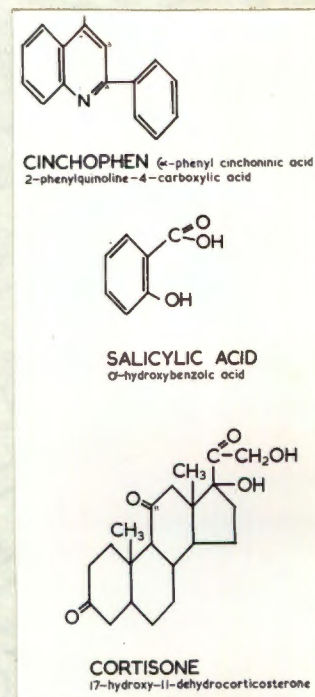
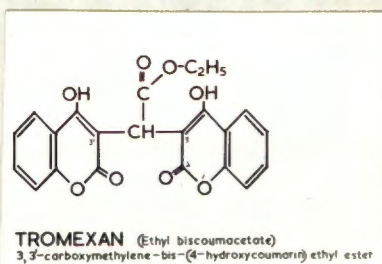
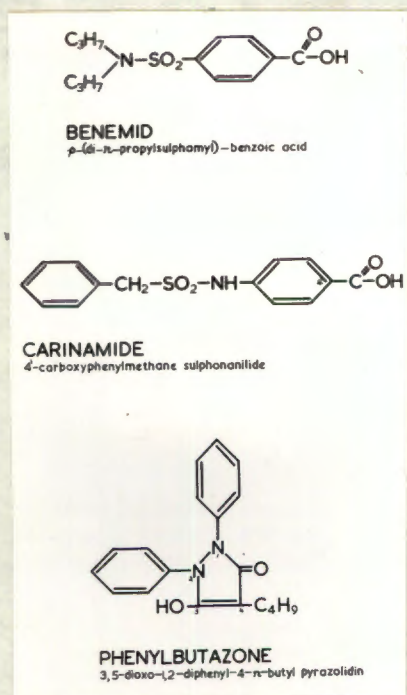
Fig. 17.

More recently a drug called PID has gained recognition for its potent action resembling that of dicoumarol and tromexan. Like them, it impairs prothrombin activity by a prime reduction of 'factor VII' synthesis. PID contains an indanedione residue which, though somewhat resembling 4-hydroxycoumarin in structure, is sufficiently different to cast doubt on the suggested specificity of the 4-hydroxycoumarin compounds as anticoagulants.

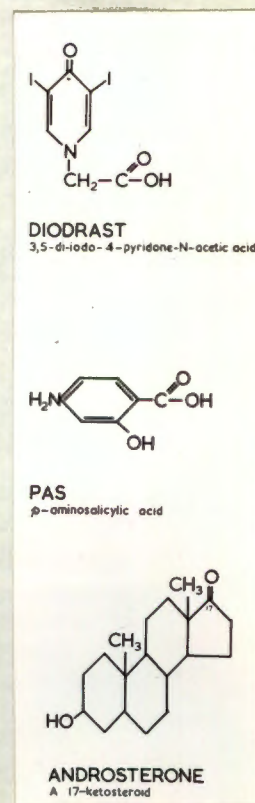
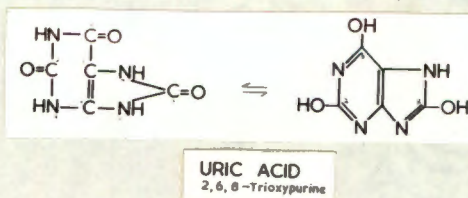
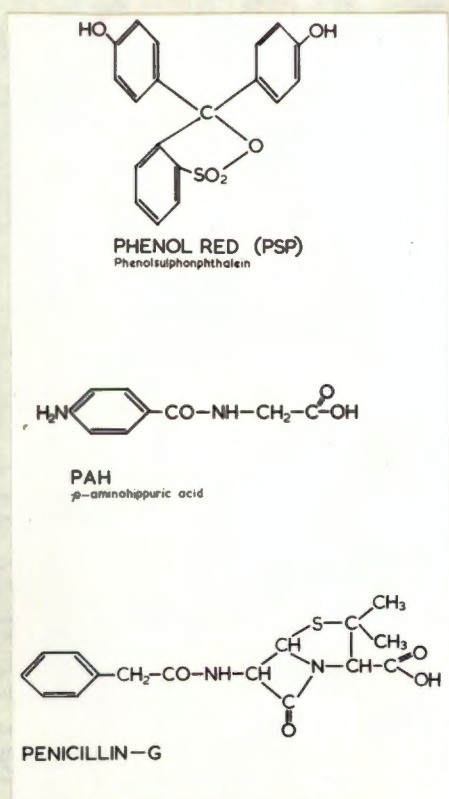
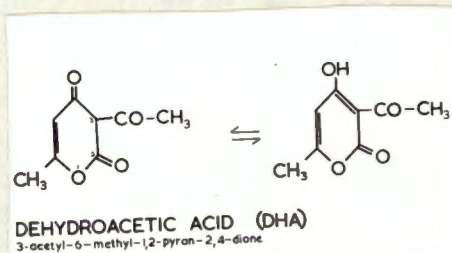
(3) Uricosuric activity

In discussing the cellular mechanisms of renal tubular transport (Chapter 2), the difficulty was noted of finding a chemical grouping common to all participants in the urate-PAH system, or shared by all compounds able to impede their transport. It seemed reasonable to conclude that, since more than one way was recognised by which transport inhibitors (including uricosuric drugs) could interrupt cellular activities, there might be more than one biologically active residue able to

produce the same net impairment of function. The addition of tromexan to the list of suppressing agents prompts another inspection of molecular structures (Fig. 18):



### Suppressors of tubular transport



### Substrates in tubular transport

Fig. 18. Molecular structures of certain tubule-active compounds.

- (i) Taggart's suggestion that -COOH was the key group through which transport is served or blocked has already been criticized, and in tromexan we have a further compound with high tubular activity and no -COOH group. (One immediately recalls that the free carboxylic acid of tromexan lacked anticoagulant properties, and it is of urgent interest to test the latter structure for uricosuric activity.)
- (ii) Of all the compounds in Fig. 18 perhaps the strongest overall resemblance to part of the tromexan molecule is displayed by dehydroacetic acid, a tool for the in vitro study of tubular mechanisms. While lacking the fused second ring of the coumarin nucleus, DHA possesses the same unusual configuration of a lactone ring with carbon residue at the 3-position and the possibility of 2, 4-keto-enol tautomerism. These features are not shared, however, by the better known transport inhibitors.
- (iii) The most profitable comparison should a priori be of those compounds with more than one functional similarity. It seems more than coincidence that besides tromexan, the uricosuric agents, salicylate and cinchophen, have been recognized as having anticoagulant properties, either experimentally<sup>53a,67</sup> or as toxic complications in their clinical use. Although Link had already remarked that degradation of the anticoagulant coumarins yielded the salicylate molecule, and thought that the delay in prothrombin impairment depended on this process, tromexan has uricosuric properties which are immediate, and any structural similarity to salicylate (or cinchophen) should be more direct to draw conclusions. At first sight such similarities are trivial: they do not include possession of a -COOH group, as tromexan lacks an unesterified carboxyl residue, and one would hesitate to assume automatic hydrolysis in vivo knowing that in one respect (anticoagulant action) the free acid is quite different from the ester.

The only other groups present as substituents in the molecules of tromexan, salicylate and cinchophen, as well as in every other compound concerned in the urate-PAH transport group, are simple -CO and -OH residues attached to aromatic, alicyclic or heterocyclic rings. If this remained the final conclusion, then the search for structurally specific features has virtually defeated itself. For one thing, however, not all -CO groups are chemically equivalent, some being ketonic and others forming part of carboxyl groups; and -OH groups have comparable differences in function. The mere smallness of these radicals would not exclude their possible importance as active participants in cellular processes, as testified by the role of keto-acids in energy production and of cyclic carbonyl groups in various enzymatic activities (e.g., riboflavin in cellular respiration; alloxan and quinone as cell poisons). The influence of a single keto group in modifying the functions of steroids is also remarkable. In noting the rather liberal distribution of such ketonic groupings among some of the transport substrates and suppressors in Fig. 18, one also wonders whether other pharmacological effects might be correlated with the presence of carbonyl substituents. Thus among the conditions for anticoagulant potency in the coumarin group, the need for a certain keto-configuration has been mentioned, and it is perhaps noteworthy that the newer drug PID resembles dicoumarol, if at all, by the presence of a keto-substituted ring. It seems possible, therefore, that active participation in intracellular enzyme reactions may be the function of very simple groups acting, for example, as hydrogen acceptors or ester-links. Their ability to engage other members of the reaction in the correct way spatially is likely to be determined by the rest of the molecule.

Where the general properties of a compound permit it, as in the case of tromexan, to enter into both hepatic and renal cellular processes, it need not perhaps be surprising that the same simple chemical groupings produce a disturbance of two dissimilar bodily functions. By analogy, one recalls the variety of effects possible from the inactivation in many sites of cellular -SH enzyme systems, few organs, for example, escaping the action of inorganic arsenic. Alloxan, however, while thought to involve a similar mechanism, selectively affects pancreatic islet cells, perhaps because of less easy 'access' to -SH groups in other cell systems.

Concerning the structural basis of uricosuric mechanisms, therefore, it seems that only a limited number of inferences may be drawn:

(a) the first is that the function of renal tubular transport, which handles so many possible substrates and which is influenced by so many dissimilar compounds, probably involves a variety of specific cellular reactions, each with its particular role, as well as susceptibility to interference.

(b) From this it follows that transport inhibitors, even of the same substrate, need not all have identical functional groupings to explain their similar end-result, if they are visualized as operating at different points in the transport reaction (Table 1).

(c) Among the chemical features qualifying for participation in tubular activities, either as substrate or inhibitor, one may recognize the following:

(i) The carboxyl group (as proposed by Taggart), noting its optimum association on a phenyl residue with ortho- or para - substituents as in salicylic acid, PAS, PAH, benemid and cerinamide.

(ii) In other compounds it is possible that activity resides in carbonyl groups, secondarily dependent on molecular properties which have enabled them to participate in the mechanism.

(iii) A final point of chemical conjecture is suggested by the property of tautomerism displayed by several members of this group of compounds. Thus uric acid itself, phenylbutazone, tromexan and DHA all have mobile hydrogen atoms whose shift determines interconvertible keto and enol forms. Such structures have special valency characteristics and an ability to form unusual bonds under certain conditions, and it may be that the participation of these compounds in vital cellular reactions is in some way a function of this property.

B. BIOLOGICAL RELATIONSHIP OF URICOSURIC,  
ANTICOAGULANT AND ANTI-RHEUMATIC  
MECHANISMS

The discovery of the uricosuric activity of tromexan focuses attention on the close relationship among the biological processes serving urate reabsorption and synthesis of the prothrombin complex, and those underlying the 'rheumatic' inflammations of joints and connective tissue.

(1) Relation between uricosuric and  
anticoagulant mechanisms

At first sight the two activities of tromexan seem distinctly separate: urate transport in the kidney is affected from the earliest entry of the drug into the blood stream, while a day must elapse before prothrombin impairment is manifested. The coincidence of uricosuric and anticoagulant properties in two older drugs, salicylate and cinchophen strongly suggests that the particular enzymatic reactions in both renal and hepatic cells are subject to interference by the same compounds and are therefore themselves similar. That such similarity of mechanism should be associated with a wide discrepancy in the times taken for the two effects to manifest themselves, is difficult to understand. Overman, Link and colleagues<sup>97</sup> considered that time was required for an active anticoagulant principle to be released from the coumarin drugs, suggesting salicylate as the functioning molecule produced; but the latter compound itself displays the same delay in lengthening prothrombin time when given in prolonged high dosage (Glazebrook, 1947).<sup>53a</sup> It seems to the writer that changes in prothrombin activity, which depend on depletion of clotting factors by their impaired synthesis, must necessarily escape detection for a variable number of hours while their existing concentration in the blood gradually diminishes; (this contrasts with the true, immediate anti-coagulant action of heparin which 'neutralizes' circulating clotting factors). The process of interference with 'factor VII' synthesis may well begin as soon as tromexan is absorbed from the alimentary tract, as seems the case with its uricosuric action. Acceptance of the latter view would remove the chief argument against the suggestion, that production

of coagulation factors in one site and urate transport in another have a step or more in common.

Relative to this particular aspect of the discussion, the following points still require experimental investigation:

- (1) Will vitamin K or  $K_1$ -oxide, which oppose the anticoagulant effect of tromexan, also oppose its uricosuric action?  
(It is likely that vitamin K plays a more specific role in the normal synthesis of prothrombin factors, and that its function does not fall into the particular sphere of overlap shared by the two enzymatic processes.)
- (ii) Will related coumarin anticoagulants necessarily display a similar uricosuric action?  
(While the foregoing reasoning implies that they might, other factors, such as the greater urinary excretion of dicoumerol and PID compared with tromexan, may alter their ability to interfere in tubular reactions. The smaller weights of the latter drugs required to impair prothrombin would make the safe demonstration of convincing uricosuria difficult.)
- (iii) Will Link's Compound 16 - the free carboxylic acid of tromexan - which is devoid of anticoagulant activity, still retain its uricosuric properties? Loss of both its functions, and restoration of both by esterification, would go a long way towards correlating the mechanisms of the two cellular processes.

Work has begun in search of some of the answers to these problems.

(2) Relation between uricosuric and anti-rheumatic activity

There appears to exist a surprising parallelism between the anti-inflammatory effect of certain old and new drugs in rheumatic fever, rheumatoid arthritis and acute gout, and the ability of those drugs to increase urate elimination. The earliest instance of this was salicylate, and cinchophen, phenylbutazone and cortisone have provided repeated examples of this phenomenon. In each case the drug has initially been

introduced for the anti-rheumatic effect, and discovery of its uricosuric action has followed sooner or later. The absence of antiphlogistic activity in a potent uricosuric drug like benemid scarcely detracts from the coincidence revealed by the others, and may be due to a structural inability to participate in the disturbed chemical reactions of the rheumatic process. Another look at the molecular formulæ in Fig. 18 reveals that in one sense benemid differs from salicylate, cinchophen, phenylbutazone and cortisone, the four of which display a greater structural predisposition to tautomerism and molecular resonance, and it is likely that even as uricosuric agents they differ from benemid in their mode of interference with tubular transport.

The biological significance of this curious, indirect correlation between the processes of uric acid excretion and acute rheumatic disorders is difficult to understand. It does point to the advisability, however, of periodically comparing progress in the two spheres of investigation.

(3) Relation between anticoagulant and anti-rheumatic activity

From the above observations it is natural to wonder whether tromexan exhibits any anti-rheumatic activity. It so happens that a few reports exist on the role of various anticoagulants in the treatment of rheumatic states, and, although the results in such cases are not uniformly acceptable, the glimmerings of a relationship appear through them:

- (a) Glazebrook and Cookson <sup>53a</sup> remarked that 'substances benefiting acute rheumatic fever, rheumatoid arthritis and anaphylactic states, have a common action in that they are all anti-coagulants - namely, salicylates in rheumatic fever, deep jaundice in rheumatoid arthritis and heparin in anaphylactic states.\* On this basis they built up a theory that the therapeutic effect of salicylate in rheumatic fever depended on its power to prevent protoplasmic clotting and cell death resulting from intra-cellular antigen-antibody reactions.

While they themselves have since refuted the

validity of their earlier concept <sup>53b</sup> ,  
 other papers have appeared on a similar theme:

- (b) Howe and colleagues <sup>66</sup> reported that a small group of patients with acute gouty arthritis was strikingly relieved by treatment with heparin or its synthetic analogue Peritol in amounts which were not necessarily anticoagulant, and without associated uricosuria. Both drugs were moderately beneficial in cases of rheumatoid arthritis, but dicoumarol was ineffective.
- (c) Glazebrook and Wrigley were unimpressed by the treatment of rheumatic fever with heparin, which they had undertaken on the new premise that it was known to inhibit hyaluronidase, a spreading factor of probable importance in rheumatic states <sup>53b</sup> . They suggested that dicoumarol might also have an anti-hyaluronidase action, as has been shown in animals, man and rheumatic subjects to be the case for salicylate.

#### (4) Conclusion

There is little to be concluded from these reports other than the inference of a shadowy relationship among certain drugs. Perhaps most remarkable is the inability of biochemists to explain the great versatility of salicylate, a simple substance with anti-rheumatic, anti-phlogistic, anti-immune <sup>53a</sup> , uricosuric, anticoagulant and anti-hyaluronidase activities. Interest is further aroused by the tendency of certain substances to display further effects drawn in groups from the same list:

Cinchophen has anti-rheumatic, anti-phlogistic, anti-immune and weakly anticoagulant properties; <sup>67, 68.</sup>

Phenylbutazone is both anti-rheumatic and uricosuric; <sup>79, 106a.</sup>

the 11-oxysteroids, cortisone and hydrocortisone, are powerfully anti-rheumatic, anti-phlogistic, anti-immune, oppose the effects of hyaluronidase in rheumatic fever and rheumatoid arthritis <sup>121</sup> and are weakly uricosuric;

heparin, a potent anticoagulant, is also a strong inhibitor of hyaluronidase and has been credited with anti-rheumatic activity;

tromexan well deserves investigation, therefore, of the possibility that with its actions as a potent anticoagulant and uricosuric agent are linked anti-rheumatic and/or hyaluronidase-inhibiting effects.

C. THERAPEUTIC IMPLICATIONS

It is highly unlikely that a substance with the anticoagulant potency of tromexan will lightly be used for purposes other than the treatment of thrombo-embolic disease, in which its place is currently well established.

The discovery, however, that tromexan has a second significant pharmacological action may prove practically applicable under the following circumstances:

(1) Further investigation among Link's 106 coumarin derivatives, most of which were useless anticoagulants, may easily reveal analogues of tromexan with renal affinities permitting uricosuric action, even if the ability to disturb factor VII synthesis has been lost.

Closest to tromexan among these compounds is its hydrolysed counterpart, Compound 16, which is known to lack anticoagulant activity and might therefore be the first worth testing for uricosuria.

(2) Tromexan itself gives promise from a few experiments described of proving to be - weight for weight - as powerfully uricosuric as benemid, hitherto the strongest agent known. In view of its larger molecular weight, this would assign the greater molecular efficiency to tromexan.

If, then, these properties can be retained in a related structure stripped of anticoagulant activity and devoid of other harmful effects, an extremely useful addition will be made to the stock of available uricosurics. Even then the advantage possessed by benemid of uniform action due to slow break-down, would be difficult to gainsay.

(3) In the light of remarks on the previous page, should tromexan prove to have some degree of anti-hyaluronidase or anti-rheumatic activity, the combination of these with its uricosuric effect would make it suitable on two counts for treating gout, provided that these properties could be retained in a non-anticoagulant compound.

(4) Recent trends in the long-term management of coronary atherosclerosis with anticoagulant drugs <sup>54</sup> may yet lead to the preferential use of tromexan for this purpose, in view of its uricosuric action:

(i) The patient with coronary disease in addition to gout, if placed on a long-term anticoagulant regime, would be receiving two treatments in one by the use of tromexan.

(ii) The finding by Gertler and White (1954) <sup>53</sup>, in marshalling the anthropometric and biochemical characteristics of 100 coronary heart disease patients under the age of 40, that the serum urate levels were significantly higher than normal is of great interest. An index derived from serum urate, cholesterol and lipid phosphorus gave them better correlation with coronary heart disease than could any other data.

Such an observation emerging from an excellently conducted study, seriously implies that the correction of moderate hyperuricaemia in coronary heart disease (regardless of the presence of gout), and for all we know even in healthy subjects, may be no less important than the controversial attempts to keep serum cholesterol down.

Certainly patients already victims to the disease, if deemed suitable for receiving long-term anticoagulant treatment, should be given tromexan in preference to other known anticoagulants if none of the latter share its uricosuric activity.

## SECTION III

STUDIES OF URICOSURIC THERAPY  
IN GOUTCHAPTER 6. CLINICAL AND DIAGNOSTIC PATTERN OF 140 GOUT PATIENTS

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## B. CLINICAL DATA

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## CHAPTER 6. CLINICAL AND DIAGNOSTIC PATTERN OF 140 GOUT PATIENTS

### A. SOURCE OF PATIENTS.

The patients in whom uricosuric therapy with benemid was studied were members of a series of 140 gout patients whom the writer has investigated and treated since January, 1952, at the Groote Schuur Hospital, Cape Town.

In the following pages the criteria for recognizing gout are reviewed. Care has been taken in this presentation to include only those patients about whose correct diagnosis there can be virtually no doubt. Accordingly, 40 to 50 other hospital patients, in whom the diagnosis of gout varied from possible to highly probable but who lacked one or more of the typical features, have been excluded from the series.

Cases encountered after September 1, 1954, have not been reported, and no use has been made of hospital records dating from previous years if the patients concerned had died, or for other reasons were not personally seen. Similarly, about 100 gout patients diagnosed and treated by Dr. Mark Horwitz in private practice, and whose clinical protocols have generously been available, do not figure in this thesis.

The patients came under observation in one of the following ways:

1. A few, known to have attended or been admitted to hospital in past years, reappeared or were recalled.
2. After admission to hospital for joint disease, or for another illness during which gout was recognized.
3. After referral to the Arthritis Clinic because of joint symptoms, by private practitioners or various other hospital departments.
4. By direct referral from a small number of private practitioners aware of the writer's interest in gout. One doctor alone contributed twenty correctly diagnosed cases during the period of study.
5. Many patients receiving treatment had friends or relatives 'with the same condition' and often brought them along to prove it.

Of the patients discussed in this chapter, 62 were first met in 1952, 61 in 1953 and 17 in the first eight months of 1954.

B. CLINICAL DATA.

1. Race

Racial distribution among the 140 patients was as follows:

White . . . . .	88 (63%)
Cape Coloured . . . . .	51 (36%)
African native (Bantu) . . . . .	1

The prevalence of gout among the white and coloured members of the population appears to be comparable, which is in keeping with observations on the essential similarity of their disease patterns<sup>28</sup>. Among the South African Bantu, however, as among negroes elsewhere, gout is rarely seen and only a few cases have been reported<sup>36, 94</sup>. In a small survey (by the writer) of a local African community, serum urate levels were similar to those in other races, and there is no ready explanation for the discrepancy in incidence, assuming its truth.

The patient illustrated in Fig. 19 has diabetes mellitus in addition to gout. His parentage is pure negro on both sides, and blood-grouping reveals the Rh-pattern cDe/-, a characteristic Bantu genotype.



Fig. 19. Bantu gout patient (case 44).



Fig. 20. Tophus over interphalangeal joint of right hallux yielded crystals of sodium urate. Note swelling near left lateral malleolus arising from uratic destruction in tarsal joints. (Case 44).



Fig. 21. Uratic lesions in bones of feet, especially in joints of right big toe. (Case 44).



Fig. 22. Chronic gouty arthritis. Note fair symmetry of joint swellings and muscle wasting. Urate crystals found in tendon nodule on dorsum of right hand. (Case 44).



Fig. 23. Bony lesions of gout well seen in left 5th and right 2nd and 3rd metacarpophalangeal joints. (Case 44).

## 2. Sex

The proportion of women with gout usually varies in reported series from 3% to 7%<sup>85</sup>. The present figures are:

Men . . . . .	129	(92%)
Women . . . . .	11	(8%)

The incidence in women may indeed be higher, but the difficulties of positive diagnosis are greater, due to the milder hyperuricaemia and relative rarity of tophi in women patients.

## 3. Age and Duration

140 patients:

Average age (years) when first seen . . .	51.1	(S.D. $\pm$ 11.4)
Average age at clinical onset . . . . .	41.9	(S.D. $\pm$ 10.2)
Average duration of clinical gout . . . . .	9.2	(S.D. $\pm$ 8.6)

Most experience their first attack of acute gout in the fourth or fifth decades of life<sup>118</sup>. Two of our patients were affected in their early teens (cases 1 and 137) and, as has been realized<sup>16</sup>, such an early onset heralded an unfavourable course. The hereditary background in such cases is usually plain, but not invariably (case 137).

First attacks in the 60's and 70's are not rare, but usually depend for their belated precipitation on factors previously absent, e.g., surgical operation, myocardial infarction.

## 4. Familial incidence.

The success met in eliciting a positive family history of gout varies widely with the persistence of the questioner and the talent of the patient. Talbott, who has worked extensively on the hereditary aspects of the disease, has recorded a familial incidence in 50-60% of patients; for most recent series the figure lies between 6% and 18%<sup>85</sup>.

Of these 140 patients, a family history of gout, or of joint trouble suspiciously like it, was given by 46 (33%).

## 5. Social status and occupation

There is no convincing evidence in this or any series that a particular class, profession or trade is specially prone to gout or exempt from it. The fact that the writer knows eight

medical colleagues with clinical gout and another twelve with gout among their immediate relatives is not considered significant.

6. Alcohol intake

The number of patients in this group who are apparently literal teetotallers is eight. Of the remainder, all take alcohol to a varying degree, but the number who were assessed to be excessive drinkers and/or chronic alcoholics is 39 (28%).

It is generally agreed <sup>116</sup> that alcohol plays, at most, an ill-understood part in modifying the onset or clinical picture of gout in those genetically predisposed to it.

7. Body build and plethora

The tendency of gout to appear in heavily built men is well recognized, and recent work <sup>53</sup> showing that urate levels are higher in the serum of such people is interesting.

Judged purely on the grounds of clinical impression, seven (5%) of the 140 have been recorded as 'lean', and 74 (53%) as either 'obese' or 'thick-set'.

The generally 'full-blooded' appearance of gout subjects is borne out by haematocrit determinations in a large proportion of our patients (Table 10). Polycythaemia vera as such was seen twice (cases 77 and 134). Unlike certain other enduring joint diseases (e.g., rheumatoid arthritis), anaemia is rarely met in gout except if (a) the patient is progressively uraemic, or (b) the disease is associated with a blood dyscrasia such as leukaemia, haemolytic anaemia or myelofibrosis.

8. Associated diseases

These occurred with the following frequencies:

- (a) Diabetes mellitus . . . . . 2 cases  
Four others had relatives with diabetes.

- (b) Blood diseases: Among the 140 patients recorded here, three (2%) suffered from the haemopoietic disturbance comprising the chronic non-leukaemic myelosis and/or myelosclerosis syndrome. This group of anaemias with splenomegaly is fundamentally related to polycythaemia vera <sup>91</sup>, and one of the three patients (case 134) began his clinical course as the latter disease. There was one other instance of polycythaemia vera complicated by gout (case 77), a woman who died intercurrently of a thyroid sarcoma. Two more cases not

included in this series are known to the writer, with non-leukæmic myelosis and myelocytic leukaemia, respectively, associated with gout.

One's concept in such cases of 'secondary' gout is that the disease has been more readily revealed in somebody essentially predisposed to gout, by the coincidental development of a blood disturbance involving increased nucleoprotein turnover.

(c) Dupuytren's contracture . . . . . 3 (2%)

(d) Psoriasis . . . . . 4 (3%)

Cases 16, 18, 110 and 139 illustrate the diagnostic difficulty that may arise when patients with gout have psoriasis in addition. Rheumatologists are familiar with the association of psoriasis and a chronic or relapsing type of rheumatoid arthritis; but in these four patients the clinical and laboratory findings left little doubt that their joint disease was gout. In case 16, a woman who had been bed-ridden for months at a time as a result of polyarticular exacerbations of 'psoriatic arthritis', urate crystals from a pre-patellar bursa showed the true nature of the disease.

(e) Liver disease (present or past acute hepatitis, clinically recognizable cirrhosis, or disturbed serum flocculation ('liver function') tests . . . . . 9 (6%)

(f) Past rheumatic fever . . . . . 7 (5%)

Past urethral discharge . . . . . 9 (6%)

In none of the patients giving a history of acute rheumatic fever was there clinical evidence of heart disease, and from their descriptions it is very probable that in some the illness was acute polyarticular gout. It is not generally realized that an acute attack may prostrate a patient for a period of months and involve many joints before it subsides. An important diagnostic feature is the lack of commensurate general illness, which accompanies rheumatic fever, infectious arthritis or acute rheumatoid arthritis.

Previous urethritis had almost invariably led to an initial diagnosis of gonococcal arthritis, with which many another patient was impugned.

(g) Coronary heart disease . . . . . 15 (11%)

Diagnosis of the condition was made on clinical evidence of

angina pectoris and/or myocardial infarction. One would hesitate to regard these figures as necessarily abnormal for this age group.

(h) Hypertension

Diastolic pressure 95 mm. Hg. or more at <u>all</u> examinations . . . . .	.46 (33%)
Diastolic pressure 95 mm. Hg. or more at <u>some</u> examinations . . . . .	.48 (35%)
<hr/>	
Total . . . . .	94 (68%)

(i) Renal disease is discussed below.

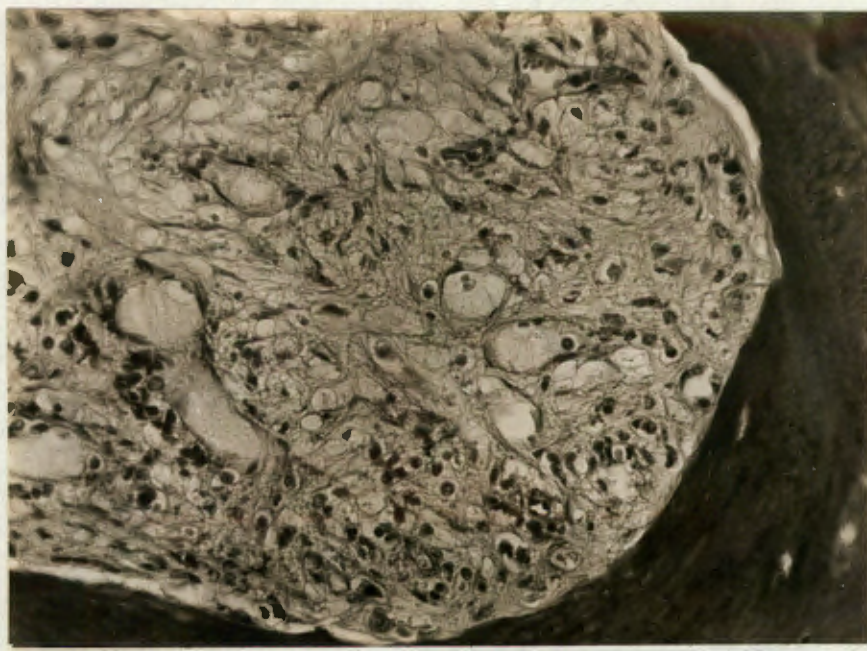


Fig. 24. Non-leukæmic myelosis with myelofibrosis and gout (case 75). Section of bone marrow surgically removed from rib for diagnosis. (x 375).

## 0. DIAGNOSTIC PATTERN

The clinical tables in this section of the thesis are intended both as a synopsis of the relevant clinical data on each patient, and as a presentation of those features which collectively (or, in the case of tophi, singly) justify the diagnosis of gout. Some items carry more weight than others, and no case has been included who did not display at least three of the following 'cardinal' features:

1. Acute attacks, of the suddenness and severity characteristic of gout, occurring usually in typical sites and often under suggestive circumstances, with complete resolution (in the earlier years of the disease) after lasting one or more days, weeks or even months.
2. Convincing therapeutic response to colchicine in an attack.
3. Unequivocal hyperuricaemia, in the absence of nitrogen retention.
4. Tophi containing sodium urate crystals.

The diagnostic pattern is further strengthened by certain highly suggestive associated clinical features:

5. Sex, age and appearance.
6. Alcoholic excess.
7. Family history.
8. Acute or chronic olecranon bursitis.
9. Renal disease and/or urinary tract calculi.
10. Hypertension.
11. Radiographic evidence of articular 'erosions'.

Relative to some of these points, the following figures are of interest:

Table 10. Clinical and diagnostic features in 90 gout patients in whom benemid was not assessed.

Case no.	Race Sex	PATIENT			ASSOCIATIONS			ACUTE ATTACKS				CHRONIC SYMPTOMS		OLECRANON BURSTITIS		X-RAY CHANGES	SERUM URATE (mg/100ml)	
		Years since first seen	Family history	Build PCV(%)	Alcohol habit	Other disease	Renal impairment	Hypertension	Annual frequency	Sites		Precipitating factors	Colchicine response	Acute	Fibrous/Uratric			
										First	Later							No. per attack
40	WM	29	I	Thin hyper-uricemic	Medium (48)	-	Agenesis left kidney & tract	+	0	+	Big toe	1	Coryza	±	0	0	0	7.6-8.6
50	WM	30	I	Thick-set	(54)	-	0	?	?	+	Big toe, ankle, big toe	1	Trauma (A.M.)	+	0	0	0	8.0-8.0
33	WM	32	I	Thick-set	(40)	-	Acromegaly	0	±	+	Big toe	1	0	+	0	0	0	7.6-8.4
37	WM	35	I	0	Medium	-	0	0	0	+	Big toe	2	0	+	0	0	0	7.4
99	CM	36	I	0	Medium	-	Renal failure (chronic)	+	++	+	Big toe	1	Uraemia	+	0	0	0	9.5-9.8
79	WM	37	I	0	(51)	-	Chronic pyelonephritis	0	+	+	Big toe	1	Exercice	+	0	0	0	7.4-8.6
25	WM	37	I	0	Obese	-	Post-rheumatic fever	0	±	+	Big toe	1	Party	?	0	0	0	7.0
94	CM	40	I	0	Thick-set (50)	+	Post-urethral discharge; R.R. +ve	0	0	+	Big toe, knee	1	Trauma	+	0	0	0	7.9-8.6
117	CM	41	I	0	Medium (44)	-	Neuro-circulatory asthenia; post-rheumatic fever	?	0	+	Ankle, big toe	1	0	+	0	0	0	5.5-5.6
120	CM	43	I	0	Medium (52)	-	0	0	0	+	Mid-foot	1	0	+	0	0	0	9.3
76	CM	45	I	0	Obese	-	Coronary and renal	+	+	+	Big toe	1	Coronary thrombosis	+	0	0	0	7.5-8.6

**KEY:** Case nos. arranged of in ascending order of clinical duration, frequency of attacks, patients' ages.

**Race and Sex:** W=white; C=coloured; M=male; F=female.

**Duration of gout:** to nearest whole year.

**PCV:** Pecked red cell volume.

**Alcohol:** (+) excessive intake (0) teetotal (-) reasonable "

**Renal impairment(+):** Urea 55+ &/or Creatinine 1.8+ (mg./100 ml. serum) &/or glomerular filtration less than 75% of std. for age and sex.

**Hypertension:** (++) diastolic > 125 (+) " always > 95 (-) " sometimes > 95

**Frequency of attacks calculated for previous 2-year period.**  
**Big toe-ankle:** counted as one site.  
**Colchicine:**  
 (+) Convincing response in 24-48 hours or less;  
 (±) Probable benefit.

**X-ray changes:**  
 O-A denotes appearance of osteoarthritis.  
 G " bony 'erosions' or 'cysts'.  
 0 " normal appearance.  
 Blank - not x-rayed.

**Serum urate.** Normal upper limit taken as 6.0 mg./100 ml. (Control figures in text.)







Table 10 (continued)

PATIENT				ASSOCIATIONS				ACUTE ATTACKS					CHRONIC SYMPTOMS			OLECRANON BURSTITIS		X-RAY CHANGES	SERUM URATE (mg/100ml)		
Case no.	Race Sex	Age first seen	Years Chir-ical seen	Family history	Build PCV(%)	Alcohol habit	Other disease	Renal impairment	Hyper-tension	Annual frequency	Sites			Precipi-tating factors	Coldchance response	Acute	Fibrous	Uratic			
											First	Later	No. per attack								
74	WM	43	8	Paternal gout	Obese (46)	+	Migraine; psychopathy	+	±	+	Big toe	Big toe, finger, shoulder	Pneumonia	+	0	0	0	0	0	0	10.7-8.9
89	CM	48	8	Paternal gout; mother brother, sister arthritis	Obese (44)	-	Hypertensive coronary disease; L.V. failure; coronary disease	0	++	+	Big toe	Big toes, ankles, knees, wrists	Marsaly injection	+	+	0	0	0	0	0	9.8-7.0
114	WM	49	8	0	Medium	-	Past coronary thrombosis	?	+	+	Ankle, big toe	Ankles, big toes, tibial tubercle	0	?	0	0	0	0	0	0	8.8
90	WM	58	9	0	Medium	-	0	0	0	+	Knee	Big toe, wrist	Trauma festivity	+	0	0	0	0	0	0	7.8-8.6
88	WM	61	9	0	Medium (45)	+	Coronary disease; urinary gravel	0	0	+	Big toe	Big toe, mid-foot	0	+	0	0	0	0	0	0	6.8-6.3
82	WM	61	6	0	Medium (45)	-	Past urinary calculus; erythromelalgia	0	0	+	Big toes	Big toes, ankles, knee, hands, elbow	Exercise	+	+	0	0	0	0	0	10.6-6.9
92	WM	43	8	Mother arthritis + diabetes; uncles leg trouble	Obese (50)	+	Effort dyspnoea	+	±	+	Ankle	Ankles, knees, wrist	Trauma	+	0	0	0	0	0	0	8.8-6.8
107	CM	48	10	0	Medium	+	Past urethral discharge	0	0	+	Big toe	Big toes, mid-foot, ankles, knees, wrists, elbows, shoulders	0	0	0	+	+	+	+	+	6.7-6.6
76	WM	67	10	0	Medium (85)	-	Non-leukaemic myelosis; congestive heart failure; renal death after haemorrhage	+	±	+	Mid-foot	Ankles, knees, wrist, elbow	Exercise; liver injections, salicylates	+	0	+	+	+	+	+	7.6-6.1



Table 10 (continued)

PATIENT				ASSOCIATIONS				ACUTE ATTACKS				CHRONIC SYMPTOMS		OLECRANON BURSTITIS		X-RAY CHANGES	SERUM URATE			
Case no.	Race	Sex	Age	Years since first seen	Family history	Build	Alcohol habit	Other disease	Renal impairment	Hypertension	Annual frequency	Sites		Precipitating factors	Colchicine response	BURSTITIS		TOPHI	SERUM URATE	
												First	Later			Acute	Fibrous/Uratric			
											O	24	5+	No. per attack					(mg/100ml)	
101	WM	M	56	20	0	Obese (47)	-	Coronary disease; arcus senilis	0	0	+	Big toe	Big toe, ankle, knee, elbow	0	+	0	0	0	0-A	8.3-7.9
81	WM	M	70	20	0	Medium (53)	-	0	0	±	+	Big toe	Big toe	0	+	0	0	0	Joint	9.4-8.9
137	WM	M	29	16	0	Obese (39)	-	Renal failure; progressive uraemia	+	++	+	Mid-foot	Big toe, ankle, knee, hands, wrists, elbows	2+	+	+	+	0-A Joint	13.8-7.1	
139	WM	M	66	21	0	Obese	-	Psoarthritis	+	+	+	Mid-foot	Feet, ankles, knee, wrist, hands	1	+	0	0	0	7.4-6.5	
108	WM	M	22	25	Path-rheumatism	Medium (45)	-	0	0	0	+	Big toe	Big toe	2	+	0	0	0-A	6.0	
56	WM	M	56	25	0	Medium (45)	-	Coronary disease; died	0	+	+	Big toe	Big toe, ankles, knees, hands, wrists, elbows	2	+	+	0	0-A Joint	8.6-7.8	
51	WM	M	59	27	0	Thick-set	-	0	0	±	+	Big toe, ankle, knee	Big toe, ankle, knee, hands, wrists, elbows	2	+	+	+	0-A Joint	10.8	
78	WM	M	58	30	0	Lean	+	Hepatic cirrhosis and jaundice; arterio-sclerotic gangrene of feet	0	0	+	Big toe	Big toe, ankle, knee, hands, elbows	1	+	+	+	0-A	8.6-6.0	
58	CM	F	64	37	Two brothers goat	Medium (58)	-	Urinary calculi; pulmonary tubercle	0	+	+	Big toe	Big toe, ankle, knee, hands, wrists, elbows, shoulders	2	+	+	+	0-A	10.5-7.8	



(a) Big toe joint involvement

In first attack . . . . . 95 (68%)

At some stage . . . . . 130 (93%)

(b) Acute olecranon bursitis . . . . . 57 (41%)

(c) Chronic olecranon bursitis.

All grades of thickening or nodularity . . 49 (35%)

-Fibrous thickening alone . . . . . 25 (18%)

-With urate, proven or suspected . . . . . 24 (17%)



Fig. 25. Acute olecranon bursitis - a typical feature of gout.



Fig. 26. Chronic uratic olecranon bursitis. (As often, the bursal and periosteal thickening merely fibrous).

(d) Precipitating factors (acute attacks)

Nothing recognizable . . . . . 71 (51%)

In the remaining cases, attacks were related to one or more of the following factors:

Trauma or exercise . . . . .	36 (26%)
Alcohol or parties . . . . .	13 (9%)
Surgical operations . . . . .	12 (9%)
Acute illness (infection, infarction, colic) . . . . .	9 (6%)
Food items (oranges in 3 cases!) . . . . .	7 (5%)
Therapeutic (injections of liver, mersalyl, vitamin B-complex, penicillin, vaccine; venesection; radiotherapy) . . . . .	7 (5%)
Exposure to cold . . . . .	5 (4%)
Holidays or travel . . . . .	4 (3%)
Worry . . . . .	3 (2%)

(Benemid administration was sometimes followed by acute gout, before simultaneous colchicine was routinely prescribed).

(e) Classification into 'acute' and 'chronic' stages

<u>Total freedom from symptoms after subsidence of acute attacks</u> . . . . .	69 (49%)
Subjective articular <u>symptoms of any grade</u> . . . . .	71 (51%)

Clinical classification of this sort is difficult, as chronicity may represent anything from mild persistent foot aches to crippling deformity. Of those listed as having chronic symptoms, the proportion suffering from significant joint disability is in reality much less.

(f) Tophi

Ear pinnae, tendons, joints, bursae . . . . . 49 (35%).

In ten reported series totalling 750 patients, analysed by McCracken, Owen and Pratt<sup>85</sup>, the incidence of tophi ranged from 23% to 69%, averaging 45%. Comparisons of this sort depend largely on the selection of patients, of which there are many in this series recognised in their first attack or soon after. The proportion of cases with tophi tends to be reduced by the presence of such patients in the group.

Correlation of tophi with frequency of attacks.

Although the appearance of tophi in a gout patient is generally a function of time, it is not clear why, in a group of patients of equal clinical duration, tophi are not necessarily equally distributed. While no statistical correlation per se proves the nature of a relationship, the following figures are of interest for their implication (recognised clinically) that the course of gout is influenced for the worse by frequent attacks.

Patients who had had symptoms for 3 to 10 years were grouped according to least frequent attacks (0-1 annually) and most frequent attacks (5 or more annually). The incidence of tophi was:

Number of patients . . . . .	61
Annual frequency 0-1 . . . . .	18; tophi in 4.
"          "          5 or more . . . . .	9; "    "    6.

Calculation of chi square shows a significant correlation between frequency of attacks and occurrence of tophi.

(g) Radiographic features

Of the 140 patients, 106 were examined radiographically. The feet were X-rayed in all of these, and various other joints according to the clinical state.

Appearance entirely normal . . . . .	17 (16%)
Joint changes compatible with gout (erosions, cystic areas) . . . . .	45 (42%)
Joint changes compatible with degenerative ('hypertrophic') osteoarthritis . . . . .	74 (70%).

(Some patients showed evidence of both abnormalities).

Little reliance should be placed on radiography in diagnosing gout, certainly in the earlier years, and even later, non-specific degenerative changes predominate over the more typical 'punched-out' lesions.

Fig. 27. Ear topi with secondary chronic chondritis of pinna (thickened and nodular).



Fig. 28. Tophus on ulnar border of forearm.

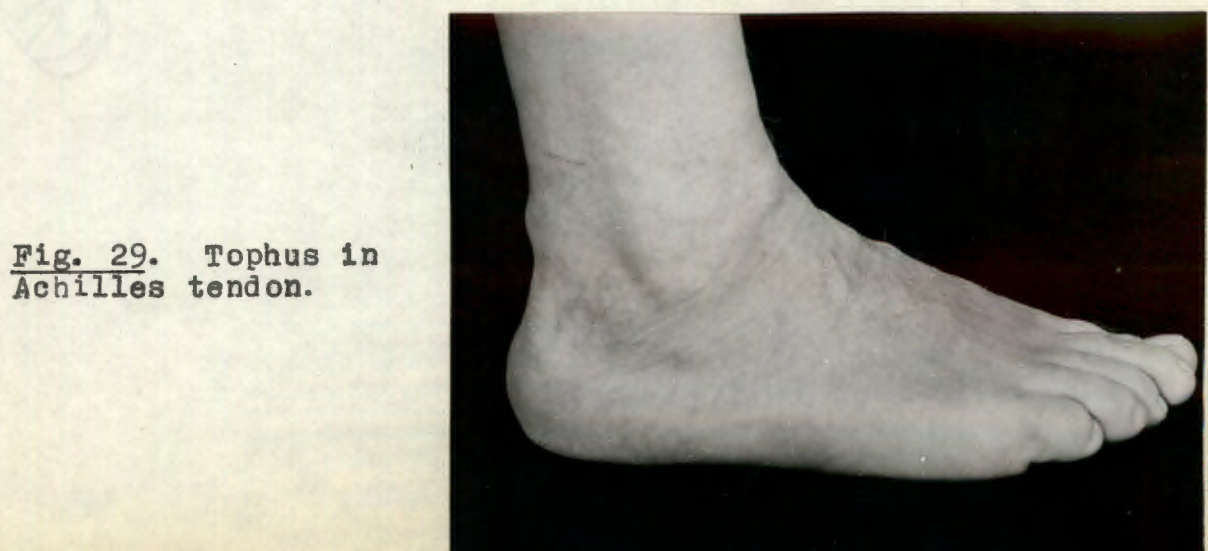


Fig. 29. Tophus in Achilles tendon.



Fig. 30.

Radiographic appearance of foot bones after 14 years of clinical gout. (Case 20). Changes of predominant osteoarthritis of first metatarso-phalangeal joints, with hallux valgus. There is one doubtful area of erosion in the head of the right first metatarsal.



Fig. 31.

Advanced gouty erosions of bones and joints, (case 3). At this stage the presence of external tophi makes the clinical diagnosis obvious.



Fig. 32. Hands of patient with chronic, tophaceous, polyarticular gout (proven by biopsy), showing remarkable resemblance to rheumatoid arthritis. (Case 8).



Fig. 33. (Case 8). Degenerative joint changes, mild osteoporosis, and one large erosion in head of left 3rd metacarpal. Appearances are also not classically those of gout.

D. SERUM URATE LEVELS1. Controls

Throughout this study, urate determinations were done by Herman Brown's modification<sup>32</sup> of Folin<sup>45</sup> and Benedict's<sup>12</sup> colorimetric techniques. Serum or plasma have been established as preferable to whole blood for analysis<sup>115</sup>, and the smallness of the non-urate chromogen fraction in serum makes the routine use of specific enzyme methods unnecessary, especially for serial estimations in many patients<sup>5</sup>.

Non-gouty subjects for control determinations were 131 hospital patients and 52 medical students. Serum urea and/or creatinine were simultaneously measured, and the following criteria of selection of controls employed:

(a) No urate values are included for subjects whose serum urea concentration was higher than 55 mg./100 ml., or whose creatinine was higher than 1.7 mg./100 ml. (The upper limits of normal for the methods used are generally taken as 40 and 1.1 mg./100 ml. respectively).<sup>3, 26.</sup>

(b) No patients were included as controls who suffered from detectable renal or urinary tract disease, congestive heart failure, or recognized hyperuricæmic states such as leukaemia or pneumonia.

Results are tabulated below:

	Males (110)		Females (73)	
	White	Coloured	White	Coloured
10-19	4.7 (33)	3.8 (9)	4.4 (7)	2.4 (3)
20-29	4.6 (18)	4.1 (9)	3.7 (8)	4.2 (2)
30-39	4.1 (5)	3.9 (3)	3.7 (9)	4.6 (5)
40-49	4.7 (6)	4.7 (4)	3.6 (8)	3.0 (3)
50-59	3.8 (6)	3.3 (5)	4.1 (15)	4.1 (2)
60-69	4.3 (6)	-	3.0 (4)	3.1 (4)
70-79	4.0 (5)	3.6 (1)	5.3 (3)	-
Mean	4.50 (79)	3.92 (31)	3.91 (54)	3.57 (19)
S.D.	0.97	1.09	1.11	1.37
(mg./100 ml.)	Mean $\pm$ S.D. = 4.30 $\pm$ 1.05 (110)		Mean $\pm$ S.D. = 3.82 $\pm$ 1.18 (73)	

Table 9. Serum urate concentration in 183 non-gouty subjects. (Bracketed figures denote no. of subjects in each group).

The above figures are comparable with most reported values, which usually range between 2 and 6 mg./100 ml. of serum<sup>108</sup>. They closely parallel those of Merson<sup>89</sup>, whose figures for 100 non-gouty persons by the same method, were men 4.54 (standard deviation 1.08), and women 3.82 (S.D. 1.00) mg./100 ml. Talbott found few normals to exceed 5 mg./100 ml., although using uricase, Gutman and YU obtained values of 5.4 and 4.1 mg./100 ml. for men and women respectively.<sup>59</sup>

The sex difference in urate levels in all recent reports<sup>109,124</sup> is borne out by the present figures. The slightly lower values, in both sexes, for Cape Coloured subjects may reflect their generally smaller dietary intake of protein.

## 2. Gout patients

All 140 patients had their serum urate levels determined on several or many occasions, exceptions being about twenty who were less intensively studied and whose blood was taken only once. For calculating the average figure of the whole series, the means of the lowest and highest value for each patient were used, or, for those only done once, their single value. Estimations performed during uricosuric therapy are not included. The range of values in each patient is shown in the clinical tables.

Serum urate concentration in 140 gout patients:

Mean  $\pm$  S.D. = 7.61  $\pm$  1.10 mg./100 ml.

The separate average of the 11 women patients<sup>118</sup> was 7.43 mg./100 ml., which does not wholly reflect the reported sex difference obtaining in gouty subjects as in normal. The explanation may lie in the care taken before including any of the women in the series as gout patients. Several probable cases, who did not 'earn' their place with unequivocal hyperuricaemia, were omitted, thereby leading to a rather high average for those listed.

Talbott<sup>118</sup> and most other authorities, accept serum urate figures above 6.0 mg./100 ml. as hyperuricaemic, leaving a boundary zone between 5 and 6 mg./100 ml. as equivocal or suspicious. Pitfalls always to be borne in mind are non-gouty hyperuricaemia due to nitrogen retention and the opposite influence of recent uricosuric therapy.

## E. RENAL DISEASE IN GOUT

### 1. Material

The problem of renal disease in gout is indicated by the following data. Emphasis will be placed on the frequency and variety of lesions among the group rather than on accounts of individual cases, which will be reserved for some of those discussed under benemid therapy.

One hundred and thirty of the 140 patients were sufficiently examined by both clinical and biochemical methods to warrant attempted assessment of their renal status. Procedures used were (a) urinalysis in all; (b) serum urea and/or creatinine determination in all, as a guide to nitrogen retention; (c) determinations of glomerular filtration rate by endogenous creatinine clearance in 53 of the patients, as well as (d) clinical examination and various special investigations, such as bacteriological culture of urine, intravenous urography and radiography of chest, when clinically indicated.

By these methods and by criteria of assessment about to be outlined, renal or urinary tract disease was present in 61 of the 130 patients. In 9 of these 61 there was no current proteinuria or azotaemia, but present or past pyuria, haematuria, organisms, gravel or calculus. These 9 patients, whose abnormalities are all ascribable to tract pathology, will not be considered further in discussing renal involvement. The remaining 52 are analyzed as cases of possible kidney disease in gout.

### 2. Terminology

Symbols used in this discussion, and in the clinical tables, have the following significance:

- (a) Proteinuria: Plus-minus ( $\pm$ ) . . . . . 'Trace'  
 One-plus (+) . . . . . 'Moderate'  
 Two-plus (++) . . . . . 'Heavy', short  
 of flocculation.
- (b) Cells or casts: Since most urines have some formed elements, only impressive numbers of red cells, white cells, tract cells and various casts are recorded.  
 One-plus (+) . . . . . 'Moderate number'  
 Two-plus (++) . . . . . 'Large number'.

(c) Hypertension:

- Plus minus ( $\pm$ ) . . . Diastolic pressure inconstantly  
95 mm. Hg. or more.
- One-plus (+) . . . Diastolic pressure constantly  
95 mm. Hg. or more.
- Two-plus (++) . . . Diastolic pressure constantly  
125 mm. Hg. or more.

(d) Azotemia:

- One-plus (+) . . . Serum urea 55 mg./100 ml. or more,  
and/or Serum creatinine  
1.8 mg./100 ml. or more.
- Two-plus (++) . . . Serum urea greater than 100 mg./100 ml.

(e) Glomerular filtration rate (endogenous creatinine clearance):

The general validity and usefulness of this procedure in appraising renal function have been discussed. In fixing an arbitrary border of normality, allowance has been made for normal differences between the sexes, and for reduction in GFR with increasing age (Homer Smith<sup>107</sup>). A further allowance of 25% is made for variability, clearances therefore being regarded as abnormal if they are less than 75% of Homer Smith's 'world average' figures for the patient's sex and age.

AGE	Normal GFR		75% figures	
	Men	Women	Men	Women
20-49	127	118	95	89
50-59	99	92	74	69
60-69	90	84	68	63
70-79	81	75	61	56
80-89	72	67	54	50

Table 11. Normal values (ml./min.) for GFR in both sexes, based on a regression of 0.72% per year after the age of 50 years. (From Homer Smith).

Table 12. Renal clearances and other data in 53 gout patients. \*

CLINICAL					CHEMICAL		RENAL CLEARANCES							
Patient Case na	Race-Sex Age	Years of clinical gout	Tophi	Protein- -uria	Serum concentration		Urine flow	Creatinine			Urate			Urate/ creatinine clearance ratio
					Urea	Creatinine		Serum conc.	Clear- -ance	Mean, per 173m <sup>2</sup>	Serum conc.	Clear- -ance	Mean, per 173m <sup>2</sup>	
					(mg/100ml)		(ml/min)	(mg/100ml)		(ml/min)	(mg/100ml)		(ml/min)	
17	WP 66	1	0	0	34	<u>1.2-1.2</u>	5.8 8.5 11.6	1.2	66.5 76.4 74.6	80.5	5.6	14.0 14.7 16.2	16.6	0.81
70	WM 27	1	0	+ to ++	34-61	1.0-1.3	4.8 5.9 6.2	1.3	131 96.6 115	110	6.5	6.3 4.6 4.5	8.1	0.046
82	WM 58	1	0	0	22-54	<u>0.9-2.6</u>	3.1 9.3 8.3	1.1	97.6 118 84.6	96.5	5.7	9.0 14.8 10.2	11.3	0.12
103	WM 36	1	0	+ to +++	20-45	<u>1.1-2.2</u>	1.8 4.6 3.7	1.1	112 102 104	82.5	7.7	4.1 4.1 3.9	3.1	0.038
14	WM 48	2	0	0	51	1.2-1.7	7.6 -	1.2	147 -	138	7.8	21.1 -	20.0	0.14
54	WM 37	2	0	+	23	0.9-1.1	3.7 3.0 1.9	0.8	130 129 142	130	6.7	6.8 7.5 10.2	8.6	0.067
140	WP 52	2	0	+	22-22	0.9-1.3	3.6 8.7 5.0	1.0	89.0 95.5 60.6	73.4	6.4	5.7 6.6 4.5	5.1	0.069
13	WM 60	3	0	0	41-54	1.2-1.7	3.7 3.3	1.5	107 93.3	77.5	7.4	11.4 10.2	8.8	0.11
23	CM 42	3	0	0	28-47	1.1-1.6	7.1 12.1 9.5	1.2	122 127 111	98.0	6.6	8.4 15.9 10.5	9.5	0.097
62	WM 49	3	0	0	-	0.9-1.0	6.4 9.5 9.9	0.9	121 150 139	120	7.1	6.4 10.5 6.8	6.5	0.067
26	CM 38	4	0	0	12-30	1.0-1.7	9.4 15.0 13.9	1.1	107 113 96.0	97.9	7.5	14.2 18.2 17.1	15.3	0.16
38	WP 57	4	0	±	41	1.0-1.2	7.2 7.7 9.0	1.0	96.7 79.9 78.9	85.2	4.7	11.6 10.9 11.1	11.2	0.13
28	CM 42	5	0	++	79-104	<u>2.6-3.2</u>	4.7 5.2 5.3	2.6	32.1 38.2 34.8	37.3	7.1	5.8 5.2 6.7	6.3	0.17
32	WM 43	5	0	0	45-49	<u>1.3-1.2</u>	2.3 5.2 4.5	1.3	114 108 109	102	7.8	11.3 9.9 7.9	9.0	0.088
57	CM 41	5	0	+	-	0.9-1.1	5.5 6.4	1.1	102 82.0	89.5	8.9	6.4 5.2	5.6	0.064
61	WM 50	5	0	0	37	1.2-1.5	2.3 4.2 4.6	1.2	77.5 75.5 71.3	70.7	6.0	8.8 11.6 9.9	9.5	0.14
6	WM 38	6	0	0	39-44	<u>1.2-2.3</u>	4.2 5.2 6.7	1.8	97.3 92.8 102	86.2	7.8	17.5 19.6 22.2	17.5	0.21
74	WM 43	8	0	0	31	1.1-1.3	2.0 -	1.3	87.4 -	60.5	5.3	7.3 -	6.5	0.11
9	WM 42	9	0	+	35-50	0.9-1.4	7.2 14.0 13.3	0.9	116 112 86.8	106	7.6	33.3 35.9 33.4	30.2	0.28
41	CM 45	9	0	0	-	0.8-1.2	3.9 9.7 4.6	1.0	148 156 96.4	113	6.8	12.9 15.9 10.1	11.1	0.098
15	WM 63	10	0	0	34-36	0.9-1.2	6.8 6.7 7.5	1.3	122 67.2 91.8	89.0	6.5	11.1 6.2 11.0	8.9	0.10
22	WM 59	10	0	0	26-34	<u>1.4-2.0</u>	6.1 6.8 7.0	1.5	76.6 73.8 73.8	63.4	7.5	4.7 5.0 5.1	4.1	0.065
42	CM 44	10	0	+ to ++	67	<u>1.5-2.0</u>	5.0 5.9 4.7	1.6	73.6 72.7 67.5	66.3	6.5	7.3 6.3 6.4	6.2	0.094
2	WP 38	12	0	+	51-88	<u>2.9-4.1</u>	1.3 1.4 1.5	2.9	37.5 32.0 31.4	36.3	7.6	4.2 4.0 4.5	4.6	0.13
11	WM 57	12	0	0	42-49	1.3-1.7	5.6 8.2 8.4	1.6	51.1 47.0 57.6	49.0	6.3	14.1 16.0 17.5	15.0	0.31
18	WM 43	12	0	±	36-63	<u>1.1-1.8</u>	3.5 5.3	1.1	109 98.4	92.6	8.1	13.3 11.3	10.9	0.12
19	WM 47	12	0	±	30-57	1.2-1.4	1.6 1.8 1.4	1.3	73.2 47.5 65.6	50.5	7.5	10.2 5.9 8.4	6.6	0.13
29	CM 49	19	0	0	28-36	<u>1.1-1.4</u>	8.4 10.9 12.4	1.4	87.3 87.9 89.0	81.1	7.1	5.3 7.1 8.1	6.3	0.078

\* Underlined values are abnormal (criteria stated in the text).

Table 12 (continued)

CLINICAL					CHEMICAL		RENAL CLEARANCES							
Case no	Patient Race-Sex Age	Years of clinical gout	Tophi	Protein-uria	Serum concentration		Urine flow (ml/min)	Creatinine			Urate			Urate/creatinine clearance ratio
					Urea	Creatinine (mg/100ml)		Serum conc. (mg/100ml)	Clear-ance (ml/min)	Mean, per 173m <sup>2</sup>	Serum conc. (mg/100ml)	Clear-ance (ml/min)	Mean, per 173m <sup>2</sup>	
68	CM 39	3	++	0	39	0.9	7.7 5.1 3.8	0.9	103 66.0 68.1	82.0			-	-
35	CM 36	4	+	0	34-37	1.2-1.4	8.3 14.1 8.4	1.4	74.0 97.0 72.0	76.0	7.5	7.0 8.7 6.4	6.9	0.091
16	WP 63	5	+	0	32-37	1.0-1.1	7.8 13.1	1.1	91.9 182	100	6.5	12.8 18.8	14.8	0.15
48	CM 46	7	++	±	22	1.2-1.6	3.0 4.3 3.0	1.2	83.0 88.0 69.0	76.6	8.8	3.9 3.8 3.2	3.4	0.046
12	CM 41	8	+	+	20-41	1.2-1.6	5.1 5.3	1.5	72.5 82.4	69.1	7.2	13.4 13.6	12.0	0.17
27	CM 47	8	+	0	27-50	1.1-1.4	10.3 11.3 10.5	1.1	124 125 132	109	6.9	9.2 15.4 11.3	9.7	0.089
59	CM 48	8	+	0	17-32	1.0-1.3	12.2 13.9 12.2	1.0	146 142 122	189	6.5	9.7 6.9 7.9	7.7	0.060
60	WM 43	8	+	±	42-65	1.5-2.0	5.5 5.5	1.5	75.1 77.3	67.4	7.8	5.1 5.7	4.8	0.071
92	WM 42	8	+	±	23-27	1.2-1.4	1.9 3.5	1.2	88.8 85.7	71.6	7.7	5.5 11.9	7.1	0.10
30	CM 48	9	+	0	30-47	1.2	3.3 6.8	1.2	98.4 101	97.5	5.7	7.0 8.4	7.5	0.077
8	WM 46	10	++	0 to +	25-61	1.6-2.2	1.7 2.0	2.2	42.3 24.8	34.2	8.0	3.2 2.3	2.8	0.083
25	CM 72	?10	++	0	50	1.0-1.4	3.4 1.8	1.4	55.6 47.5	51.6	8.1	6.1 4.1	5.1	0.099
44	NM 52	10	++	0	19-27	0.7-1.2	2.1 1.9 3.7	0.9	132 84.4 80.4	94.0	7.2	9.1 5.3 4.9	6.1	0.088
75	WM 66	10	+	± to ***	28-101	1.1-2.7	1.7 2.1	1.4	51.0 46.6	47.0	7.8	8.2 6.2	6.9	0.15
20	CM 44	12	+	++	40	1.0-1.8	5.1 6.0 4.9	1.2	49.8 53.0 50.8	62.9	8.8	5.5 6.5 5.6	7.3	0.11
21	CM 64	12	+	±	27-33	1.4-1.7	5.1 9.1 8.0	1.4	89.0 89.1 82.7	77.1	8.0	6.2 7.6 5.9	5.9	0.076
36	CM 39	12	+	0 to ++	25-38	1.3	10.9 11.0 9.4	1.3	89.3 75.6 83.6	80.4	6.2	9.3 6.5 4.5	6.5	0.082
4	WM 62	14	++	0	43-51	1.4-2.4	6.6 6.2 2.0	1.4 1.6	155 100 81.2	103	7.6	17.8 6.9 5.0	9.1	0.087
5	WM 48	16	++	0	37-48	1.0-1.6	1.4 1.6 5.5	1.3	77.0 65.2 81.6	69.8	4.6	8.4 5.8 10.1	7.6	0.11
10	CM 43	16	++	+	21-49	1.3-1.7	8.3 7.8	1.4	71.6 66.1	62.4	8.1	12.8 12.2	11.3	0.18
33	WM 56	17	+	0	39-41	1.4	5.4 7.6	1.4	90.3 89.3	79.2	7.4	8.6 8.9	7.8	0.098
40	CM 55	17	+	±	-	1.4-1.9	4.1	1.4	103 -	96.0	7.0	9.0 -	8.4	0.088
37	WM 54	18	+	0	37	1.2-1.4	9.7 11.8 12.5	1.2	127 119 121	103	5.8	11.8 11.2 10.3	9.5	0.091
7	WM 72	27	++	0	43-47	2.2-2.7	5.0 7.3	2.7	37.1 20.9	25.7	7.6	11.2 14.9	11.6	0.452
3	WM 68	50	++	0	43-52	1.5-1.8	3.2 4.9 7.3	1.8	111 65.5 59.7	74.2			-	-

Mean creatinine clearance in 53 gout patients... 81.6 ml./min. (± 24.6 S.D.)  
 " urate " " 51 " " ..... 9.2 " " (± 5.0 S.D.)  
 " u/c clearance ratio " " " " ..... 0.112 (± 0.074 S.D.)

### 3. Clinical and laboratory findings.

Of 130 gout patients studied, 52 had proteinuria, azotemia or impairment of creatinine clearance, either singly or in combination. Formed elements in the urine were commonly associated (cells more often than casts) and hypertension of all degrees was a prominent accompaniment. Concentrating power was lost in the worst cases, but was not investigated often enough (other than routine measurement of casual S. G.) to include in this analysis.

The following grouping of results, made after careful assessment of the particular features of each case, is informative. While simplification of some degree is implicit in the presentation, the complexity of problems involved may render this permissible and even advantageous.

#### Group 1. Dominant feature SEVERE URAEMIA: number of patients . . . 8

(a)	Azotemia . . . . .	8 (++)
(b)	Proteinuria . . . . .	3 (++) 4 (+) 1 (±)
(c)	Cells or casts . . . . .	3 (+) 5 'nil'
(d)	Impaired clearance (GFR) . . .	.8 (grossly)
(e)	Hypertension . . . . .	.6 (++) 1 (+) 1 (±)

Average age (years) when first seen . . . . . 42.4

" duration " of clinical gout . . . . . 8.9 (1-19)

Visible tophi . . . . . in 3 of the 8.

REMARKS. Clinically this group resembles the advanced stages of 'chronic Bright's disease', of which the commonest origins are diffuse glomerulo-nephritis or 'healed' pyelonephritis. Not one gave a history compatible with acute Type I, or Type II, nephritis. Several had had illnesses suggestive of urinary tract infection; but in none was there any active infection. No calculus was detected among the group. Although 3 of the eight have died, and perhaps a fourth, the striking feature of the living is their exceptional well-being over many months with blood ureas between 100 and 250 mg./100 ml. This certainly opposes a malignant hypertensive basis for the renal failure, and is in keeping with modern experience of chronic (atrophic) pyelonephritis. This group has the youngest average age and a variable severity of gout. In 3 of them, renal disease is known to have preceded the onset of clinical gout.

<u>Group 2.</u>	<u>Dominant feature PROTEINURIA:</u>	<u>number of patients</u> . . 13
(a)	Proteinuria . . . . .	5 (++) 8 (+)
(b)	Cells or casts . . . . .	2 (++) 6 (+) 4 'nil' 1 not done
(c)	Impaired clearance (GFR). . .	8 2 normal 3 not done
(d)	Azotaemia . . . . .	5 (+) 8 normal
(e)	Hypertension . . . . .	8 (+) 3 (±) 2 normal
Average <u>age</u> (years) when first seen . . . . .		44.9
" <u>duration</u> " of clinical gout . . . . .		8.9 (1-21)
Visible <u>tophi</u> . . . . .		in 5 of the 13

REMARKS. While considerable variability exists within this group, all appear to conform to some phase or type of 'nephritis', with proteinuria always out of proportion to any cells present, significant casts in several, and a high incidence of impaired nitrogen excretion and of hypertension. None had symptoms directly attributable to their renal condition, and although 4 had been discovered previously to have proteinuria or haematuria, none gave a history compatible with acute nephritis. Calculus was present in only one of the group; he has constant proteinuria, with no spun deposit, even after its removal from his bladder by litholopaxy. Evidence of definite urinary infection was absent in all. These 13 patients also had an average age well below that of the total series, and also a somewhat shorter than average duration of clinical gout. The severity of the latter varied widely, but only one was badly disabled. In 3 of the group renal disease is known to have preceded symptoms of gout.

Group 3.      Dominant feature CELLS:      number of patients . . . . 7

(a)	Cells (wbc, rbc, tract) . . . . .	7 (+)
(b)	Proteinuria . . . . .	1 (+) 5 (±) 1 nil
(c)	Impaired clearance (GFR) . . . . .	3 1 normal 3 not done
(d)	Azotaemia . . . . .	3 (+) 4 normal
(e)	Hypertension . . . . .	2 (+) 4 (±) 1 normal

Average age (years) when first seen . . . . . 56. 0

" duration " of clinical gout . . . . . 14.7 (4-37)

Visible tophi . . . . . in 4 of the 7.

REMARKS. It is not surprising from these findings that 3 of this group had urinary calculi and the rest proven or probably urinary tract infection. In 4 of the 7 there was in fact no evidence of impaired functional capacity of the kidneys, as was the case also with the calculus-patient in Group 2, and with one other man who presented severe hypertension and possessed a renal stone. These latter 6 patients, included in the 52 being analysed because of some proteinuria, may therefore be deducted in counting the over-all incidence of renal functional impairment.

Impairment of renal function, in terms of clearance reduction and azotsemia as outlined above, was therefore present in 46 of the 130 gout patients in whom it was sought, an incidence of 35%.

Group 4.      Dominant feature FUNCTIONAL IMPAIRMENT:      number of patients . . . 23

(a)	Impaired clearance (GFR) and/or Azotemia (+) . . . . .	23
(b)	Proteinuria . . . . .	6 (±) 17 nil
(c)	Cells or casts . . . . .	23 'nil'
(d)	Hypertension . . . . .	4 (+) 10 (±) 9 normal

Average age (years) when first seen . . . . . 52.6

" duration " of clinical gout . . . . . 10.0 (1-50)

Visible tophi . . . . . in 12 of the 23.

REMARKS. The need for a clinical 'name' to this group is paralleled by the similar need in Groups 1 and 2, but certain differences are plainly seen. Like Group 3 before it, these 23 patients belong to a distinctly older average group. They include some of the most tophaceous cases of gout, and the incidence of degenerative changes such as coronary heart disease is the highest of the whole series, Groups 3 and 4 providing 13 of the 15 instances of coronary disease among all 140 patients. The incidence of impressive hypertension, on the other hand, is low. Two members of Group 4 had urinary tract calculi, bringing the total for the 52 patients to 7; only one of these belonged to Groups 1 or 2. (In the whole series of 140, 11 had a history or signs of definite calculus; these need not always be urate in composition - Fig. 35).

It is tempting to infer that these 23 patients in Group 4, whose renal abnormality is one of moderately reduced function associated with little or no hypertension, a liability to degenerative coronary disease, and well established gout, are examples of a low-grade vascular renal process - nephrosclerosis - perhaps contributed to by the presence of urate itself in the interstitial tissue of the kidney. They seem closely related to the 7 patients of Group 3, in whom the urinary abnormalities could also be attributed to 'renal irritation', secondary infection or calculus formation, as a fairly direct effect of urate itself.

They bear a far more obscure relationship to the generally younger gout patients in Groups 1 and 2, in whom features of parenchymatous renal disease, whatever its origins, are strongly in evidence.

#### 4. Correlation of renal impairment with other clinical features

In Table 12 are shown, among other relevant renal data, the values for endogenous creatinine clearance in a large number of gout patients. All figures which are abnormal by the criteria previously stated are underlined, and such patients have just formed part of the discussion on the laboratory and clinical spectrum of renal disease in gout.

##### (a) Renal impairment and age of patients

The average age for the whole gout series was 51.1 years. Of the 46 patients who were shown to have impaired renal function in terms of reduced GFR and/or azotaemia, it was observed that 30 are below the average age, and only 16 are 51 years or older. (The total number of patients is equally distributed above and below the mean age).

This is a corollary of the previous observations, that renal disease among these patients was apparently more than a result of age, degenerative changes or the long-standing accumulation of urate.

##### (b) Renal impairment and duration of gout

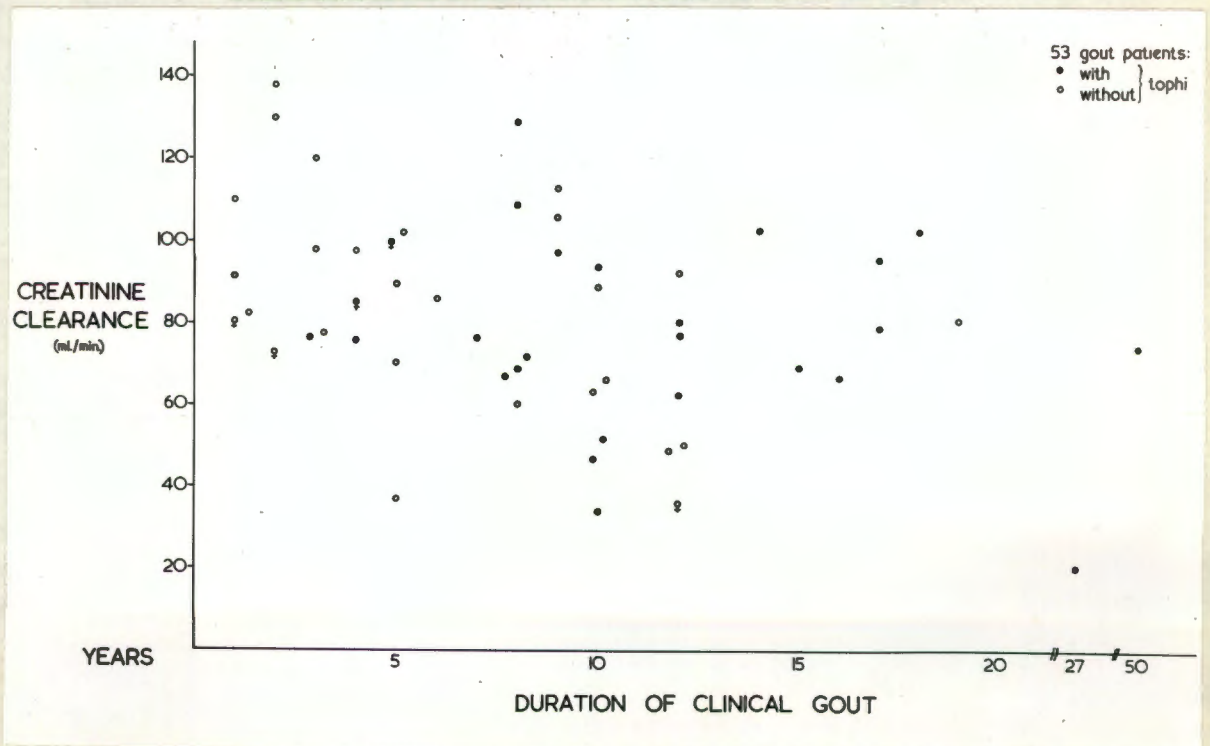


Fig. 33a. Graph of endogenous creatinine clearance vs. duration of gout; no significant slope of correlation.

It is apparent from Fig.33a that impairment of glomerular filtration rate, in this series of gout patients, is not a direct function of the duration of clinical symptoms. This is to be expected in view of the relative earliness with which some patients (Groups 1 and 2 in the foregoing discussion) fall victim to an apparently diffuse renal lesion which, in some, actually precedes the clinical onset of gout.

(c) Renal impairment and visible tophi

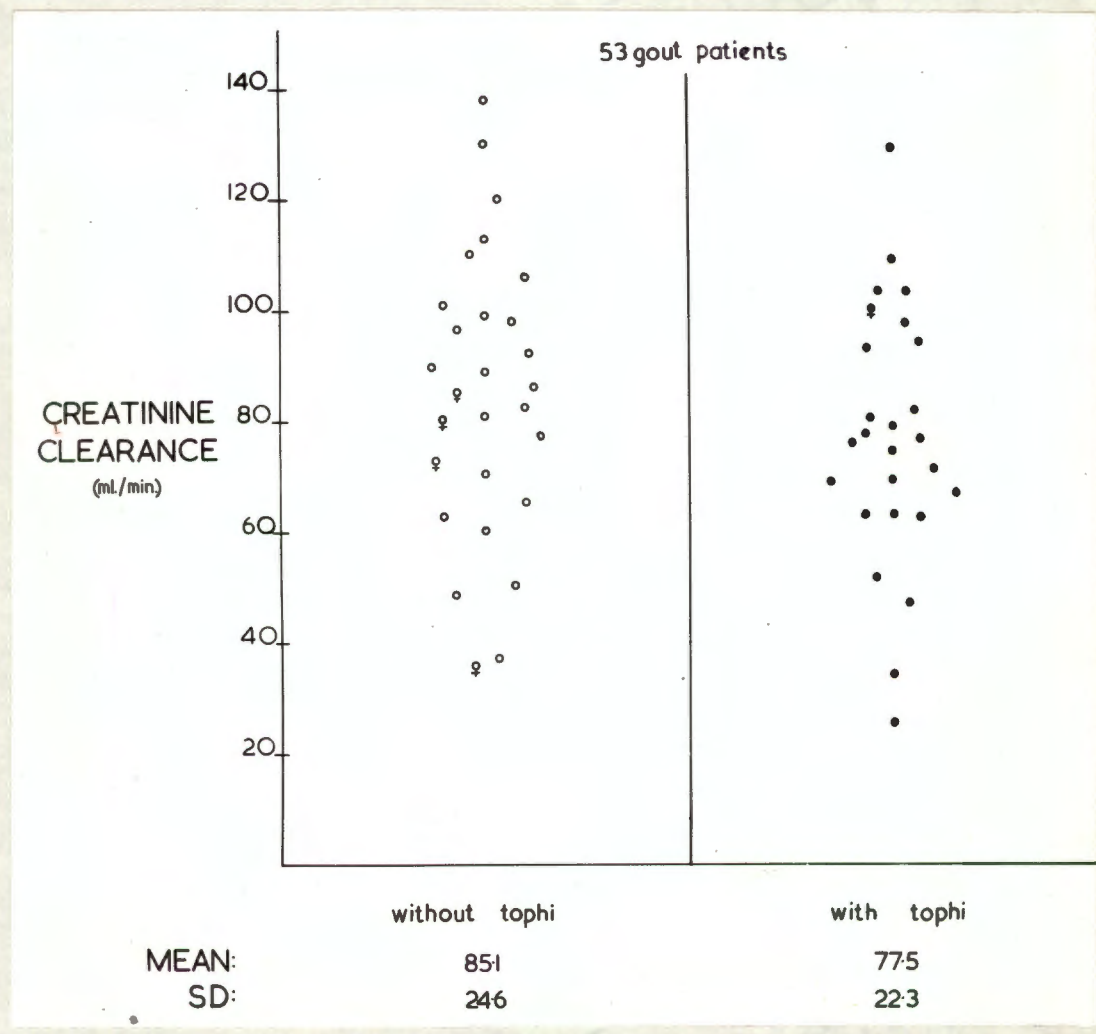


Fig. 33b. Creatinine clearance in 53 gout patients with and without tophi: there is little difference between the two groups.

It seems fair to conclude that external tophi do not reflect the functional state of the kidney in gout as correctly as they usually do the condition of the joints. This suggests, but does not prove, that internal urate deposition in the kidney substance is not the main basis for impairment of renal function in gout.

## 5. Concepts in pathogenesis

### (a) Pathological lesions

It is doubtful if a single pathological basis exists for all cases of what earlier writers called 'gouty kidney'. At autopsy the following lesions are most commonly recognised, either singly or in combinations <sup>33, 115</sup>:

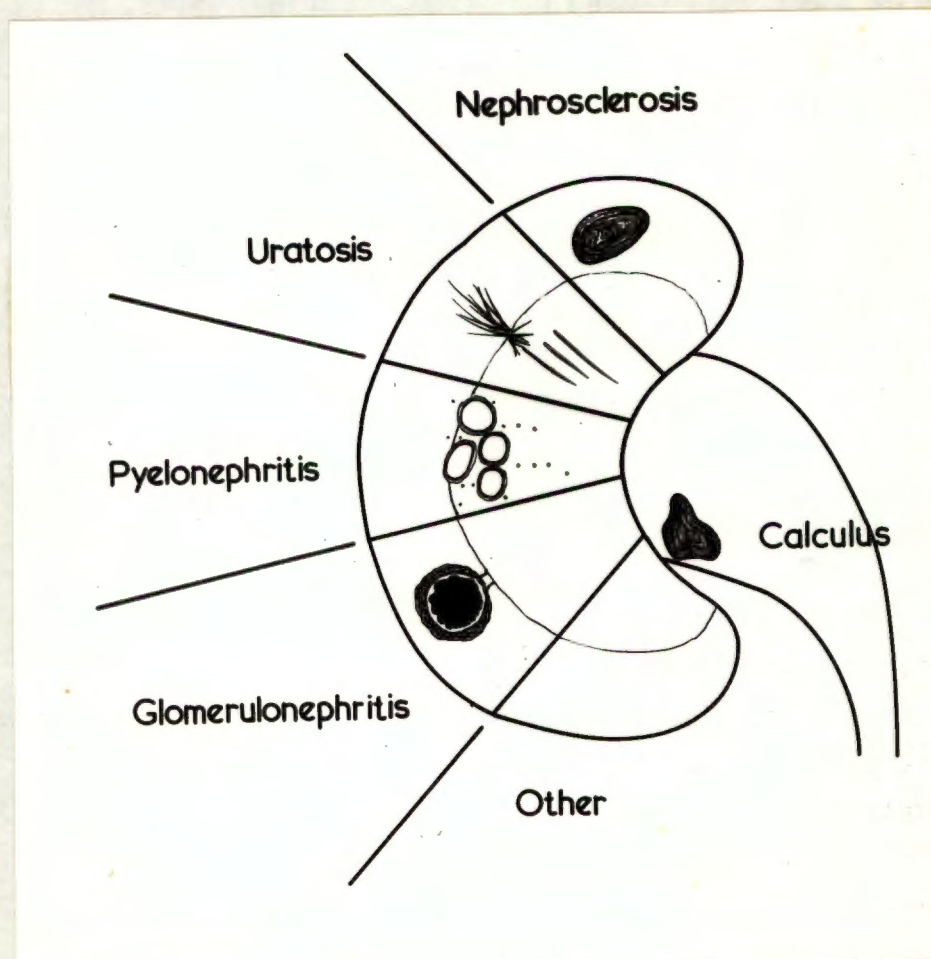


Fig.34. The spectrum of renal lesions in gout.

(1) Nephrosclerosis, producing lesions of so-called vascular nephritis. Most authorities agree that this is the most constant lesion in kidneys of gout patients who are examined post mortem. Features of renal disease in life, therefore, are thought by many <sup>5, 101</sup> to be a result of unusually early nephrosclerosis, a lesion to which gout patients are prone as they seem to be to general vascular sclerosis and hypertension.

(ii) Urate deposition in both cortex and medulla has frequently been found. Analysis of several reports shows this to be true mainly for older patients dying after gout of long duration. Urate evokes its customary chronic cellular reaction in the interstitial tissue - renal tophus formation. This occurs chiefly in the medulla, which is reached by the crystals uncertainly, either by local precipitation or by bursting from the walls of obstructed tubules. Resultant fibrosis contributes to a histological picture of 'chronic interstitial nephritis', in which tubules not already dilated by obstructive crystals may be strangled and undergo atrophy. It is speculative to what extent such lesions of 'uratosi' are responsible per se for severe renal functional impairment in gout patients.

(iii) Pyelonephritis, acute and chronic, is readily conceived as complicating the multiple tubular obstruction wrought by urate deposition, and has recently been emphasised as a common lesion of long-standing gout<sup>33</sup>.

(iv) Urate calculi complicate gout in about 10% of cases<sup>59</sup>, possibly seeding round epithelial debris and urate crystals. Infection may succeed their formation, perhaps explaining in part why the stones are sometimes mixed.

(v) Chronic glomerulonephritis has been encountered, and interpreted as a coincidental association<sup>115</sup>. Hyalinized glomeruli, however, may form part of any of the pictures of 'vascular nephritis', 'interstitial nephritis' or ascending pyelonephritis.

(vi) Coincidental acute or chronic kidney lesions have been found in gout patients, including amyloid and 'lower nephron' nephroses<sup>33, 115</sup>. The writer knows of hydro-nephrosis due to aberrant renal vessels, and unilateral agenesis with disease in the single kidney.)

(b) Attempted clinical correlation

Solution of the clinical problem posed by a patient with gout and evidence of renal disease is no mere academic matter. There are at least two practical reasons for striving to understand how such a person's clinical and laboratory signs of renal mischief are related to the underlying process in the kidney:

one concerns the need for prognosis and the other the advisability or otherwise of uricosuric therapy.

An increased knowledge of the pathology has not provided adequate understanding of the patients' course in life, and clinical publications have varied widely in the details and interpretation of the features encountered 38, 96, 101. It is not within the scope of this thesis, nor the ability of the writer, to attempt to solve these complex relationships with the data available; but it is felt that the observations offered on so large a clinical group, with good prospects of long-term study, may be of future value.

i. The impression gained in this study is that there are not only diverse anatomical renal lesions involved, but that they bear different sequential relationships to the associated gout. It is suggested that certain clinical patterns of renal impairment are fairly easily interpreted, such as the changes in older gout subjects with long-standing uratosis of kidney - as of joint - and accompanying nephrosclerosis, the latter predisposed to in an obscure way by the 'gouty diathesis' or by the hyperuricaemia itself, and reflected to a certain extent by accompanying coronary artery disease. In addition to functional impairment on a vascular and mechanical basis, such gout patients run the risk of uratic and epithelial debris in tubules or tract being complicated by calculus and/or secondary pyelonephritis. It is believed that the patients of this series who have schematically been placed in 'Groups 3 and 4' are clinically recognizable counterparts of such renal changes.

ii. At the other extreme are frightening instances of renal failure, often in young patients whose gout is not pronounced, and often preceding joint symptoms in onset. While any chronic gout subject with moderate, long-standing renal damage may eventually die in uraemia, most of the patients in 'Group 1' show such disparity between either the durations, or tempi, of their gouty and renal conditions that it is difficult not to infer that the kidney disease came first. This could imply one of two possibilities: (a) the existence of 'primary renal gout', an entity conceived by earlier writers, in which urate deposition is thought to affect the kidney before the rest of the body, with rapid and dire results; or (b) chronic glomerulo- or pyelonephritis, occurring as it may in any young person, evokes clinical gout in someone genetically predisposed, who otherwise may have manifested it later, if at all. A counter-

part to this idea exists in the suggested mechanism of gout 'complicating' certain marrow diseases.

iii. One is finally left to speculate whether, apart from the recognised spectrum of renal lesions in gout patients, there exists a separate pathological entity justifying the true use of the term 'gouty kidney'. It seems that any answer to this point should be provided by the patients in 'Group 2'. One is hard put to account for the clinical and laboratory features (excessive proteinuria, cylindruria and azotemia) of the unusual type of nephritis which characterizes these patients:

(a) Is the underlying process one of uratosis or nephrosclerosis, essentially similar to that encountered in cases of chronic gout at autopsy, but masquerading - perhaps temporarily - as 'chronic nephritis'?

(b) Is the underlying process in fact a true glomerulonephritis, in which case the frequency of the coincidence is strange?

(c) Is there, perhaps, a specific anatomical change in this phase of gout, analogous to the intercapillary glomerulosclerosis of diabetes, which, by the time the gout patient reaches autopsy, is altered both clinically and pathologically by the better known vascular, uratic and inflammatory lesions usually found? Certainly the diabetic renal lesion remains detectable after similar anatomical complications, and the likelihood of a hitherto unrecognized process in the kidney of gout seems small.

If, then, the pathological possibilities are already known to us, the realisation has to be faced that the development of at least one important clinical type of renal disease in the natural history of gout is not yet understood.

THE DIVERSITY OF RENAL LESIONS  
ASSOCIATED WITH GOUT

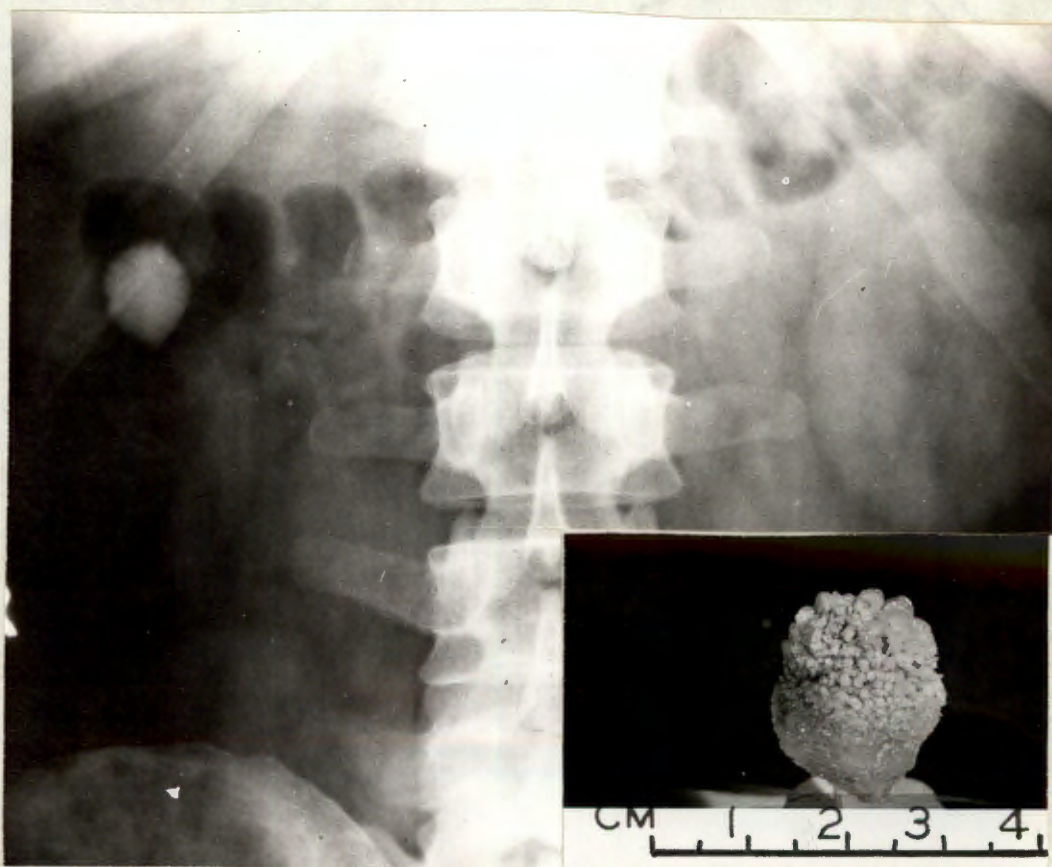
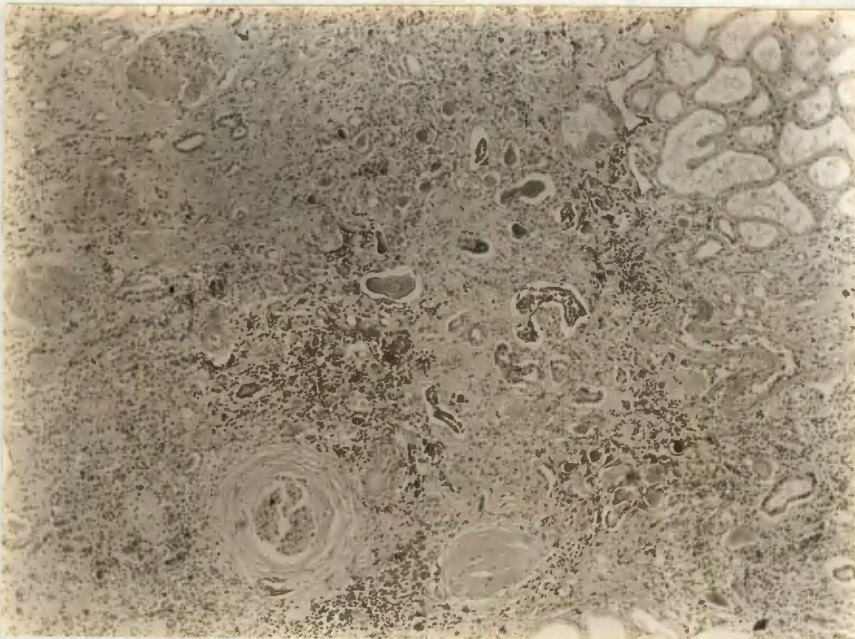


Fig. 35. Oxalate stone in renal pelvis of severely hypertensive patient, aged 42, with gout of 3 years' duration and no impairment of renal function (case 23). No urate was chemically detectable in the stone, the nature of which was suggested radiologically by its jagged outline. (Pure urate calculi are not radio-opaque).

**Fig. 36.** Small, scarred, granular kidney studded with countless retention cysts, probably due to chronic (healed) pyelonephritis.

(Case 111: 60-year old man with advanced tophaceous gout starting 19 years previously. Death in hypertensive uraemia).

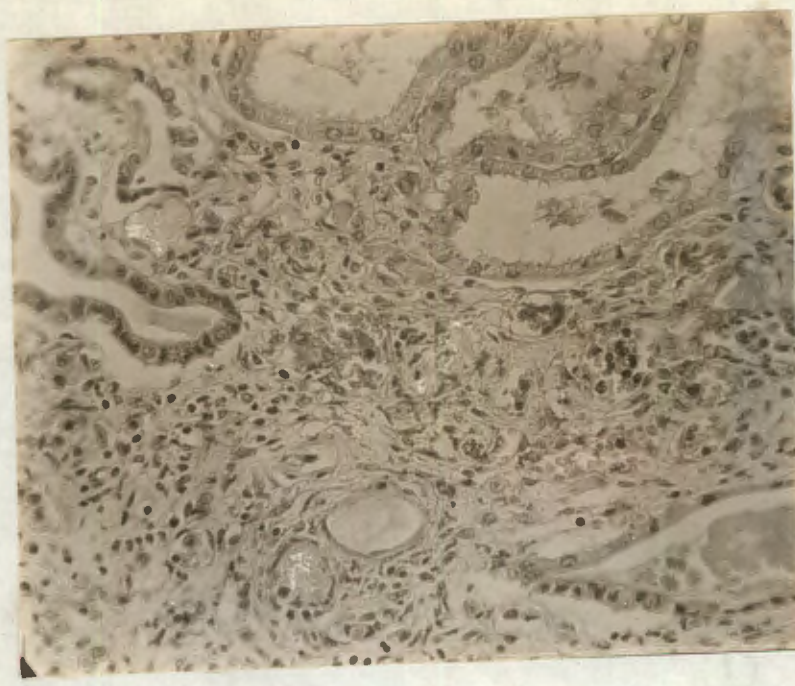


**Fig. 37.** Histological appearance of kidney (case 111) showing

- (i) glomerular hyalinization (top left and below);
- (ii) dilatation and atrophy of tubules (top right and centre);
- (iii) extensive scarring;
- (iv) zone of inflammatory reaction by lymphocytes and polymorphs (lower left and centre);
- (v) arteriolosclerosis.

Changes suggestive of chronic, healed pyelonephritis and hypertension. (x75).

Fig. 38. (Case 111),  
Photomicrograph  
(x 375) taken through crossed  
polarizers, showing doubly  
refractile material in  
degenerate tubules (top left  
and below), and in interstitial  
tissue (centre) with apparent  
mild round cell reaction.



Despite their  
situation, these foci may not  
be sodium urate which is  
soluble and disappears from  
microscopic sections unless  
specially prepared. Crystal  
structure is not apparent  
either.

Naked-eye evidence  
of uratosis in this kidney  
was slight (Fig. xiii in  
Chapter 1), and histological  
'tophi' cannot be found,  
perhaps because of diffuse  
scarring.

Fig. 39. (Case 111).  
Two small renal  
arteries showing hyper-  
tensive vascular lesions  
of medial hypertrophy and  
intimal reduplication.  
(x 95).

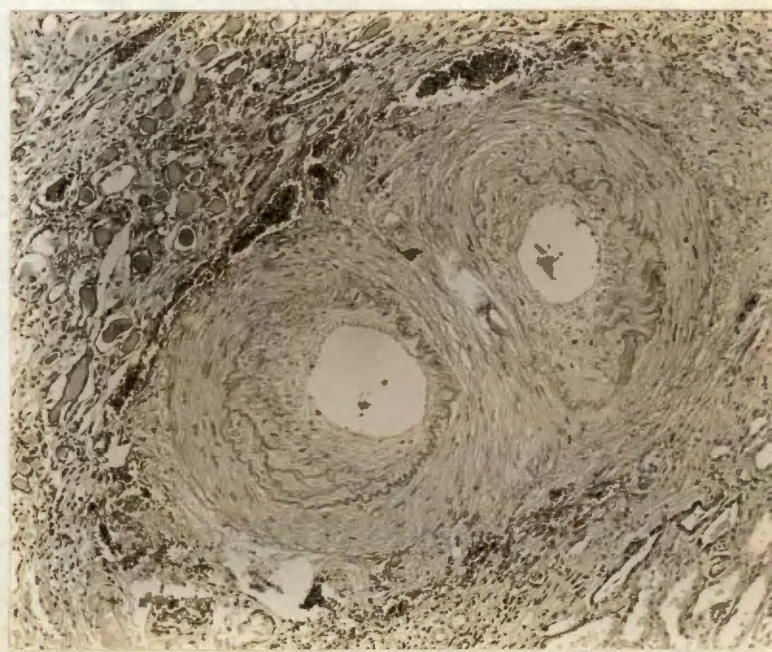


Fig. 40. Atrophic, scarred kidneys (combined weight 150 G.) from a 42-year old man with non-tophaceous gout of 5 years' duration (case 28). Note simple cyst and aberrant renal vessels at lower pole of the portion of right kidney, in picture.

The cut surface showed minimal uratic streaking of the medulla. Naked-eye appearances are those of chronic glomerulo-nephritis or healed pyelonephritis.

The patient died in hypertensive renal failure of multiple vascular accidents (simultaneous aortic dissection and cerebral haemorrhages). Urate was present in two joints opened.

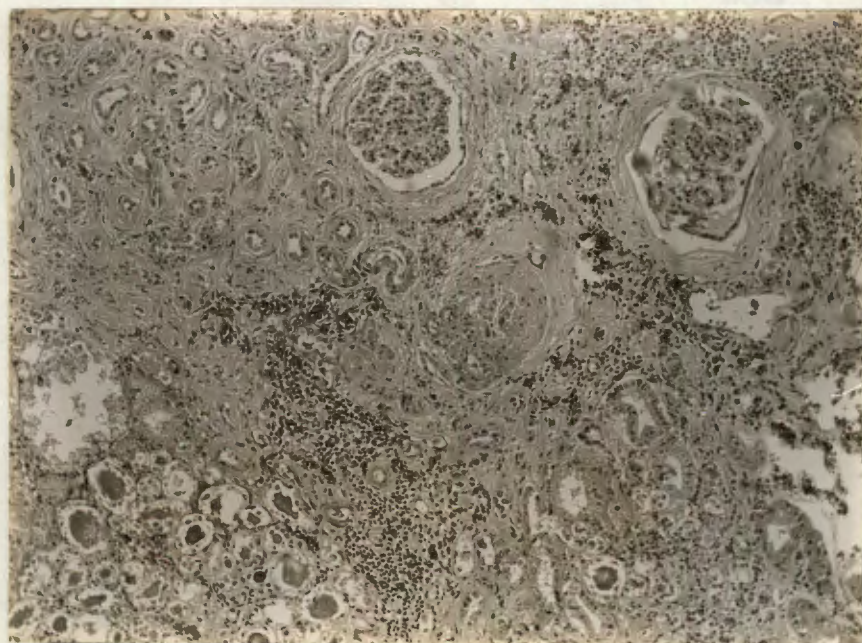
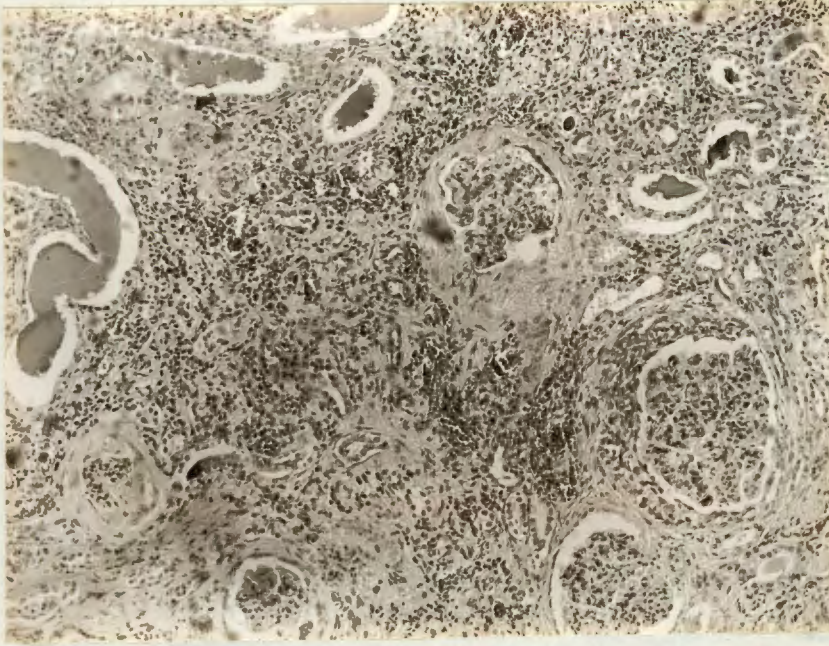


Fig. 41. Renal histology (case 28), showing  
 (i) glomerular scarring of varying degrees, from peri-glomerular fibrosis to complete hyalinisation;  
 (ii) tubular degeneration and dilatation;  
 (iii) interstitial scarring;  
 (iv) inflammatory cell infiltration.  
 Appearances compatible with chronic, healed pyelonephritis or chronic glomerulonephritis more likely the former.  
 (x 95).

Fig. 42. Histology of kidney from a 52-year old woman (not listed in the series who died soon after admission to hospital of hypertensive renal failure with pulmonary oedema and uraemia. A history was obtained of post-menopausal attacks of big toe arthritis, and gout confirmed at autopsy by finding sodium urate crystals in the joint.



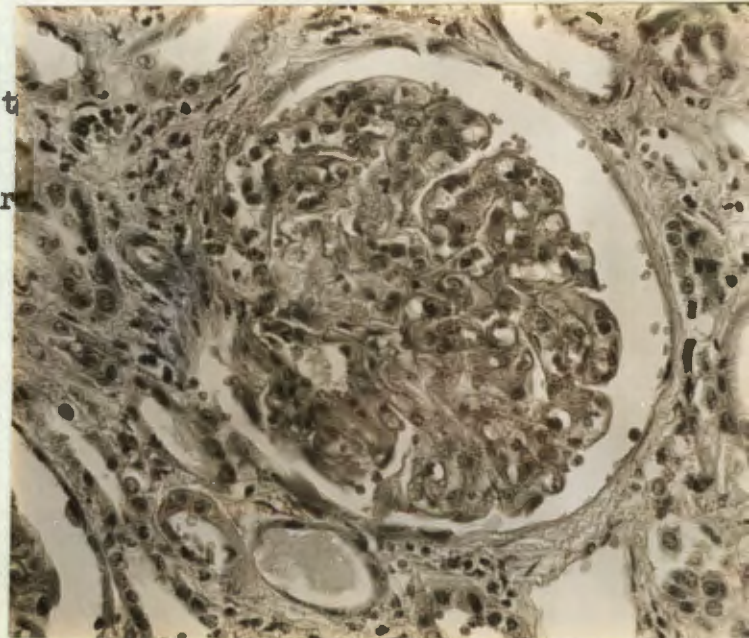
The renal lesion

includes:

- (i) Large, cellular glomeruli with crescent formation (right indicative of subacute glomerulo-nephritis);
- (ii) peri-glomerular fibrosis (centre) and other grades of glomerular scarring;
- (iii) dilated, cast-filled tubules;
- (iv) interstitial fibrosis and chronic inflammatory cell infiltration;
- (v) small foci of reaction doubtfully signifying possible urate deposition, which was not evident on the cut surface.

The histological appearances are those of subacute (Ellis Type I) nephritis, in a kidney previously damaged by probable chronic pyelonephritis. (x95).

Fig. 43. (Case 75). Intra-capillary glomerulitis in kidney of 67-year old patient with myelosclerosis and gout of 10 years' duration. The lesion consists of endothelial cellular proliferation and basement membrane thickening of the capillary tuft, and is usually associated with 'nephrotic' (Ellis Type II) glomerulo-nephritis. This was absent clinically, but the anaemia was accompanied in the last months of life by congestive heart failure, increasing proteinuria and progressive uraemia. (x375).



CHAPTER 7. STUDIES OF BENEMID IN GOUTA. INTRODUCTION

1. Aims in management of gout
2. Premises of uricosuric therapy
3. Known uricosuric drugs
  - (a) Cinchophen
  - (b) Salicylate
  - (c) ACTH and cortisone
  - (d) Phenylbutazone

B. BENEMID THERAPY IN 50 GOUT PATIENTS

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  - (c) Diet
  - (d) Dosage of benemid

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2. Urinary urate excretion
3. Urate clearances
4. Effect of benemid on renal function
5. Influence of renal disease and tophi on action of benemid
6. Salicylate in relation to benemid therapy.

D. CLINICAL RESULTS OF BENEMID THERAPY

1. Criteria of assessment
2. Acute attacks
3. Chronic active arthritis
4. Tophi and deformity
5. Radiographic signs
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7. Conclusions

E. BENEMID THERAPY COMBINED WITH SMALL DOSES OF CORTISONE

1. Premises of treatment
2. Results

CHAPTER 7.      STUDIES OF BENEMID IN GOUT

A.      INTRODUCTION

1.      Aims in the management of gout

There is no prospect at present of fundamentally curing the genetically determined disorder of gout. Consequently, control and correction of its clinical features entail several requirements:

- (a) Prevention of occurrence of acute gout episodes;
- (b) Relief of symptoms during the attacks;
- (c) Palliation, usually in later years, of articular disability due to persistent pain and stiffness;
- (d) Prevention or correction of chronic tophaceous deformity of joints;
- (e) Understanding of and appropriate treatment for the renal and vascular diseases associated with gout.

While effective treatment for acute gouty arthritis is available in the form of colchicine, and has recently been reinforced by the application of potent new remedies including ACTH <sup>61, 100, 125</sup> and phenylbutazone <sup>76, 80</sup>, only partial success has been achieved in abolishing the liability to attacks or in preventing and treating their chronic sequelae.

2.      Premises of uricosuric therapy

As observed in Chapter 1, there can be no doubt about the importance of preventing uric acid deposition in gout, nor about the theoretical approach to doing so. If levels of circulating urate could be kept normal there should be no likelihood of its precipitation in the tissues, and two ways suggest themselves for correcting the hyperuricaemia.

- (a) Diminishing production of urate can be exploited to a limited extent only. Strict purine-free diets have resulted in modest reductions in serum urate concentration of about 1.2 mg./100 ml. in two reported series <sup>59, 90</sup>. Prolonged adherence to a lacto-vegetarian diet is involved, without adequate promise of reversing the flow of urate from blood to

tissue. Moreover, foods other than nucleoprotein can help to maintain high urate levels, for example, excessive fat <sup>34</sup>, and, as shown recently, carbon and nitrogen fractions in many items of diet <sup>9</sup>.

(b) Enhancing urate excretion is the alternative approach to its depletion in the body, and a variety of drugs achieve this. Practical difficulties are associated with the use of all of them, but the premises on which they are employed are basically sound. A small, persistent reduction in the amount of urate which the tubules reabsorb into the circulation can lead to substantial urinary loss and impressive lowering of serum urate levels. It is reasonable to expect such a situation, if maintained, to lead to the following benefits:

(i) Cessation of further urate deposition, both visible and occult.

(ii) In view of past and recent work indicating that part of the urate present in the solid phase is included in the miscible pool <sup>56, 34</sup>, it is conceivable that creation of a negative balance through urinary depletion may draw part of the precipitated material back into solution. Small tophi may consequently shrink and disappear, and large ones become reduced in size.

(iii) Patients at the stage of chronic gouty arthritis may experience improved comfort and mobility of joints.

Certain features of gout, however, are less easily predictable in their anticipated response to uricosuric therapy:

(iv) Frequency and severity of acute attacks. Since urate itself cannot be blamed for the features of acute gout (Chapter 1), there is little reason for expecting purely uricosuric drugs to abolish the incidence of attacks. Agents in established use as prophylactics are either antiphlogistic as well, or, in the case of colchicine, solely so. Nevertheless, it is conceivable that the correction

of hyperuricaemia, which is so integral a part of the gouty state, might achieve some beneficial result in this respect also, even if the pathogenesis of the acute attacks is unknown and their relation to uric acid obscure. Such a view is purely speculative, however, and one would await evidence in this sphere with special interest.

(v) Renal lesions. One fear in considering uricosuric measures is the possibility of complications resulting from urate crystalluria or concretions. With adequate volumes of urine, perhaps rendered alkaline, and gradual reduction in the quantity of urate mobilized from the body, this danger should be minimal.

Whether or not any renal lesions already present will undergo resolution as a result of urate drainage, depends on their pathogenesis. Renal 'tophi' might dissolve if urate deposits elsewhere are able to, and, as some have theorised<sup>59</sup>, diminution of urate reabsorption by the proximal tubules may reduce the change of tubular damage and interstitial deposition.

It is unlikely that established renal lesions such as infection or nephrosclerosis could be modified by uricosuric therapy, unless they too are attributable, however indirectly, to hyperuricaemia and could be averted by its early correction.

### 3. Known uricosuric drugs.

Few of the compounds discussed earlier have been used with any success in the long-term management of gout. The better known ones, and their limitations in achieving the theoretical ideals outlined above, are considered briefly.

(a) Cinchophen and its derivatives. Hueper's review<sup>68</sup> has provided a fair appraisal of cinchophen in its versatile role as uricosuric, antiphlogistic and analgesic agent. Introduced in the early part of this century, several excellent accounts have testified to its value in relieving acute and chronic joint distress and minimizing the incidence of acute attacks of gout<sup>4, 56, 68</sup>. On account of its potential hepato-toxicity - a hazard apparently greater among patients ill with joint diseases

other than gout - its administration was of necessity intermittent and marred by fear and caution; moreover, interruption of dosage detracted from its full uricosuric effectiveness in eliminating urate. Until recently, opinion was still divided about the justifiability of using it even in refractory cases of gout. Those eschewing cinchophen completely believe its great effectiveness to be outweighed by its danger, however small, of which newer remedies are devoid. Neocinchophen, a safer derivative, is reportedly less active in eliminating urate

(b) Salicylate. It is universally recognized that salicylate in high dosage is a potent uricosuric agent in addition to its analgesic and antiphlogistic properties<sup>58, 77, 89</sup>. Lacking the inherent risks of cinchophen, it has been a popular gout remedy in acute attacks as well as in the intercritical and chronic phases<sup>71</sup>. An oddity of its action is the replacement of uricosuric effect by urate retention at low dosage levels<sup>59, 77</sup>.

The large amount of salicylate required for sustained uricosuric action is considered by many to be a serious practical disadvantage<sup>5, 59</sup>. The unpleasant symptoms of salicylism, including gastro-intestinal disturbance, tinnitus and deafness, mental confusion and hyperpnoea, which the requisite dosage of about 5 G. daily may produce, has also led to its use in interrupted schedules<sup>71</sup>. Not only does this curtail the full effect of the drug, but even in patients managing to take salicylate for long periods Bauer and Klemperer found that serum urate levels returned slowly to normal despite adequate dosage<sup>77</sup>.

A carefully conducted study of long-term salicylate therapy in gout has recently been described by Marson<sup>89</sup>. For periods of up to 34 months, he maintained adequate reduction of serum urate levels in 27 of 29 gout patients who received between 4 and 9 G. of sodium salicylate daily. Parallel with this, the patients experienced considerable alleviation of the symptoms of chronic gout, and destructive changes due to urate deposition were arrested and partially repaired. Twenty of the patients lost all pain and stiffness of joints, and several cripples among them were restored to normal activity. Marson was satisfied that salicylate can be tolerated in high dosage for prolonged periods, and that refractoriness to its uricosuric action did not supervene.

While the gratifying success of this programme is a tribute to uricosuric measures, it is plain that the ideal relationship was not struck between therapeutic action and unpleasant side-effects. 'Toxic symptoms sufficient to prevent continuation of treatment occurred on two occasions only'. 'Tolerance to the drug usually develops within a few weeks.' 'Eleven patients remained entirely free from toxic symptoms after a few weeks of therapy'. 'Of a total of 200 estimations performed in 16 patients, a fall in prothrombin concentration to below 50% of normal was seen on 12 occasions . . . and three results . . . were below 25% of normal.' 'With reasonable control there is little risk of hæmorrhagic complications'.

It is fair to observe that there is room for improvement even on the satisfactory results reported above, both as regards potency of drug and incidence of side reactions.

(c) ACTH and cortisone. The relatively weak uricosuric properties with which these newer agents have been credited<sup>46,121,12</sup> their high cost and the care required in their clinical use, probably explain their failure hitherto to be used continuously in gout. As treatment for acute gouty arthritis, however, ACTH is a particularly valuable innovation<sup>61, 64, 125</sup>, given concurrently with colchicine to maintain its effect.

(d) Phenylbutazone. It has become apparent that in phenylbutazone there exists a potent drug for treating acute and chronic gouty arthritis<sup>80</sup>, displaying uricosuric as well as analgesic actions<sup>106a</sup>. Kuzell and his colleagues<sup>79, 80</sup>, assessed its use among 200 patients and concluded that its main efficacy was in the acute episodes. Although maintenance therapy with 100 mg. to 600 mg. daily in chronic cases greatly reduced the frequency and severity of the acute exacerbations, the incidence of toxic complications was substantial (26% of patients) and serum urate concentrations were not uniformly lowered. The continuous administration of phenylbutazone would therefore be inadvisable in the long-term management of gout.

## B. BENEMID THERAPY IN GOUT

Benemid was first used in 1950 as an adjunct to therapy with penicillin and p-aminosalicylic acid<sup>22</sup>. Gutman, noting Wolfson's discovery that the related compound, carinamide, was uricosuric when given in high dosage<sup>128</sup>, demonstrated that benemid was a more potent and apparently harmless urate diuretic, and began to observe its effects in gout<sup>58</sup>. In January, 1952, when gout studies were started in Cape Town, only two preliminary reports had appeared of the initial clinical use of benemid<sup>58, 120</sup>, and it was decided to investigate its therapeutic possibilities in our own growing series of patients.

### 1. Choice of patients

At the time of writing, 50 patients from among the 140 discussed in this thesis have received continuous benemid treatment for periods of between 6 and 30 months. The majority (37) began this programme during 1952. In that year the only criterion of selection was the willingness and ability of the patient to co-operate in the investigation and follow-up of his condition. Mainly because some of the worst cases of gout were referred to us in the first few months of the study, the average duration and severity of gout within this group of 50 patients are slightly greater than for the whole series. In addition, a certain amount of selection was introduced towards the end of the first year, in that patients seen after their first or second attack, who were not apparently pursuing an adverse course, as well as others with severe renal disease, were not as readily given benemid in the first instance.

There are 16 patients, apart from the 50 reported here, who either started to take benemid under supervision and defaulted, or who have not yet taken it long enough (arbitrarily six months) to be included in this discussion. Thus 66, or approximately 1 in 2 patients diagnosed as having gout, were offered this new form of treatment, the remainder comprising very early cases, uraemic patients, and patients who were unlikely to co-operate for technical or temperamental reasons.

## 2. Clinical data

The 50 patients receiving benemid (case numbers 1 to 50 in the clinical tables) <sup>showed</sup> the following salient features, the percentages of which are compared with those for the whole series of 140 patients:

- (a) Race: White . . . . . 28 (56%) In whole series, 63%  
 Cape Coloured . . . . . 21 (42%) " " " 36%  
 Bantu . . . . . 1
- (b) Sex: Men . . . . . 46 (92%) " " " 92%  
 Women . . . . . 4 (8%) " " " 8%
- (c) Age: Average (years) when first seen . . 49.3 (S.D.  $\pm$  10.2);  
 (Whole series, 51.1  $\pm$  11.4)  
 Average age at clinical onset . . . 37.7 (S.D.  $\pm$  9.9);  
 (Whole series, 41.9  $\pm$  10.2)  
Average duration of clinical gout . . 11.6 (S.D.  $\pm$  9.3);  
 (Whole series, 9.2  $\pm$  8.6).
- (d) Familial incidence . . . 23 (46%) In whole series 33% .
- (e) Alcoholic excess . . . . 13 (26%) " " " 28% .
- (f) 'Obese' or 'thick-set' . 32 (64%) " " " 53%.
- (g) Associated diseases:
- |                              |         |   |   |   |       |
|------------------------------|---------|---|---|---|-------|
| Diabetes mellitus . . . . .  | 1 ( 2%) | " | " | " | 1%.   |
| Psoriasis . . . . .          | 2 ( 4%) | " | " | " | 3% .  |
| Liver disturbance . . . . .  | 8 (16%) | " | " | " | 6% .  |
| 'Rheumatic fever' . . . . .  | 2 ( 4%) | " | " | " | 5% .  |
| Urethral discharge . . . . . | 4 ( 8%) | " | " | " | 6% .  |
| Coronary disease . . . . .   | 3 ( 6%) | " | " | " | 11% . |
| Urinary calculus . . . . .   | 6 (12%) | " | " | " | 8% .  |

(h) Hypertension:

Diastolic always <u>95</u> or <u>more</u> . . .	14 (28%)	In whole series	33%.
" sometimes 95 " " . . .	26 (52%)	" " "	35%.
	<u>40 (80%)</u>		<u>68%.</u>

(i) Renal impairment:

Abnormal clearances and/or azotaemia  
(by criteria stated in Chapter 6) . . . . . 25 (50%)

(In whole series, 35%).

The 'dominant' features among these 25 patients were:

Uræmia (++) . . . . .	3 patients	('Group 1')
Proteinuria (++) . . . . .	3	"
(+) . . . . .	<u>2</u>	"
	l.e. 5	('Group 2')
Cells (+) . . . . .	2	" ('Group 3')
Impaired function . . . . .	15	" ('Group 4')

Three other patients, in the group of 50 treated with benemid, displayed a trace or one-plus of proteinuria without impairment of glomerular filtration or nitrogen excretion, and are therefore not included in the foregoing tally of disturbed renal function. One had persistent proteinuria, without formed elements, after removal of a bladder calculus (case 9); one had severe hypertension and a renal stone (case 23); the third (case 38) was subject to recurrent urinary tract infection.

Yet a further 6 patients in the benemid group had (without impaired function or proteinuria) evidence of urinary infection and/or calculus. Thus 34 of the 50 showed some signs of renal or urological abnormality, and in half the group (25 of 50) renal function was impaired.

### 3. Diagnostic pattern

- (a) Clinical classification: Using the patients' subjective symptoms between acute attacks as the criterion, there was a greater proportion of 'chronic' cases among the 50 given benemid than among the general series.

Complete freedom from articular symptoms  
between attacks . . . . . 15 (30%);

(In whole series, 49%).

Chronic gouty arthritis  
of all degrees . . . . . 35 (70%);

(In whole series, 51%):

Of the latter 35 patients with interval symptoms, 22 suffered significant interference with their daily activities, among whom 10 patients who were regarded as crippled.

- (b) Tophi:

Ear pinnae, joints, tendons, bursae . . . . . 25 (50%)

(In whole series, 35%).

- (c) Radiographic changes:

The feet were X-rayed in 49 of the 50 patients, and usually other joints were examined as well, depending on the story and clinical state.

Entirely normal appearance . . . . . 4 ( 8%)

(In whole series, 16%).

Appearance compatible with gout . . . . . 27 (55%)

(In whole series, 42%).

" " " osteoarthritis . . . . . 33 (67%)

(In whole series 70%).

- (d) Serum urate:

Many hundreds of urate determinations were done before and during benemid therapy. For comparability with the rest of the whole series, many of whom only had two estimations, the average figure given here for the 50 benemid patients is derived from the means of each patient's highest and lowest values before treatment, as was done in calculating the general average.

Serum urate in 50 patients before benemid therapy:

Mean  $\pm$  S.D. = 7.34  $\pm$  0.83 mg./100 ml.

(For whole series, mean  $\pm$  S.D. = 7.61  $\pm$  1.10 mg./100 ml.)

COMMENT: The foregoing data indicate that the 50 patients in whom the effects of benemid were studied showed features of gout which were generally more established than among the other members of the whole series, with a high incidence of associated renal impairment. It is perhaps surprising that the average serum urate concentration is ostensibly a little lower.



Table 13 (continued)

PATIENT				ASSOCIATIONS				ACUTE ATTACKS						CHRONIC SYMPTOMS		OLECRANON BURSTITIS		TOPHI	X-RAY CHANGES	SERUM URATE
Case no	Race	Sex	Years since first seen	Family history	Build	Alcohol habit	Other disease	Renal impairment	Hypertension	Annual frequency	Sites			Precipitating factors	Colchicine response	Bursitis		Tophi	X-ray changes	Serum urate (mg/100ml)
											First	Later	No. per attack			Acute	Fibrous/Urate			
45	CM	M	41	0	Thick-set (40)	0	0	±	+	Big toe, ankle, knee	Big toe, ankle, knee, leg	5	0	+	0	0	0	0	0-A	7.7-6.6
33	CM	M	48	3	Obese (42)	-	Hypertensive L.V. strain; renal calculus, nephrectomy	0	++	+	Big toe	Big toes, ankles, knees, wrist	2	0	+	0	0	0	0-A	7.6-7.2
43	WM	M	62	4	Obese (49)	-	Spermatocoele; trichomonas prostatitis	0	0	+	Big toe	Big toes elbow	2	0	+	0	0	0	0	7.6-6.4
47	CM	M	51	3	Medium (47)	+	Past rheumatic fever	0	±	+	Mid-foot	Mid-foot, ankles, knee, elbow	1	0	±	0	+	+	Gout	9.4-6.0
14	WM	M	49	3	Medium	+	Disturbed "liver functions"; past gc, urethritis	0	±	+	Wrist	Big toe, mid-foot, knee, wrist	1	0	±	0	0	0	0	9.7-7.0
46	WM	M	51	4	Thick-set (44)	+	Peptic ulcer; past Wassermann reaction positive	0	0	+	Big toe, ankle, elbow	Big toes, ankles, hand	1	0	+	0	+	+	Gout	8.1-6.7
36	CM	M	57	5	Cousin; gout; set mother diabetes	-	Sciatica	+	+	+	Knees	Knee, ankle	1	Trauma	+	0	0	+	0-A	6.7-6.0
26	CM	M	38	5	Obese (58)	-	Chronic bronchitis; episodic pyuria	0	±	+	Big toe	Big toes, ankle, knee	1	Penicillin in injection	+	0	0	0	0	6.8-6.7
28	CM	M	48	5	Medium (45)	-	Renal failure (chronic pyelonephritis); died	+	++	+	Wrist	Wrist; big toe, ankle, knee	2	0	+	0	0	0	0-A	7.5-7.1
38	WM	M	43	5	Medium (49)	+	Past ?pefit mal; past wrist fracture	+	+	+	Wrist	Big toe, heel, ankle	1	Exercise	+	0	0	0	Gout	6.2-6.0
34	WM	M	43	8	Medium (48)	-	0	0	0	+	Big toe	Big toe, ankle, hands	1	Alcohol	+	0	0	0	0-A	6.3-6.0
49	CM	M	34	7	Thick-set	+	Alcoholic gastritis	0	±	+	Big toe	Big toes, knee	1	Alcohol	+	0	0	0	0	9.5-7.4
18	CM	M	41	8	Medium (48)	+	0	+	+	+	Mid-foot, knee	Big toes; joints of all four limbs	Sev-eral	0	+	0	+	+	0-A	6.3-6.6

Table 13 (continued)

PATIENT				ASSOCIATIONS				ACUTE ATTACKS				CHRONIC SYMPTOMS			OLECRANON BURSTITIS		TOPHI	X-RAY CHANGES	SERUM URATE				
Case no.	Race	Sex	Age (yr)	Years since first seen	Family history	Build (PCV%)	Alcohol habit	Other disease	Renal impairment	Hypertension	Annual frequency	Sites		Na per attack	Precipitating factors	Cochicine response	Acute	Fibrous	Uric				
											O	2	4	5+	First	Later							
27	CM	M	47	8	0	Obese (45)	-	Past urethral discharge	0	+	+	Big toe	Joints of all four limbs	3	0	+	+	+	0	0-A	8.5-6.4		
6	WH	M	39	6	0	Thick-set (49)	-	Dyspepsia ("functional")	+	-	+	Mid-foot	Mid-foot; big toe, ankles.	1	0	+	0	0	0	0	7.9-6.2		
31	CM	M	54	6	0	Thick-set (48) (51)	-	Bladder calculus; hypertensive L.V. strain	0	-	+	Big toe	Big toe, ankle, wrists	1	0	+	0	0	0	0-A	8.9-6.4		
48	CM	M	47	7	0	Medium (47)	-	Positive Berger and Kahn reactions	+	0	+	Ank-les	Knees, ankles, big toes, elbows, hands	2	0	+	+	+	0	Gout	9.3-7.1		
41	CM	M	45	9	0	Obese (43)	-	0	0	-	+	Ank-le, toe	Ankles, big toes	2	0	+	0	0	0	0-A	7.0-6.6		
30	CM	M	48	9	0	Medium (44)	-	0	0	-	+	Ank-les, big toe, knee	Ankles, big toes, knee	2	0	+	+	+	0	0-A	6.0-5.2		
15	WH	M	63	10	0	Thick-set (52)	-	Chromidrosis; dermatitis	0	-	+	Big toe	Big toes	1	0	+	0	0	0	0-A	6.5-6.2		
9	WH	M	42	9	0	Obese (39)	+	Bladder calculus; alcoholic gastritis; disturbed "liver functions"	0	+	+	Big toe	Big toes, ankles, knees	1	Holl-days	+	0	0	0	Gout	8.9-7.4		
42	CM	M	44	10	Path-etic	Thick-set (40)	-	Hypertensive and renal; easy bleeder	+	+	+	Ole-cra-non	Big toes, ankle, wrist	2	Trauma Alcohol	+	+	+	0	0-A	8.6-6.9		
44	WH	M	52	10	0	Obese (47)	-	Diabetes; pyuria; disturbed "liver functions"	0	+	+	Ank-le	Big toes, ankles, hands, elbows	2	0	+	+	+	0	0-A	8.0-6.7		
22	WH	M	59	10	Sis-temic rheumatism	Thick-set (45)	0	0	+	+	+	Big toe	Big toes, 5th toe, ankle, knees, thumb	1	Worry, holl-days	+	0	0	0	0-A	7.9-6.8		
39	WH	M	60	10	0	Thick-set (44)	+	Gastritis; middle-ear deafness	0	-	+	Big toe	Big toes, wrists, elbow, neck, rib	1	Trauma	+	+	+	0	0-A	7.3-5.9		
25	CM	M	72	10	Bro-thers & fat-her	Medium (37)	+	Colitis; anac-mia; senility; died	+	-	+	Big toe	Big toes, hands, elbow, shoulder	2	0	±	+	+	0	0-A	6.1-7.6		

Table 13 (continued)

PATIENT			ASSOCIATIONS				ACUTE ATTACKS					CHRONIC SYMPTOMS			OLECRANON BURSITIS		TOPHI	X-RAY CHANGES	SERUM URATE	
Case no.	Race	Sex	Age first seen	Years since gout	Family history	Build	Alcohol habit	Other disease	Renal impairment	Hypertension	Annual frequency	Sites			Precipitating factors	Cachectic response	Acute	Fibrous	Uratric	SERUM URATE (mg/100ml)
												First	Later	No. per attack						
8	WH	M	46	10	Father gout	Medium (36)	-	Renal disease	+	-	+	Big toe	All limbs and neck joints	Several	0	+	+	+	0-A Gout	8.0-7.2
19	WH	M	47	12	Father Dupuytren's contracture	Obese (44)	-	Dupuytren's contracture	+	-	+	Joints of all four limbs	Neck joints of all four limbs	Several	Alcohol	+	0	0	0-A Gout	7.7-7.3
11	WH	M	57	12	Mother's father rheumatism	Medium (50)	-	Past asthma	+	-	+	Big toe	Big toe, wrists	1	Parties	+	0	0	0-A	7.0-7.6
13	WH	M	70	13	Sister's gout	Obese (45)	-	Episode of pyuria	0	+	+	Big toe	Big toe	1	0	+	0	0	0-A Gout	8.7-8.6
5	WH	M	48	18	Grandfather gout	Lean (45)	-	Chronic bronchitis; "liver functions"	+	0	+	Shoulder	Shoulder, ankles, hands, elbows, shoulders, neck	Several	Week-ends; operation; vacation	+	+	+	Gout	4.6-3.6
18	WH	M	43	12	0	Obese (56)	-	Poriasis; renal calculus	+	-	+	Big toe, ankle, knee	Big toe, ankles, knees, hand	1	Oranges; sardines; peas exercise	+	0	0	0-A	8.6-7.2
20	CM	M	44	12	Father rheumatism	Medium (44)	+	RENAL disease	+	+	+	Big toe, ankle, knee	Big toe, ankle, wrist, elbow	1	Alcohol	+	0	0	0-A	9.1-8.1
21	CM	M	64	12	0	Obese (53)	-	0	0	0	+	Big toe	Big toe, ankles, wrist, elbow	2	0	+	+	Gout	9.2-6.9	
4	WH	M	62	14	Brother gout	Obese (45)	-	Past renal calculi; xanthoma; "liver functions"; coronary disease; died	+	-	+	2nd toe	Joints of all four limbs	Several	Exercise	+	+	+	Gout	8.7-6.8
36	CM	M	39	12	Mother's father arthritis	Medium (45)	+	Renal disease; past urethral discharge	+	-	+	Toe, ankle, leg	Toe, ankle, leg	Several	Trauma; exercise; alcohol	+	+	+	Gout	8.0-6.6



#### 4. Management of benemid programme.

(a) Investigation and supervision of patients. Whenever possible, patients about to receive benemid were admitted to hospital for full clinical and laboratory assessment of their gout status. Daily serum urate estimations were done for at least a week, in addition to any values previously obtained, and urate excretion measured by analysis of 12-hour urine collections and by clearance determinations. As a check on urine volumes, total creatinine was serially estimated also, and endogenous creatinine clearances were done as a guide to renal function. The techniques used for all these procedures have been described in Chapter 3. Daily serum and urine urate values were obtained for a week or more after starting benemid therapy in hospital patients, and the clearance tests repeated before discharge. Many of the patients were unable to enter hospital for investigation, so that renal clearances and total urate excretion could not be studied in 14 of the 50 patients in the group. None began treatment, however, without first having 5-7 or more serum urate estimations for comparison with values during benemid therapy, an exception being case 1 whose treatment started hurriedly before laboratory facilities were ready. Some out-patients were also able to spend a few mornings having clearance tests done before and during benemid administration.

Details of the patients' history and clinical progress were carefully recorded at regular visits after leaving hospital or after beginning the programme as out-patients. The clinical medicine laboratory at the Groote Schuur Hospital became a popular venue for scores of gout patients, whose arranged frequency of attendance was usually 2 or 3 times weekly for a short period after starting treatment, then fortnightly for several months, decreasing thereafter to monthly or three-monthly visits according to the patients' clinical state and estimated reliability in taking tablets. They were encouraged to attend, in addition, for intercurrent illnesses or acute attacks.

(b) Treatment of intercurrent acute attacks. An important aspect of close clinical supervision in gout is the opportunity to observe and treat numerous acute attacks, thereby shortening morbidity in the disease, gaining the co-operation of patients, and enabling large-scale comparison of various forms of

treatment. In assessing a prolonged therapeutic programme, however, the possibility that prompt relief of acute gouty arthritis exerts a beneficial influence per se on the ultimate course must be taken into account.

During the management of large numbers of gout patients together with Dr. Mark Horwitz, the writer has studied the relative efficacies, in many acute attacks, of colchicine given orally, colchicine combined with one day's administration of ACTH<sup>125</sup>, oral cortisone, oral and intramuscular hydrocortisone, and orally administered phenylbutazone<sup>76</sup>. There is no doubt that colchicine is still the mainstay of treatment in acute gout. Tablets of the pure alkaloid are preferable to the less predictable tincture and wine, and the 1/100 grain size permit finer regulation of dosage than 1/64 gr. tablets. A few taken judiciously at the first threat of an attack may prevent its development, failing which the drug is taken at two-hourly intervals to the point of diarrhoea or nausea, and daily thereafter in smaller doses (3-4 tablets in 24 hours) until the episode has subsided. The taking of small prophylactic amounts of colchicine for some weeks after an attack is a useful measure, and some prescribe it as regular interval treatment<sup>59, 118</sup>. Colchicine given intravenously is said to act faster, with less likelihood of gastro-intestinal distress<sup>59</sup>.

With extremely few exceptions, the combination of moderate doses of colchicine with ACTH (e.g. one injection of 100 units of the gel), has produced striking relief more quickly and more completely than heavier doses of colchicine given alone. In cases where the attack is known to take days rather than hours to respond to colchicine, and where joint swelling and stiffness persist disproportionately long, the newer treatment is likely to prove highly gratifying<sup>61, 125</sup>. Only one injection of ACTH is usually needed for effect, and smaller amounts of colchicine may be taken, thus avoiding bowel symptoms. Daily small doses of colchicine must be maintained for 3-4 weeks if a recurrence is to be avoided. (This apparent specificity of ACTH in acute attacks has led Wolfson to evolve a theory of the adrenocortical origin of acute gouty arthritis<sup>124</sup>, supported by various electrolyte and endocrine abnormalities said to be associated with the clinical pattern of gout<sup>119, 124</sup>. Good evidence has been produced to refute some of the underlying premises for a hormonal pathogenesis<sup>81, 82, 59</sup>, but the controversy does not detract from a valuable therapeutic contribution.)

Phenylbutazone has proved useful in some slowly resolving

attacks, and hydrocortisol by mouth (the free alcohol of Compound F) has dramatically relieved a few particularly severe gouty seizures. Parenteral hydrocortisone acetate, and orally administered cortisone acetate, are less impressive in acute gout.

(c) Diet. No special dietary restrictions were imposed on the patients who were given benemid, other than avoidance of items with a specially high nucleoprotein content (liver, kidney, etc.) which constitute a needless burden on urate metabolism in gout. Evidence that many food fractions can contribute to the uric acid molecule makes detailed dietary measures unreasonable, and it is fair to expect a successful uricosuric agent to outweigh the influence of ordinary foods on serum urate levels. Many patients in the group needed and received Talbott's advice to reduce weight, but few succeeded in complying. Those who recognized particular precipitants of acute attacks, including certain varieties of alcoholic drink, usually avoided them without special proscription.

(d) Dosage of benemid. Each patient was supplied with benemid and instructed to take one tablet (0.5 G.) three times daily, a dose which early reports had shown to be effectively uricosuric <sup>58</sup>. Potassium citrate, 6 G. daily in a flavoured mixture, was simultaneously prescribed in order to alkalinize the urine against urate crystalluria, but in most cases was discontinued after a few months. The mixture was neither appetizing nor particularly effective, and greater emphasis was placed on the patients' drinking copiously to diminish urinary urate concentration. For similar reasons, patients commencing uricosuric therapy in the earlier part of this study took 1.0 G. instead of 1.5 G. of benemid for the first week, but the absence of all complications in the first 30 recipients led to the subsequent use of the intended 1.5 G. from the beginning of the treatment. After observing that 11 of the first 30 patients experienced acute gout within a fortnight of starting benemid <sup>64</sup>, and reading that others had encountered the same phenomenon <sup>58, 99</sup>, it was decided to prescribe colchicine in 'prophylactic' amounts (gr. 1/100 t. d. s.) for the first three weeks of benemid therapy. Of the next twenty patients, only one subsequently treated experienced a iatrogenic attack on the latter regime.

Care was taken not to promise any special benefit from the regular use of benemid, the newness and mode of action of which were explained. Patients were in fact warned that acute attacks might continue at their usual frequency, but were dissuaded from taking colchicine other than early in a real attack. Enough benemid was given periodically to ensure that no one ever ran out of tablets during a reasonable absence from attendance at the clinic, and patients were advised to divide supplies between their home and place of work so that regular dosage could be maintained. A few preferred to take the daily amount in two doses, to which there was no apparent pharmacological objection.

### C. BIOCHEMICAL RESULTS OF BENEMID THERAPY

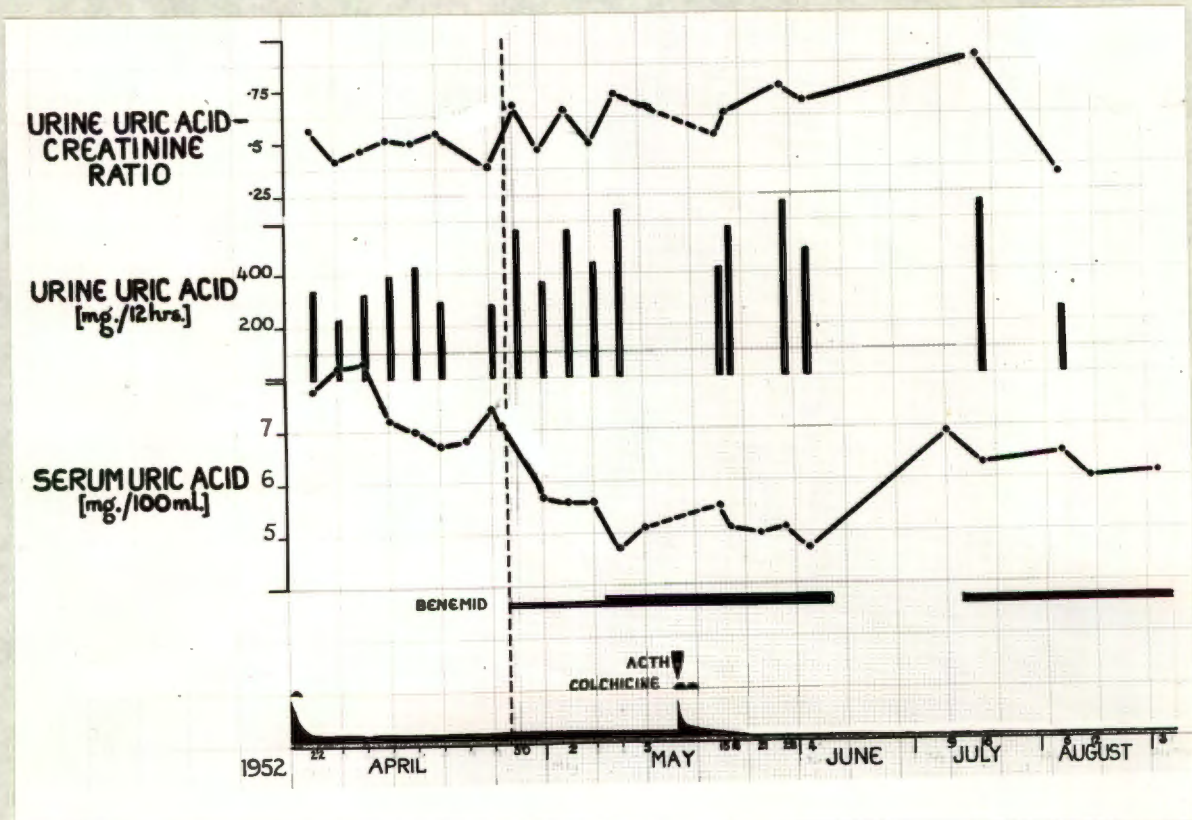
The following pages illustrate the outstanding efficacy of benemid as a long-term uricosuric agent in patients with gout.

#### 1. Serum urate levels

A prompt reduction in serum urate concentration accompanied the onset of benemid therapy (Figs. 44, 45). In 49 of the 50 patients the level was determined between one and three days after starting the drug ('Immediately after' column in Fig. 45), and the degree of reduction ranged from 52% to 5% of the pre-benemid level, with a mean fall of 33%. It is remarkable that the latter figure represents the effect, in most cases, of one day's dosage (1.0 or 1.5 G.) of benemid, and in all cases not more than 4.5 G. by the time of the first analysis.

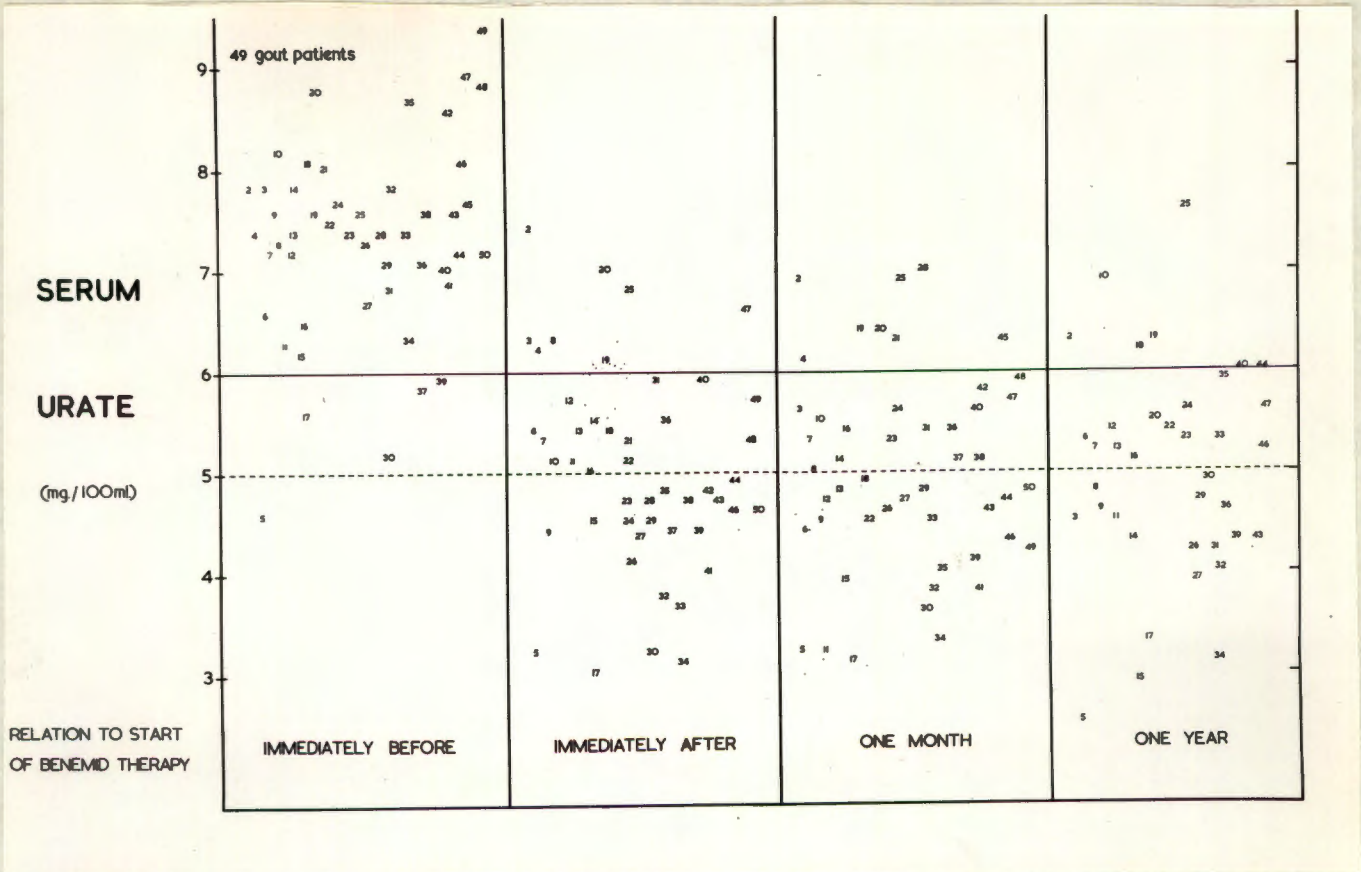
An alternative calculation was made by taking the mean of the 3 lowest serum urate readings during the month before benemid, and the mean of the 3 highest readings during the first month of treatment, for each patient. Despite the fact that the degree of reduction is minimized in this way, serum urate levels in the 49 patients fell from a low average of 7.0 mg./100 ml. to a high average of 5.1 mg./100 ml., a 28% reduction. In only 3 cases was the fall less than 10%, all having severe renal impairment, two of them with frank uraemia (cases 2 and 28).

In Fig. 45 the relative constancy with which benemid maintains greatly reduced serum urate levels is illustrated, the average value at one year being, by remarkable coincidence, no different from the earlier average values. Admittedly the figures in the 'one year' column are each patient's best at or about that time, but higher values appearing after months of treatment were invariably explicable by temporary cessation or irregularity of dosage. There is no doubt, from the urate patterns of several co-operative patients during periods of up to 2½ years, that the continued ingestion of benemid in dosage of the order of 1.5 G. daily maintains a constant reduction of serum urate concentration. As is the case with all uricosuric agents, cessation of the drug permits levels to rise to former heights, and in gout patients whose abnormally large metabolic pool may not yet have been adequately drained, this rebound may occur quite quickly (Chapter 3.) Evidence of true pharmacological 'tolerance' to benemid in the absence of interrupted dosage or a progressive renal lesion opposing its effect, has not appeared in this study.



**Fig. 44.** Biochemical and clinical effects of benemid administration (1-2 G. daily) to a patient with chronic tophaceous gout (case 12). Note immediate and sustained uricosuric response in both serum and urine, which is renewed on resuming therapy after interruption for a month. The apparently smaller effect during July and August is partly due to inconsistent medication.

The clinical diagram below the graphs shows the occurrence of acute gout one week after starting benemid, its successful treatment, and the gradual diminution during the next 5 weeks of previously present chronic symptoms, leading the patient to suspend benemid therapy without consultation.

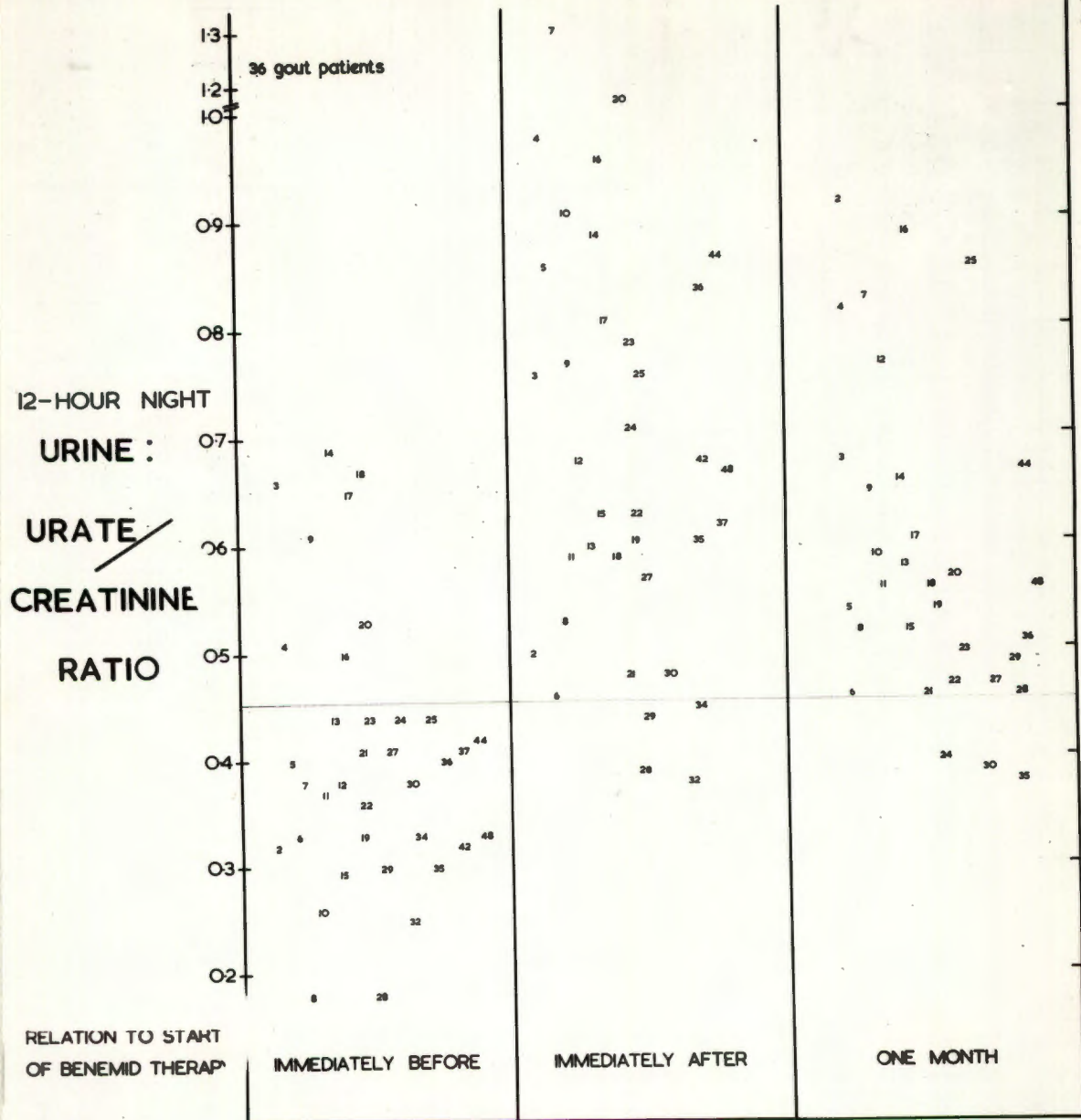


<u>Mean:</u>	7.31	4.99	5.00	4.99
(± S.D.)	(± 0.95)	(± 0.99)	(± 1.00)	(± 1.08)
<u>Per cent. fall:</u>		33%	33%	33%

Fig. 45. Scatter-diagram showing changes in serum urate concentration during benemid therapy (1.5 G. daily). The patients' case numbers have been used as the points in the diagram.

- Note (a) Rarity of initial levels lower than 6 mg./100 ml.  
 (b) Reduction of majority to normal values.  
 (c) Maintenance of effect (in those studied long enough) for the first year of treatment.

(Cases 1-30 began therapy on 1.0 G. daily for the first week, before increasing to 1.5 G. daily. The average serum urate figure "immediately after" would probably have been somewhat lower on a uniformly larger initial dose.)



Mean:

0.41

0.69

0.59

Fig. 46.

Scatter-diagram of urate/creatinine excretion ratios in 36 gout patients commencing benemid therapy. The daily dosage in most cases (those numbered 1-30) was 1.0 G. for the first week, thereafter being uniformly 1.5 G. for all.

Note (a) Uricosuric effect greatest at start of benemid administration.

(b) Urate/creatinine ratio still significantly raised in urines collected one month (actually 2-6 weeks) after onset of therapy. The return of the average figure towards normal represents progressive depletion of available body urate. The serum urate levels in Fig. 45 testify to the persistence of uricosuric activity.

## 2. Urinary excretion of urate

Fig. 46 shows the changes in total urate excretion among 36 of the 50 receiving benemid, measured in accurately timed 12-hour urine specimens and related to simultaneous creatinine output for obviation of collection losses or alterations in glomerular filtration rate. Although many more excretion values were determined than are shown in the diagram, three single figures were purposely used to show a pattern of uricosuric response which would not have been depicted by a presentation of averages. Comparison of the urate/creatinine ratios for the 12-hour specimens collected in the night immediately before, the night immediately after and a night 2-6 weeks after the start of benemid therapy, shows that the excessive urate excretion is greater after the first few doses of benemid than later on, and if followed long enough, the urine values return to normal figures as the body reserves of urate diminish. That this excretion pattern does not reflect a loss of the uricosuric effectiveness of benemid may be seen from the corresponding serum urate levels at one month (Fig. 45) which on the average are no different from the initial low figures after starting the drug.

One practical implication of this general finding concerns the theoretical danger of urate crystalluria during uricosuric therapy. The chances of its occurrence, and the need for precautions like copious fluid intake and perhaps alkali ingestion, are apparently greatest during the beginning of treatment in those patients whose metabolic pool is not virtually inexhaustible.

Allowing for considerable individual variability, the urinary urate output as expressed in Fig. 46 was enhanced by an average of about 75% under the uricosuric influence of benemid. This result is to be distinguished from changes in the renal clearance of urate, which is commonly doubled or trebled.

### 3. Changes in urate clearance and urate/creatinine clearance ratio

Urate clearances in 51 members of the whole gout series were recorded in Table 12 (Chapter 6), and were seen to average 9.2 ml./min. This value is no different from the urate clearances reported by most observers for normal people, ranging from 6 to 12 ml./min.<sup>27, 38, 115,</sup> or from urate clearances in other gout series. The modern contention<sup>59, 115</sup> that there is no primary defect of urate clearance to account for the hyperuricaemia in gout is thus supported by the writer's findings.

The urate/creatinine clearance ratio in the same group of 51 patients was 0.112, rather greater than the ratio found in normals, which has been reported as 0.08-0.10<sup>107</sup>, and which the writer found to be 0.095 in a group of seven normal young men. This relative increase of urate clearance to creatinine clearance in gout reflects the frequency of impaired glomerular filtration in the disease.

Table 14 lists the changes in urate clearance in 35 of the 50 gout patients receiving benemid. An impressive increase, especially in the more revealing urate/creatinine clearance ratio (which corrects for any differences in glomerular filtration during the two tests) occurred in all but one patient (case 7). There was no doubt about his uricosuric response to benemid by other criteria, and the anomalous clearance results were probably due to erroneously high control figures obtained during a phase of urinary infection. A graphic quantitative analysis of the clearance results and their relation to renal disease and tophi, is presented in Fig. 48.

Table 14. The effect of benemid therapy on urate clearance and other indices of renal function in 35 gout patients. \*

PATIENT					CLEARANCES			CHEMICAL		URINALYSIS					BP. range (mm.Hg)	Relation to start of Benemid therapy		
Group	Case no.	Race Sex Age	Tophi	Impaired renal function	Creatinine  (ml./min)	Urate	Urate/ creatinine clearance ratio	Serum concentration (mg./100ml)		S.G.	Protein	Cells					Casts	Crystals
								Urea	Creatinine			RBC	WBC	Renal or Tract				
A	14	WM 48	0	0	138	20.0	0.14	51	1.2-1.7	1024							155 80	Before
					84.5	21.5	0.26	28	1.2-1.6	1018								
	54	WM 37	0	0	130	8.8	0.067	2.3	0.9-1.1	1025	+				Urate		170-120 110-80	B
					88.7	11.2	0.13	?	?	?	?	?					?	
	26	CM 38	0	0	97.9	15.3	0.16	12-30	1.0-1.7	1008							145 95	B
					115	26.6	0.23	43	0.8-1.2	1008								
	9	WM 42	0	0	106	30.2	0.28	35-50	0.9-1.4	1026	+				Urate		135 95	B
					114	39.2	0.35	32-50	1.1-1.9	1022	+							Urate
	15	WM 63	0	0	89	8.9	0.10	34-36	0.9-1.2	1022	0				0		130 80	B
					102	19.0	0.19	28-44	1.0-1.4	1022	±							Oxyl. Urate
B	16	WF 63	+	0	100	14.8	0.15	32-37	1.0-1.1	1010			+				230-205 130	B
					76.9	15.8	0.21	34-37	0.9-1.3	1010					+			
	27	CM 47	+	0	109	9.7	0.089	27-50	1.1-1.4	1010							170-160 100	B
					110	28.7	0.26	30-32	0.8-1.3	1020								
	59	CM 48	+	0	129	7.7	0.060	17-32	1.0-1.3	1012	±						255-185 155-110	B
					90.2	7.6	0.10	?	1.0-1.1	?	?							
	30	CM 48	+	0	97.5	7.5	0.077	30-47	1.2	1016				+			150 110	B
					86.7	20.5	0.24	44	1.0-1.6	1020						++		
	44	NM 52	+	0	94.0	6.1	0.065	19-27	0.7-1.2	(Sugar)	0		+	+			205-170 110-100	B
					85.5	9.5	0.11	19-40	0.8-1.6	"	±	++	++					
	21	CM 64	+	0	77.1	5.9	0.076	27-33	1.4-1.7	?	±						150 90	B
					87.2	9.5	0.11	40-41	1.1-1.6	?	±							
	33	WM 55	+	0	79.2	7.8	0.098	39-41	1.4	?	0				0		120-110 75-70	B
					101	17.2	0.17	31-56	1.1-1.3		0						Phos.	130-110 80-60
	37	WM 54	+	0	103	9.5	0.091	37	1.2-1.4	1024							130-120 80	B
					78.2	15.8	0.20	31	0.9-1.3	1020								
C	17	WF 66	0	+	80.5	16.6	0.21	34	1.2-1.9	?							220-170 115-95	B
					80.6	38.0	0.47	?		1015								
	28	CM 42	0	+	37.3	6.3	0.17	79-104	2.6-3.2	1010	++	+	±	±	++		220 135-120	B
					25.7	8.5	0.33	?	?	1012	++	±	+	+	++			
	61	WM 50	0	+	70.7	9.5	0.14	37	1.2-1.5	1020	0						145-120 75-70	B
					80.0	19.0	0.24	?	1.1-1.3	?	?							
	6	WM 38	0	+	86.2	17.5	0.21	39-44	1.2-1.3	1018					Urate		145 100	B
					68.8	19.3	0.28	31-41	1.0-1.7	1016							0	

\* Group A: No tophi; no impairment of renal function  
 " B: Tophi; " " " " "  
 " C: No tophi; impairment of renal function.  
 " D: Tophi; " " " " "

Table 14 (continued).

PATIENT					CLEARANCES			CHEMICAL		URINALYSIS					B.P. range (mm.Hg)	Relation to start of Benemid therapy		
Group	Case no.	Race-Sex Age	Tophi	Impaired renal function	Creatinine (ml/min)	Urate	Urate/creatinine clearance ratio	Urea	Creatinine (mg/100ml)	S.G.	Protein	Cells (RBC, WBC, Renal or Tract)					Casts	Crystals
	22	WM 59	0	+	63.4 77.0	4.1 13.0	0.065 0.170	26-34 41-52	1.4-2.0 1.4-1.8	?	0 0						145 90 200-160 120-100	B A
	42	CM 44	0	+	63.3 62.4	6.2 16.8	0.094 0.25	67 34-64	1.5-2.0 1.5-1.9	1014 ?	+						230-150 130-100 175-160 115-100	B A
	2	WF 58	0	+	36.3 23.6	4.6 7.4	0.13 0.51	81-88 95-239	2.9-4.1 3.3-7.0	1010 1012	+						145 115 230-150 110-100	B A
	11	WM 57	0	+	49.0 64.0	15.0 27.7	0.31 0.43	42-49 39-61	1.3-1.7 1.0-2.0	1008 1020					0	Phos.	155 95 145-150 100-80	B A
	19	WM 47	0	+	50.5 87.0	6.6 17.9	0.13 0.21	30-57 31-65	1.2-1.4 1.2-1.6	1010 1016	± ++	0 +	± +		± +		115 75 165-140 110-90	B A
	29	CM 49	0	+	81.1 93.5	6.3 11.9	0.078 0.13	28-36 33	1.1-1.4 1.1-1.4	1022 1022							140 80 145-120 100-80	B A
D	35	CM 36	+	+	76.0 110	6.9 16.2	0.091 0.15	34-37 ?	1.2-1.4 0.9-1.3	1022 1022						Oxal. 0	160-135 115-105 155-120 100-100	B A
	48	CM 46	+	+	76.6 85.3	3.4 10.2	0.046 0.12	22 ?	1.2-1.6 1.1-1.2	1010 ?	± ?						120 75 135 85	B A
	12	CM 41	+	+	69.1 85.3	12.0 26.3	0.17 0.31	20-41 17-32	1.2-1.6 0.9-1.3	1008 1016	+				?	Phos. 0	160-150 110 160-120 105-75	B A
	60	WM 43	+	+	67.4 77.9	4.8 5.5	0.071 0.071	42-65 ?	1.5-2.0 1.5	1020 ?	± ?		++ ?				145-135 95-90 ?	B A
	8	WM 46	+	+	34.2 90-2	2.8 10.7	0.083 0.11	25-61 40-104	1.6-2.2 1.2-2.8	1024 1016	+				+		170-110 125-70 150-120 100-80	B A
	25	CM 72	+	+	51.6 72.7	5.1 9.1	0.099 0.13	50 56-79	1.0-1.4 1.3-1.7	1018 ?	0 ±		± +		0	Phos.	180-150 90-75 200 105-90	B A
	20	CM 44	+	+	62.9 76.5	7.3 15.2	0.11 0.16	40 41-59	1.0-1.6 1.0-1.4	1014 1024	++ ++				0	Urate	150 90 210-140 115-95	B A
	36	CM 39	+	+	80.4 101	6.5 18.3	0.082 0.18	25-38 34-39	1.3 0.8-1.2	1020 1015	+				0	Urate	150-140 95-90 165-140 105-90	B A
	4	WM 62	+	+	103 52.1	9.1 13.0	0.087 0.27	43-51 46-125	1.4-2.4 1.5-2.8	1014 1018	0 +		0 +		0 +		170 95 180-130 110-80	B A
	5	WM 48	+	+	69.8 100	7.6 23.0	0.11 0.23	37-48 36-58	1.0-1.6 0.9-1.6	1020 1025			± +	± +	0	Phos.	135 85 145-105 85-65	B A
	10	CM 53	+	+	62.4 59.8	11.3 16.6	0.18 0.28	21-49 20-49	1.3-1.7 0.8-1.8	1012 1015	+			++ ++	± +		120 95-90 165-125 105-90	B A
	7	WM 72	+	+	25.7 41.0	11.6 8.4	0.45 0.21	43-47 41-73	2.2-2.7 1.3-2.5	1014 ?	0 ±		++ +	± 0	± +		190 120 165-130 95-70	B A

#### 4. Effect of benemid therapy on renal functions

Table 14 presents various criteria of renal function in the 35 patients whose urate and creatinine clearances were determined before and during benemid administration. In all of the remaining 15 studied, an equally close watch was kept on urinary findings, serum urea and creatinine and blood pressure readings. The performance of special urine concentration tests was limited to relatively few, and the specific gravities recorded in Table 14 were usually routine values. While some of the clearance data were obtained in the first week after starting treatment, and may not indicate later alterations on benemid, most were determined after an interval of several weeks or months, and the other tabulated clinical and chemical indices of renal function represent serial testing throughout each patient's treatment period.

There were no convincing indications by the available methods of assessment that benemid exerted any beneficial or adverse effects on renal function in gout patients. Some patients, who had significant kidney disease at the start of treatment, showed evidence of slow progression at a rate which was considered compatible with what is known of chronic renal lesions. Other patients showed mild fluctuations in renal efficiency in both directions which could not be related to the taking of benemid. Cessation of the drug in a young woman (case 2) whose blood urea had risen from 80 to 140 mg./100 ml. during a year's benemid therapy, had no effect in slowing her renal failure, and merely permitted a prompt rise of serum urate (Fig. 65).

It is felt that a much longer period of study is required before the long-term effect (if any) of benemid on renal efficiency can be decided. On the evidence to date from this series and from a few others<sup>59, 118</sup>, there is no way of judging whether uratic kidney lesions (with their associated mechanical and infective complications) will be resolved or even averted by timely uricosuric therapy, or whether the prolonged use of benemid may even prove harmful by an unrecognized nephrotoxic action or by facilitating urate crystalluria within the tubules.

The unproven possibility that hyperuricæmia per se predisposes to vascular damage both in the kidneys and systemically<sup>53</sup> tips the balance of speculation about the ultimate role of benemid a

little to the side of optimism, offering as it does one extra theoretical benefit to be derived from persistent uricosuric therapy.

##### 5. Influence of renal impairment and of tophi on uricosuric effect of benemid in gout

Because the uricosuric action of benemid takes place at a renal level, and because others have denied that any effect is displayed in the presence of substantial kidney disease<sup>98</sup>, it was considered important to analyse the biochemical results of benemid therapy in relation to renal function. Both kidney disease and gouty tophi constitute important criteria of the clinical severity in an individual patient. Accordingly, the extent to which both features influence the prospects for successful uricosuric therapy was examined, and illustrated by the grouped results in Figs. 47 and 48.

(a) Reduction of serum urate levels. Given a patient with gout and impairment of renal function, there appear to be no grounds for withholding benemid on the premise that it will be ineffective. Groups C and D in Fig. 48 include three patients with frank renal failure (cases 2, 8 and 28) in addition to others with smaller degrees of azotaemia and all grades of impaired glomerular filtration and proteinuria (Table 12). Despite this, and despite basing the fall in serum urate on the 3 highest figures in the month after starting benemid, these two 'renal' groups show an impressive response not much smaller than the average fall of 28% for the whole series in the diagram.

However, it is equally plain that the presence of advanced renal disease with nitrogen retention does minimize the uricosuric response, and this fact, coupled with as yet unanswered doubts about the possible harm resulting from the use of tubule-active drugs in damaged kidneys, led the writer to withhold benemid therapy from severely uraemic gout patients later in the study.

Gout patients with tophi (in both categories of renal function) are seen to exhibit smaller reductions in serum urate levels than those without. This finding (as discussed in Chapter 3, and illustrated by columns A and B in Fig. 48) reflects readier replenishment from a larger metabolic pool of urate, rather than any modification of the essential action of benemid.

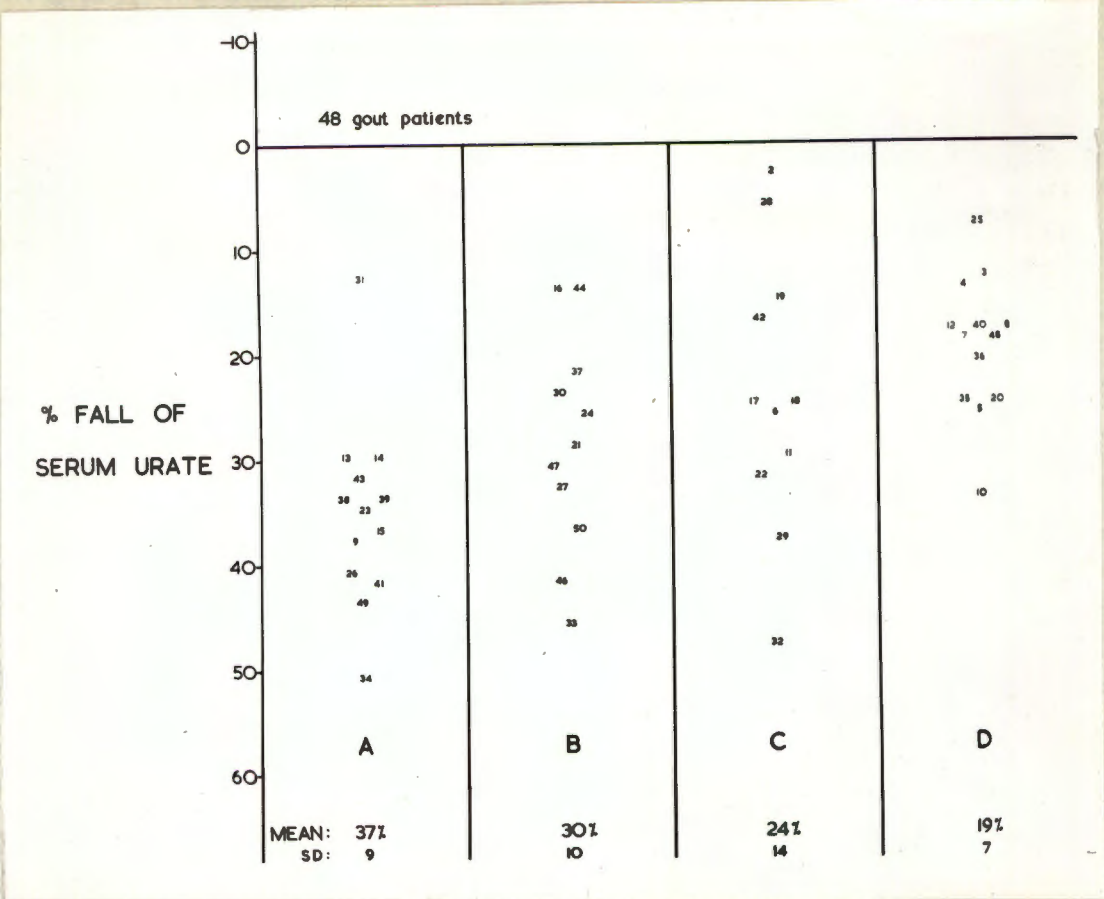
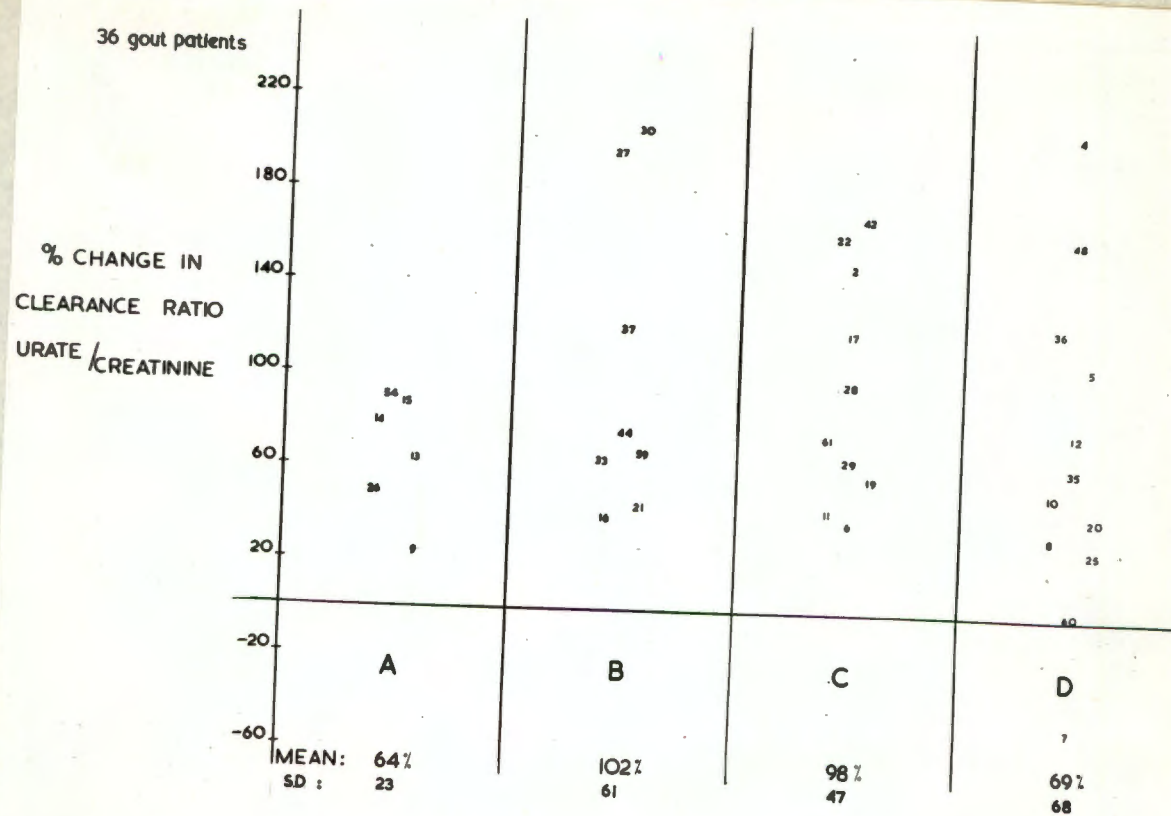


Fig. 47. Effect of benemid therapy on serum urate levels in 48 gout patients. (The values for each patient used in calculating these figures were the mean of the 3 lowest readings in the month before benemid, and the mean of the 3 highest readings in the first month of therapy).

- Group A: No tophi; no impairment of renal function
- " B: Tophi; " " " " "
- " C: No tophi; impairment of renal function
- " D: Tophi; " " " " "



For patients tested in first week of therapy

88% (2)	127% (3)	94% (4)	70% (5)
---------	----------	---------	---------

Fig. 48. Effect of benemid administration on urate/creatinine clearance ratio in 36 gout patients.

- Group A: No tophi; no impairment of renal function
- " B: Tophi; " " " " "
- " C: No tophi; impairment of renal function.
- " D: Tophi; " " " " "

(b) Increase in urate/creatinine clearance ratio.

Examination of the figures similarly grouped in Fig. 48 confirms the effectiveness of benemid administration to those with impaired renal function. In relatively few of the patients depicted in columns C and D it is possible to ascribe the increased clearance ratio mainly to a progressive diminution of creatinine clearance. (Table 14). The greatest percentage rise in urate/creatinine clearance ratios is shown by patients with tophi and intact renal function (Group B). This is the case even when comparing those patients who were tested at approximately the same stage of benemid therapy, namely, in the first week, and may be interpreted as indicating the largest urate diuresis among the four groups. Such a finding is in keeping with the current concepts of urate metabolism and with the mobilization by uricosuric agents of gouty deposits, and lends weight to the persistent use, especially in patients with tophi, of an effective uricosuric agent like benemid.

6. Salicylate administration during benemid therapy.

The well documented observation that the uricosuric action of benemid may be cancelled by simultaneous salicylate medication <sup>98, 15</sup> was not specially explored in this study, but care was taken to prevent the combination of drugs from occurring during treatment.

## D. CLINICAL RESULTS OF BENEMID THERAPY

### 1. Criteria of assessment

Judging the value of therapeutic measures in a disease like gout is beset with clinical difficulties, many of which will emerge in the following account, and discipline had to be exercised throughout the study in the interpretation of results.

Although ideally any scientific investigation is strengthened by the use of experimental controls, it was considered impractical to conduct a 'controlled therapeutic trial' in its usual rigid meaning. The division of all available patients into two comparable groups, of which only one would receive benemid, would in itself have entailed many problems and few ultimate advantages: (a) The study was envisaged as necessarily continuing indefinitely, during which time half the patients in our care would be deprived of a potentially beneficial new drug. (b) The number of patients in whom the therapeutic effects of benemid could be observed, and hence the quantitative value of the study, would be halved. (c) The usual advantages of having a control series would be minimized by the great practical difficulty of finding two groups of gout patients really comparable in terms of acute attacks, chronic symptoms, extent of urate deposition and associated diseases.

On the other hand, the nature of the disease in question is often so characteristic for each patient that every one who has reached a certain stage in its development provides, in a sense, his own control. Even allowing for the occurrence of spontaneous alterations in the clinical pattern of an individual gout patient, assessment of his progress by comparison with his own previous course and with the known natural history of gout is likely to be as valid as comparison with other specially untreated patients, provided the period of observation and the criteria used are adequate.

The following clinical features were carefully analysed in assessing the therapeutic value of prolonged uricosuric therapy with benemid:

- (1) The frequency of occurrence of acute attacks,  
their severity and ease of precipitation.

- (ii) Degree of any chronic, active articular symptoms such as pain, persistent inflammatory swelling, and stiffness.
- (iii) Structural changes of gout, such as tophaceous deposits, skeletal deformity, and mechanical rigidity of joints.
- (iv) Radiographic evidence of gout lesions.
- (v) Systemic effects (including vascular and renal), and toxic reactions possibly resulting from the use of benemid.

Seven of the patients reported here have been separated from the rest of the group and will be presented last. They were patients with severe grades of gout who received, for reasons which will be explained, continued small doses of cortisone in addition to benemid. The other 43, treated with benemid alone, are depicted in the clinical charts on the following pages (Figs. 49-52).

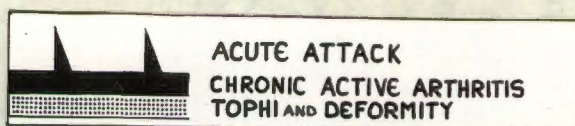
#### Explanation of clinical charts:

Figs. 49 and 50 represent patients who had acute attacks of gout only, without any interval symptoms. Patients with all degrees of 'chronicity', in addition to acute attacks, constitute Figs. 51 and 52.

As an indication of the effect of renal impairment on the clinical results of benemid therapy, those patients with disturbed renal function - by the criteria outlined - have been drawn separately within the acute and chronic groups, and form the second figure in each (Figs. 50 and 52).

The clinical course of every patient studied is indicated for the 24-month period preceding the onset of benemid therapy. This was derived from meticulous and repeated questioning about the details of acute attacks and of the interval condition, with specific attention to concrete items of evidence such as duration of enforced bed rest, absence from work, ease of every-day activities (dressing, walking, climbing and descending stairs), state of joints on waking, liability to precipitation of attacks, periodicity of attacks, need for taking medicines, intercurrent illnesses, and the like. In addition, several patients were observed personally for some months before starting treatment, and a few

had well documented hospital records as a check on the currently taken history.



—KEY to clinical diagrams in Figs. 49-52 and Fig 66—

From the time of beginning benemid administration, the clinical progress of each patient, as observed personally from questioning and examination at repeated attendances, is charted until the present, the individual periods of study varying from 6-30 months.

An attempt was made to chart the severity of attacks, and the degree of chronic pain and stiffness, and the extent of tophi plus mechanical disability, on a quantitative basis as well as temporally. The results are necessarily somewhat arbitrary, but represent careful comparison of relative disabilities among the whole group and of each patient's condition before and after commencing treatment.

In the bottom right-hand corner of each chart is a short vertical line indicating a 'standard' acute attack, of typical intensity, involving one site only. The height to which each patient's acute attacks rise above his base line or his chronic symptoms was determined by the clinical intensity of symptoms and signs in as many joints as were affected each time. The width of each attack indicates roughly the time taken to return to the pre-attack level of symptoms.

2. Acute attacks

(a) Difficulties in assessment. Few patients refrained from minutely reporting trivial or transient joint pains, which in fairness were usually then recorded as mild acute attacks. Such symptoms previously might not have rated as attacks when the patient gave his clinical history, with the result that merely by attending at the gout clinic the patients' recorded frequency of attacks was likely to rise while on benemid. Careful weighing, therefore, of what did or did not constitute a typical episode of acute gout had to be done in each case, and while relatively easy in those not yet suffering from interval symptoms, differentiation in those subject to

Figures 49-52: Diagrams of clinical records of 43 gout patients, during 24 months before commencement of benemid therapy and during period of treatment.

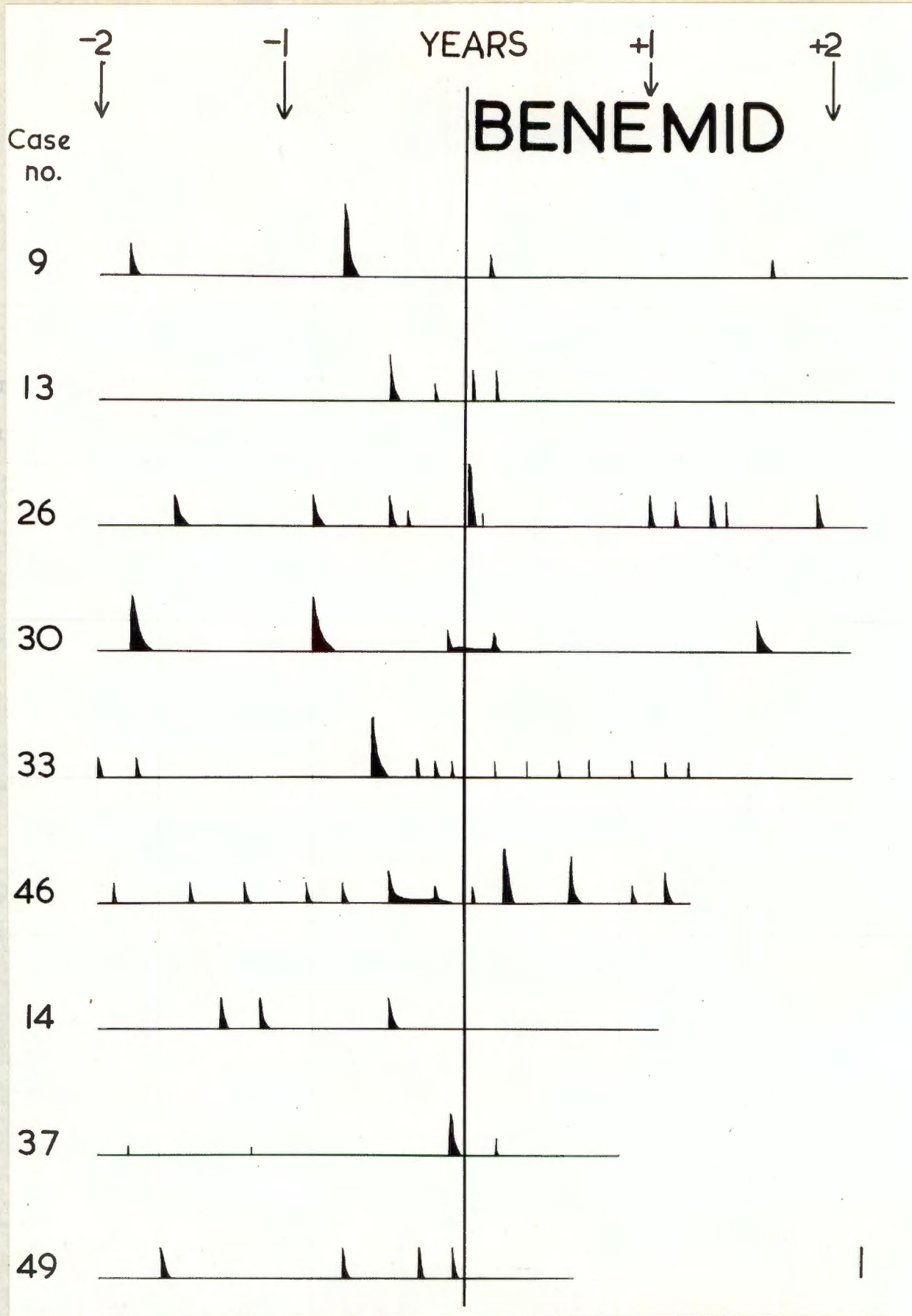


Fig. 49. (Nine patients). Status: Acute attacks only; no renal impairment.

- Diagram of clinical record during 24 months before benemid and during period of treatment.

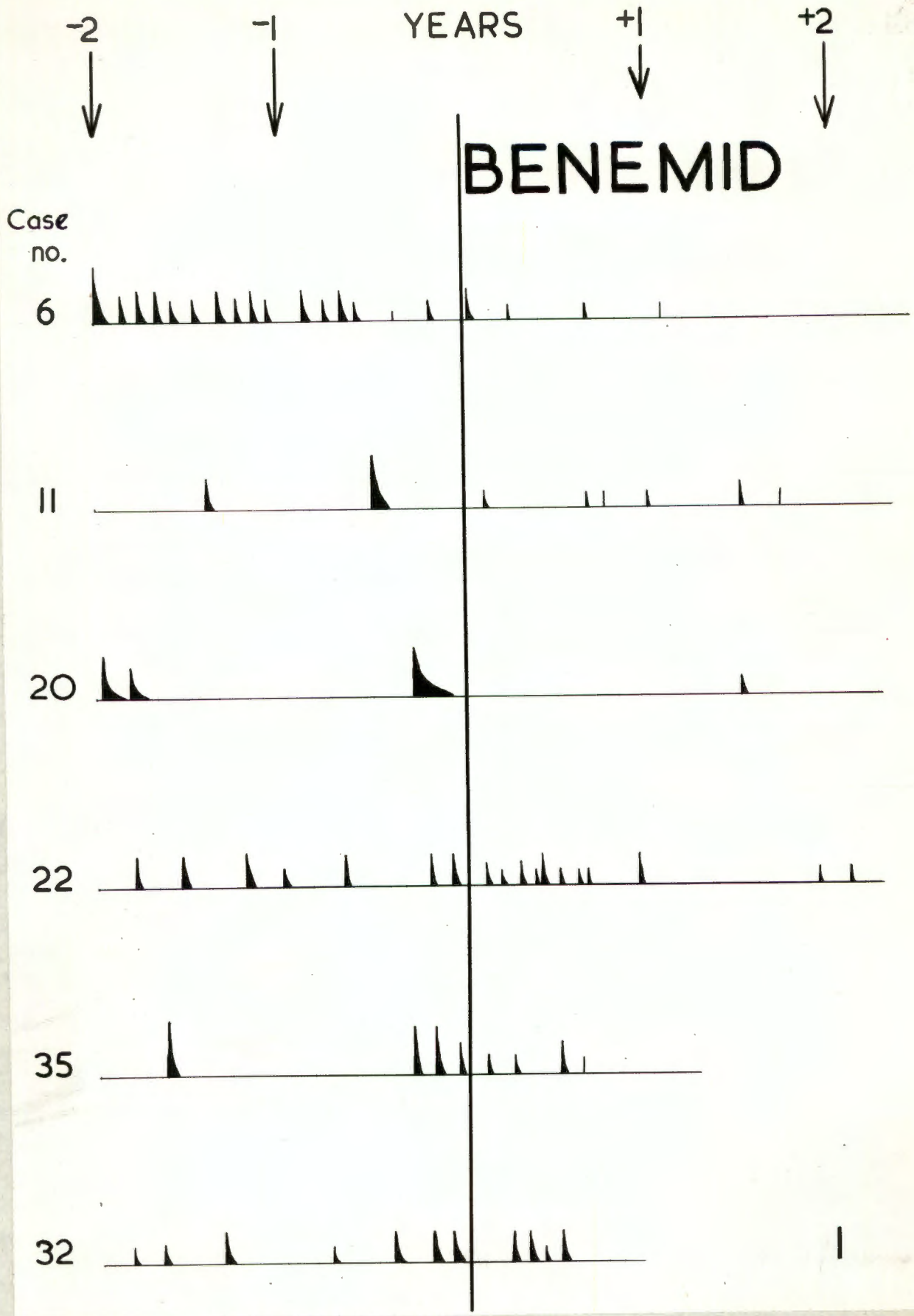
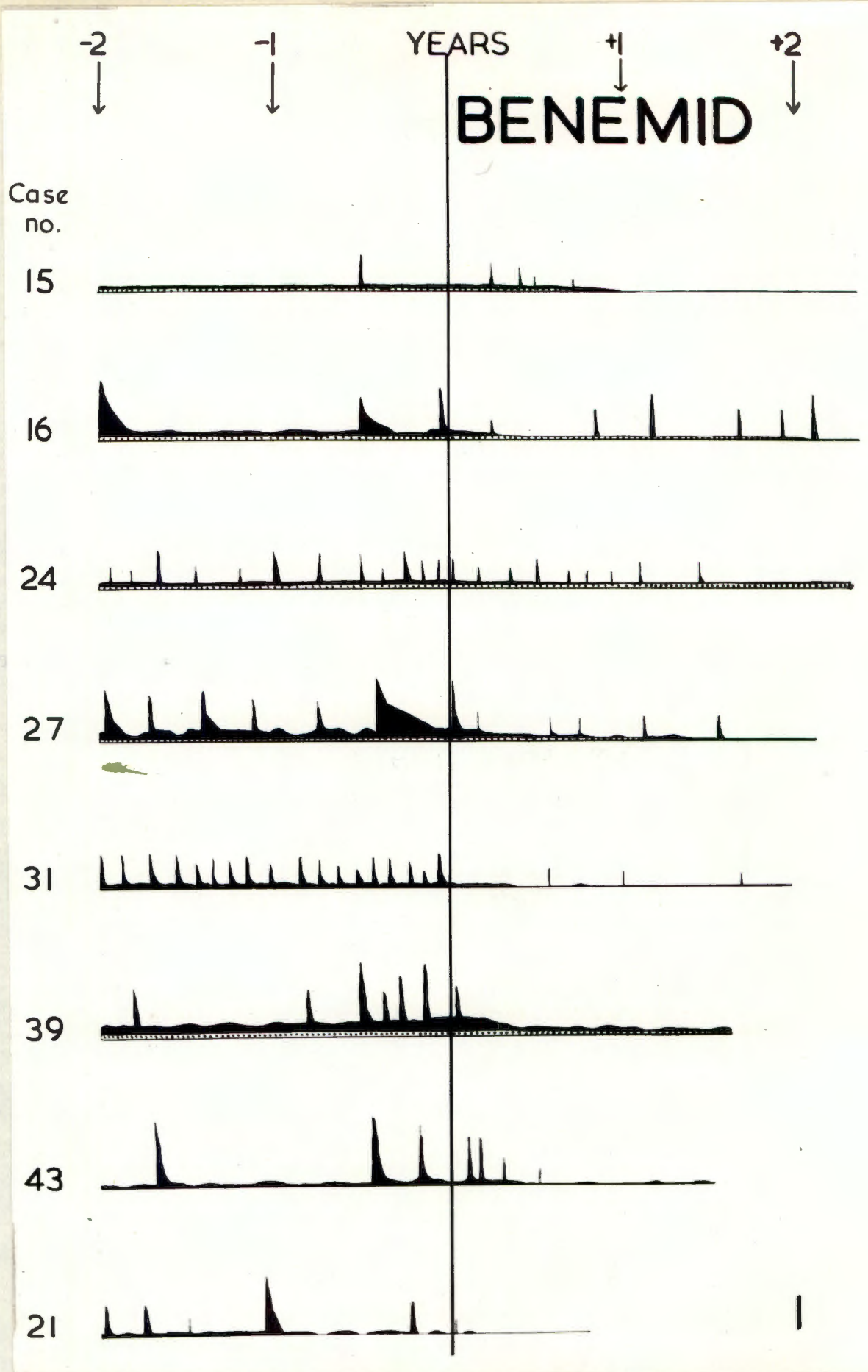


Fig. 50. (Six patients). Status: Acute attacks only; varying renal impairment.  
Computed frequency of attacks for 15 patients in Figs. 49 & 50.  
Pre-benemid { average 24 months } : One in 5.1 months, per patient.  
Benemid { " 21 " } : One " 5.6 " " "

Fig. 51. (16 patients).

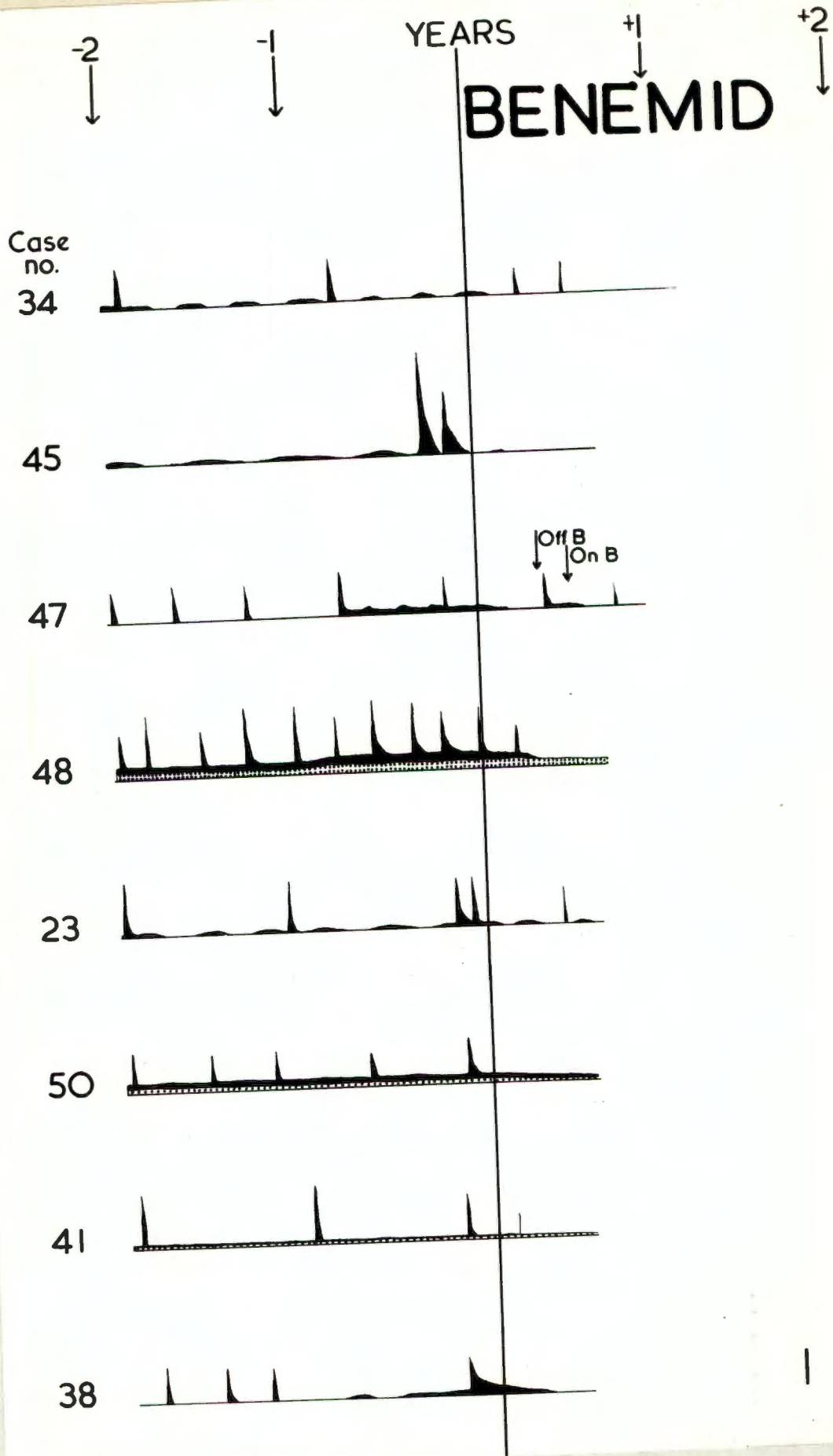
Status: Chronic symptoms; no renal impairment.



(Fig. 51)

Computed frequency of attacks for 16 patients:-

Pre-benemid (average 24 months): One every 4.4 months, per patient  
Benemid ( " 15 " ): " " 6.0 " " "



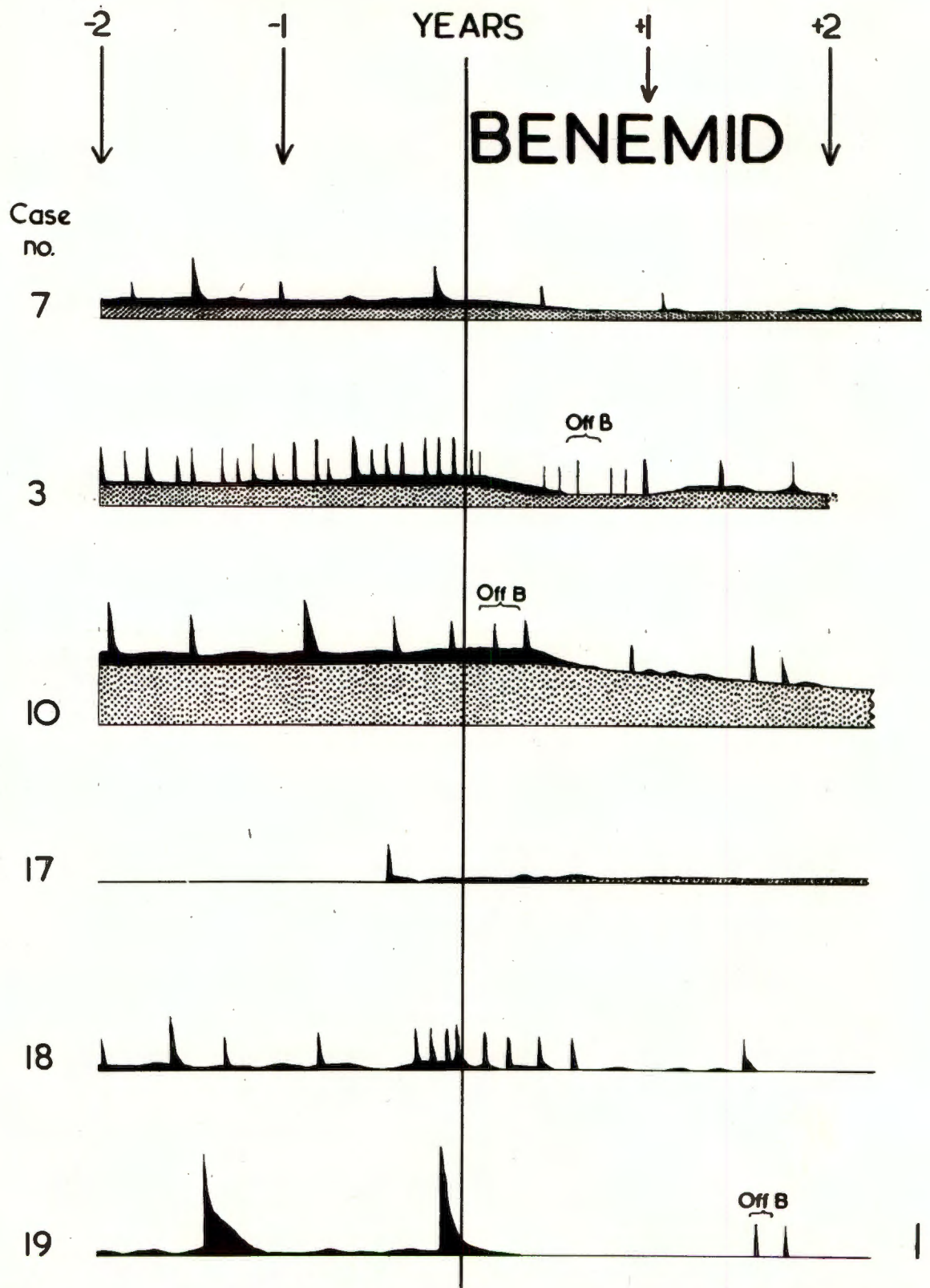
(Fig. 51, contd.)

Change in chronic, active articular symptoms in 16 patients:

Diminished . . . . .	13
Unchanged . . . . .	2
Inconclusive . . . . .	1.

Fig. 52. (12 patients)

Status: Chronic symptoms;  
varying renal impairment.

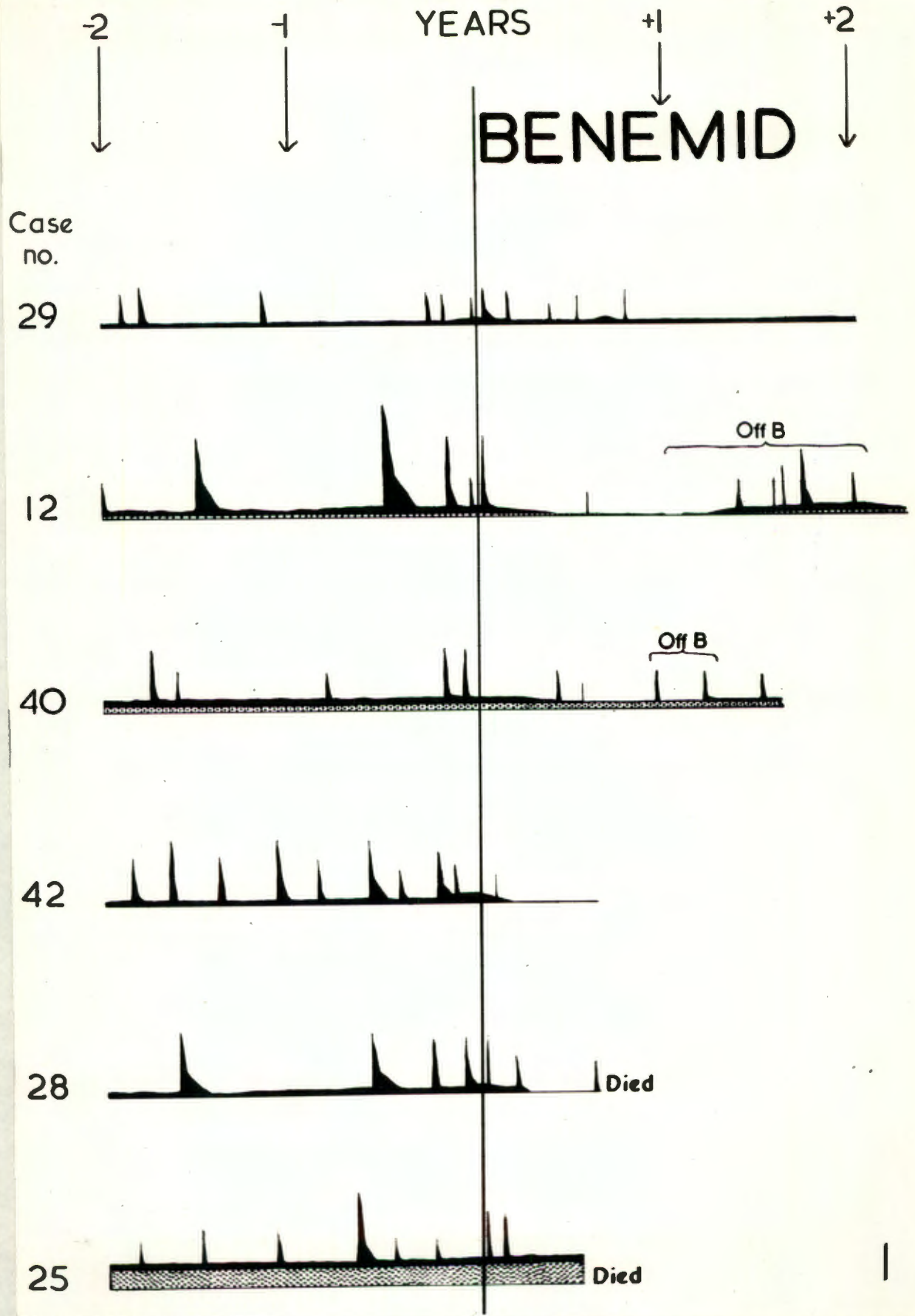


(Fig. 52).

Computed frequency of attacks for 12 patients:-

Pre-benemid (average 24 months): One every 3.9 months, per patient

Benemid (average 19 " ): " " 6.1 " " "



(Fig. 52, contd.)

Change in chronic, active articular symptoms in 12 patients:

Diminished . . . . .	9
Unchanged . . . . .	3

fluctuating joint pains was often difficult.

Against this factor, however, was the uncertain effect of timely colchicine therapy for threatened or florid attacks, in tending to reduce the frequency with which acute episodes occurred or were reported. Patients were enjoined to reserve such measures for 'real' attacks, which most did, but then the severity of the reported episode would be less than that usually experienced by the patient. Of greatest value in assessing the influence of benemid on this aspect of gout, therefore, were those patients (the minority) who already knew colchicine well and had followed a certain course despite its full use.

Equally valuable in judging altered incidence of attacks were those patients whose usual pattern of acute gout was a high-frequency one (e. g., four, five or many more attacks annually). Patients experiencing fewer annual attacks, however regularly, would require to be followed for much longer than one or two years before deciding the significance of any alteration in frequency.

(b) Clinical findings.

(1) Frequency. The 43 patients treated with benemid alone received it for an average period of 18.5 months (range 6-30 months). Computed purely arithmetically, the average rate of acute attacks per patient had been one in 4.5 months (based on the 2-year period before benemid), and was one in 6.0 months for the period of continuous benemid therapy. Similar calculations (Figs. 51 and 52) for those with and without renal impairment showed no appreciable differences. Expressed in terms of individual cases, the frequency of acute attacks was arithmetically less in 26 of the 43 patients, and greater in sixteen.

Clinically speaking these figures do not represent a predictable or impressive effect of benemid on the incidence of acute attacks, especially bearing in mind the difficulties cited above. Mention has been made of the inexplicable liability to acute gout during the first 2 or 3 weeks of benemid administration, if colchicine is not taken in prophylactic doses during that period. Subsidence of such an attack has not been followed by recurrences as clearly attributable to the use of benemid, but a phase of quite unaltered - and perhaps slightly increased - frequency ensues in several patients (Figs. 49-52).

However, continued therapy (in those patients with a sufficiently definite pattern of attacks) appears to result in a significant diminution in the number of attacks occurring after a period of 6-12 months or more from the time of beginning benemid. Illustrations of this tendency are provided by the diagrams of cases 33, 6 and 22 in Figs. 49 and 50, of cases 24 and 27 in Fig. 51, and of cases 18 and 29 in Fig. 52. Talbott<sup>118</sup> gained the identical impression in his recent publication. It is clear, however, that the suppression of occurrence of acute attacks is by no means a cardinal action of benemid, nor is it apparent at all in the majority of patients to date.

(ii) Ease of precipitation of acute episodes by particular items, in those recognizing such factors, was enquired after during benemid therapy. Fourteen were able to pass opinion on this point, but only six felt that their liability to acute gout after episodes such as traume, exercise or parties had diminished while on treatment. In the other eight, items which had previously provoked an attack - usually injuries or strains incurred through work or exertion - continued to do so. It seems reasonable that such a result should parallel that for the over-all liability to attacks.

(iii) Severity of attacks as a function of benemid therapy was almost impossible to assess, as nearly all the patients benefited at our hands from improvements in the treatment of their attacks. Several averred that the episodes had altered in intensity, and reference to the clinical charts shows this to be true for the majority; but in few, if any, could the effects of colchicine (used for the first time, or more promptly, or in larger dosage, or combined with ACTH) be discounted in judging the attack itself.

### 3. Chronic active arthritis

(a) Difficulties in assessment. Of all three modalities of joint disturbance being considered, that of persistent articular pain or stiffness between acute episodes is the least objective. Evaluation of its severity before treatment is difficult, and changes subsequently reported by the patient must be distinguished from the psychological benefits experienced in his newly found circumstances of care and interest. Patients were always required to express their interval symptoms not only in terms of absolute discomfort but of interference with daily domestic or occupational activities. Any improvement recorded was felt, therefore, to be genuinely experienced, whether entirely as a result of benemid administration or merely in association with it. Signs of persistent low-grade inflammation (unresolved effusions in joints, overlying warmth), also falling under this heading, were more easily gauged objectively.

Criticism must also be met concerning the possible long-term benefits which effective termination of acute episodes confers on the course of the disease. Special attention in assessing these symptoms was therefore paid to those patients who had already exploited colchicine to the full without benefit, and to those few with prominent chronic symptoms in whom acute attacks (with their periodic need for 'extra' measures) were infrequent.

(b) Clinical findings. It may be seen from Figs. 51 and 52 that of all the clinical features of gout, that of chronic active arthritis (shown by the horizontal black layer in the diagrams) underwent the greatest degree of improvement during continuous benemid administration. Among the 43 patients receiving benemid alone, 28 started treatment in a state of chronic gouty activity. Relief of pain and stiffness and - in those showing it - of low-grade inflammation in joints, began to be felt by all but 6 of the 28 after a typical lag period of one to three months. Those who experienced 'post-benemid acute gout' found, on recovering from the episode (which hardly raised their initial enthusiasm), that slowly progressive improvement was taking place in their state of articular comfort and ease of daily activities.

The six patients in the group who reported no reduction of interval symptoms included only one whose condition was

disabling when treatment began (case 25). He was a debilitated old man with advanced gout who died at home of intercurrent infection six months after starting to take benemid, without subjective or objective relief of pain and stiffness during the period of observation. The others reporting no benefit included 3 patients (23, 50 and 41 in Fig. 51) followed for only six or seven months without definite alteration in previously minimal symptoms. In only two patients, therefore, (cases 17 and 29 in Fig. 52) were moderate interval joint symptoms not relieved by long continued uricosuric therapy with benemid.

On the other hand, among the 22 showing a clinical response were 15 who had previously suffered significant interference with their daily activities. All improved considerably, in some cases to a remarkable degree (nos. 16, 27, 31 and 48 in Fig. 51; and 7, 3, 10, 12 and 42 in Fig. 52). Among the latter were a few with advanced structural joint changes who lost all chronic discomfort other than residual mechanical disturbance. One of them (case 48), despite tophaceous deformity of both hands, was enabled to return to full time work as a lorry driver after an absence of a year. Cases 27 and 31 were both labourers whose frequency of attacks and persistence of interval symptoms took heavy toll of their number of annual working days in the two years before receiving benemid. The onset of uricosuric therapy marked the beginning of great clinical improvement, not attributable to concomitant treatment of acute episodes, which fell sharply in frequency.

The writer was struck by the constancy of an initial delay preceding the relief of chronic active arthritis. Two implications were attached to this observation: (a) it militated somewhat against a purely psychological mechanism of clinical improvement which, in a susceptible patient, might have occurred with illogical rapidity; (b) it conformed to the theoretical manner in which benemid, by constant uricosuric action gradually resulting in a negative urate balance, might relieve joint symptoms by preventing further urate deposition and possibly draining some already present.

Patients with renal impairment were not observed to respond differently, in terms of chronic gouty symptoms, from those with intact renal function. This constitutes important clinical confirmation of the effectiveness of benemid as a uricosuric agent in the presence of renal disease.

#### 4. Tophi and structural joint changes

(a) Difficulties in assessment. A joint or tophus which has recently been the seat of an acute attack, and is spuriously stiff or enlarged at the time of measurement, may lead to false conclusions about the effectiveness of uricosuric therapy begun during the process of subsidence. Tophi of the ears are liable to spontaneous extrusion or removal by the patient, which are factors to be excluded in observing changes. Tophaceous expansions of joints are more easily judged photographically than by serial plaster casts or caliper readings, but even the camera may mislead if details of angle and lighting are overlooked.

#### (b) Clinical findings.

(i) Tophi. Nineteen of the 43 patients treated with benemid alone had external tophi on commencing treatment. At the time of writing, 6-30 months later, reduction in size has taken place in 5 cases, no alteration is detectable in 12, and in 2 a tophus has burst and discharged.

The tophi which became smaller were on the ears in 4 of the 5 cases. In one extrusion may have been responsible (Fig. 54). In two others, the tophi had been pin-head in size and disappeared in the first year of therapy (cases 27 and 30), and the fourth underwent slight shrinkage (case 37). The greatest degree of reduction in size of tophi is shown by the patient in Fig. 58 (case 7), an old man with advanced tophaceous gout whose biochemical and clinical responses to benemid were excellent.

It is significant that no new tophi have appeared in any patient during the period of benemid ingestion, despite the fact that many already had deposits which might have been expected to increase in size and number (Fig. 53). This speaks volumes for the success of uricosuric therapy in preventing urate deposition. Evidence of urate removal, on the other hand, while a remarkable phenomenon when it occurs, has on the whole been unimpressive.

The two tophi which burst (cases 3 and 25) were both of many years' standing and already distending the skin overlying easily injured sites. Their eventual abrasion and discharge while on benemid therapy came as no surprise.

(March 1953)

(September 1954)

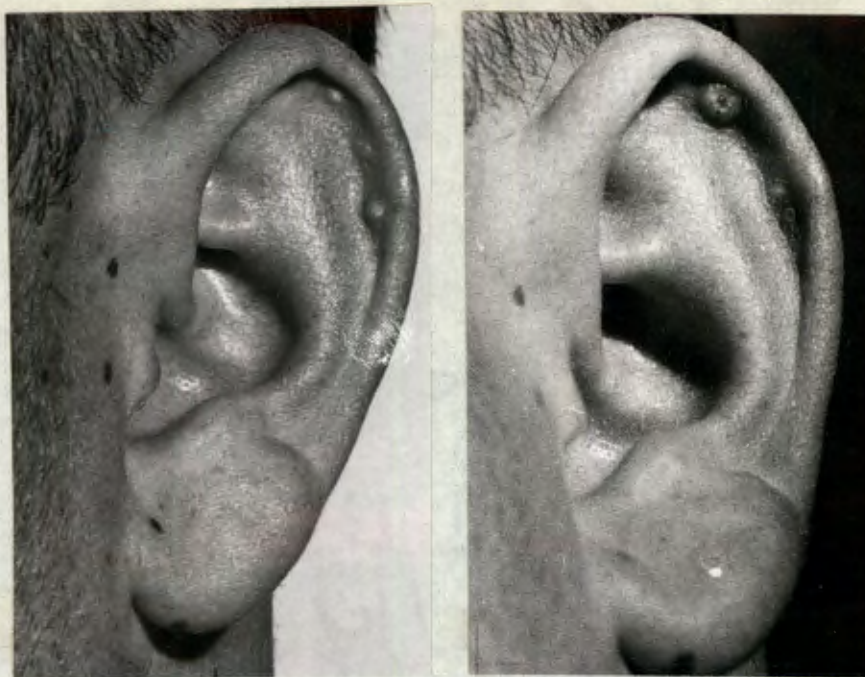


Fig. 53. (Case 137). Enlargement of ear tophi during 18 months in a patient with renal failure not receiving benemid.

(May 1952)

(May 1954)

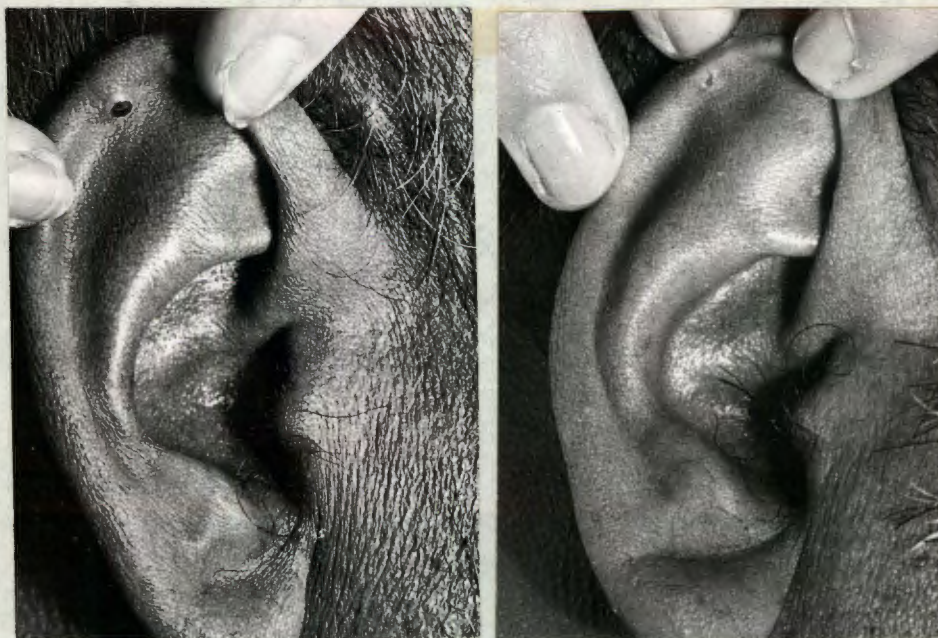


Fig. 54. (Case 10). Change in ear tophus during 24 months of benemid therapy in patient with crippling, tophaceous gout. Note partial extrusion of tophus before benemid began, rendering the evidence unreliable. No new tophi have appeared, however, and the patient's joint state is much improved.

(Jan. 1954)

(Sept. 1954)



Fig. 55. (Case 48). No change in ear tophus after 7 months of benemid administration. (Joint symptoms significantly less. Part of the ear nodule may be overlying fibrous thickening).

(Feb. 1952)

(Aug. 1952)



Fig. 56. (Case 3). No apparent change in foot contours after 6 months of benemid therapy; mobility of great toe improved. (Cf. Fig. 63).



Fig. 57. (Case 7). Improved fist closure after 10 months of benemid therapy.



Fig. 58. (Case 7).

Impressive shrinkage of urate deposits during 26 months of regular benemid ingestion. Compare

(a) lump in right extensor tendon;

(b) uratic expansion of both middle fingers,



in each photograph.

(Above - July 1952; below - September 1954).

(ii) Rigidity and deformity. Among the 28 patients with chronic symptoms depicted in Figs. 51 and 52, there were 15 in whom two or more joints showed restricted mobility of a permanent kind, not reflecting inflammatory pain or stiffness. Common sites for this feature of advanced gouty joint degeneration were both great toe joints, often together with adjacent mechanical difficulty in the mid-foot and ankle joints, and associated wrist or fist impairment. The worst cases (no. 48 in Fig. 51, and nos. 7, 3, 10 and 25 in Fig. 52) were partially or totally crippled by polyarticular rigidity and tophaceous deformity, associated with variable grades of chronic, active, inflammatory symptoms, and acute episodes of high or low frequency.

In 10 of the 15 patients with structural impairment of joints, convincing objective evidence of slowly improving range of movement was forthcoming, in addition to the important functional benefit of diminished pain and stiffness. Such mechanical improvements usually took six or more months to become perceptible, and led in the milder cases (limited toe or ankle mobility) to a normally functioning joint. In the majority, however, there appears understandably to be a limit beyond which loosening does not progress. The patients with the worst joint degeneration cited above still have disabling chronic arthritis (case 25 having died unimproved after six months); but each is highly satisfied with his own improvement. In case 7 movements of the hands and lower limbs have become freer, in case 3 a hobbling gait and great difficulty with stairs have been replaced by a relative nimbleness permitting formal dancing, and case 10 - progressively crippled since his earliest attacks - has stood out of his wheel-chair and walked with crutches for the first time in the past few years. Considering the degenerative nature of late gouty arthritis, even these degrees of improvement from uricosuric therapy are surprisingly gratifying, and emphasise the preferability of preventing urate deposition in the first instance.

Of the 5 patients in whom rigidity has remained unchanged, one died before any alteration in his degree of crippling took place, three have moderate permanent stiffness in the lower extremities which has not improved, and one (case 17, an elderly woman observed during and since her first attack) has experienced progressive fixation of a metatarso-phalangeal joint despite chemically successful uricosuric therapy. The explanation seems to lie in the development of osteoarthritic changes as a sequel to gouty arthritis (Fig. 60).

Results in this category were also uninfluenced by renal disease.

(Jan. 1952)

(Sept. 1954)



Fig. 59. (Case 13). Absence of progression, and possibly re-calcification, in uratic erosions near first metatarso-phalangeal joint. (Thirty months of benemid therapy).



Fig. 60. (Case 17). Changes in first metatarso-phalangeal joint of a woman gout patient during 31 months on benemid. The original area of rarefaction - presumably uratic - has diminished and sclerosed, but progressive hypertrophic degeneration has aggravated the joint state.



September  
1951

(3 months  
before  
benemid).



February  
1953

(15 months  
of benemid  
therapy).

Fig. 61. (Case 1). No appreciable changes attributable to uricosuric treatment. If anything, destructive changes in the index finger have increased slightly. However, no new lesions have appeared during a course which was previously progressive. (Amputation of a finger preceded the beginning of benemid therapy).



Fig. 62. (Case 1). Close-up of left 5th finger in Fig. 61, illustrating the difficulty of radiological assessment. The middle phalanx and joint outline appear to have deteriorated, while partial bony healing may have occurred in the head of the first phalanx. (15 months on benemid).

(May 1952)

(June 1953)



Fig. 63. (Case 3). The bony lesion medial to the first metatarsophalangeal joint has completely closed during 13 months of benemid therapy, and the tophaceous gap across the inter-phalangeal joint has narrowed. Presumably this signifies urate absorption, as the soft-tissue swelling is no bigger, and none has discharged.



Fig. 64. (Case 7). Radiographic evidence of successful uricosuric therapy (26 months of benemid). The most convincing change is diminution of the lesion in the left first metatarso-phalangeal joint, with closer approximation of its two edges. In addition, numerous 'cysts' in the foot bones are less obvious in the 2nd photograph, which may not entirely be due to differences in x-ray penetration.

## 5. Radiographic signs

(a) Difficulties in assessment. When seeking subtle radiographic changes during the course of uricosuric therapy, comparison of serial films may be completely vitiated by small differences in the technique on each occasion, as rarefactive lesions vary widely according to the penetration. Other difficulties concern the interpretation of findings, and emerge from the illustrations in Figs. 59-64. Specially puzzling is the significance of a cystic urate lesion which decreases in size; does it mean actual gouty progression, with weakening of the surrounding bone to the point where normal stresses impact or collapse the edges, or is it a direct result of urate absorption? Presumably the absence of increased soft tissue bulging or sinus formation would favour the latter interpretation (Figs. 63 and 64).

(b) Results. Serial radiography twice annually failed to show a single instance of definite progression of gouty lesions which were present at the onset of benemid therapy. In no case, moreover, did a single new area of erosion appear. While it is impossible to predict the usual rapidity of development of lesions seen radiographically, it is reasonable to think that some evidence of urate deposition would normally have appeared in this time among so many patients, several of whom were deteriorating before treatment.

Signs of radiological improvement in gouty lesions during uricosuric therapy have thus far been absent or arguable, and the likeliest instances are demonstrated in the accompanying photographs. In a few other cases, radiologists have commented on increased bone density surrounding lesions of unaltered size, but the effect of different x-ray penetration could not be excluded. It is likely that some of the changes shown in Figs. 59-64, notably those in cases 3, 7 and 17, signify slow regression and healing of bone lesions in patients taking benemid for many months. It is understandable that such changes should take longest to be recognized, and that they should be limited in extent. Hitherto, no reports have appeared to the writer's knowledge of similar alterations in gouty lesions seen radiographically, although the absence of progression and of new appearance has been remarked 59, 118. In his study of prolonged salicylate therapy 88, Merson has observed three patients with

x-ray signs of decreased erosions and recalcification of bone, essentially similar in appearance to the present cases. Further study may confirm this as another beneficial result of effective uricosuric therapy; its role in the prevention of such lesions is already strongly suggested by the available evidence.

## 6. Toxicity and systemic effects of benemid

(a) Toxic reactions. No definite side effects were encountered during the long-term administration of benemid in daily dosage of 1.5 G., and no patient had to discontinue taking the drug because of intolerance. Symptoms mentioned by a few patients, at different times in the course of treatment, were: mild dyspepsia (3), morning headache (3), polyuria (2) and dermatitis of the ears and eyelids (1). In no case was benemid definitely inculped, and nearly always the symptom had gone at the time of the next visit. Those mentioning dyspepsia blamed the combination of the potassium citrate mixture with benemid, and were advised to take benemid alone, preferably not on an empty stomach. Polyuria, requiring the patient to pass urine two or three times nightly, may have been due partly to the ingestion of potassium citrate, since a significant pharmacological effect of benemid on salt and water excretion has not been stressed. Stopping benemid medication for a month in the patient with an exudative dermatitis, and then re-starting it, had no effect on its course for better or worse, the lesion slowly subsiding while benemid continued to be taken.

### (b) Systemic effects

(i) The liability to occurrence of acute gout in the first few weeks of benemid therapy, noticed early in this study, has been mentioned. The use of 3 or 4 tablets of colchicine (gr. 1/100) daily together with benemid for the first three weeks, rarely fails to prevent this puzzling phenomenon, for which no adequate explanation has been found.

(ii) No instance of urinary tract complications resulting from urate crystalluria occurred in this series. It is probably important to maintain a high water intake during continuous benemid therapy, especially in the first few weeks, during which the ingestion of an alkali like sodium bicarbonate

or potassium citrate may be advisable as well.

(iii) As observed in connection with renal function during benemid therapy, no significant pattern of change occurred in the cardiovascular - renal status of patients taking the drug for long periods. Blood pressures were recorded regularly (Table 14) and showed no changes attributable to using benemid. The wide variability of individual readings, especially when abnormally high, was a reflection of the difficulties of assessment in hypertensive studies.

In addition to variable rates of progression of previous renal disease in some patients, three of the 50 (one of whom was also receiving cortisone) sustained myocardial infarction at intervals of up to two years after starting to take benemid. It would be reasonable neither to ascribe these complications to the drug itself, nor to blame it for failing to prevent their occurrence. Only greatly prolonged observation would justify conclusions about the possible mitigating effect of continuous uricosuric therapy on the vascular and renal conditions associated with gout.

(iv) A final interesting observation concerns the subjective feeling of well-being experienced by a large proportion of patients within a few weeks of starting therapy with benemid alone. Admitting the intangibility of such a finding (which was clearly differentiated, by 14 of the 43 taking benemid, from any improvement in symptoms of pain or discomfort), the writer noted with interest the monotonous similarity of these patients' testimonies. Six of the 14 had been classified as having acute attacks only, without any interval features whatever; the other eight belonged to the 'chronic' group. All volunteered, after a period of about 3-12 weeks on benemid, that they were feeling 'fitter' than ever before, more zestful and energetic, less 'tired', 'wonderful' and rejuvenated. Those taxed with never having indicated that they felt otherwise before (out of attacks), accepted the remark but defended the truth of their newly found well-being. Such a state of affairs led in some cases to a patient, whose frequency of attacks had remained unaltered during the first year, claiming clinical improvement during that period.

The constant lag period before such information was volunteered, by those who did so, lends a little more credence to a clinical observation which might otherwise not merit it.

The interesting, if as yet faint, possibility exists that the uricosuric action of benemid is coupled with an unknown effect on steroid metabolism, producing subjective symptoms comparable to those arising during cortisone or testosterone administration. The reported observation that urinary 17-ketosteroid excretion was diminished by benemid<sup>50</sup> may in fact prove to be clinically significant.

## 7. Clinical conclusions

Prolonged administration of the uricosuric agent benemid represents an important advance in the successful management of gout. Its particular advantages are great biochemical potency and negligible - if any - toxic effects.

Varying degrees of benefit from its use result in most of the clinical features of gout. Its greatest therapeutic value seems to lie in relieving the chronic, active, articular symptoms present between acute episodes in those patients with gout usually of some years' standing. Of 28 patients with such symptoms, 22 experienced definite improvement, which, to 15 of them with considerable previous disability, meant complete or partial freedom from pain, stiffness and low-grade inflammation in the interval periods.

The effect of benemid on the incidence of acute gout during this study is less well defined. There is almost no doubt that a small proportion of patients enjoy a greatly reduced frequency of attacks quite soon or several months after starting benemid, not attributable to the concomitant use of other medication. In most others, an apparent slight reduction will require a longer period of observation for critical appraisal. In a few, finally, as many or more attacks have followed the onset of benemid therapy as preceded it, though usually of diminished severity, and further study may show whether or not this pattern might yet change for the better.

A gratifying result of successful uricosuric therapy has been the apparent cessation of urate deposition as judged by the absence of newly appearing tophi or of enlargement of those present. In addition, a few tiny tophi have disappeared, and in one patient after prolonged benemid ingestion larger urate deposits have

undergone unequivocal shrinkage. Generally, however, evidence of alteration in established tophi has been less impressive than the fact that they have ceased to be formed. Joint impairment by rigidity and tophaceous deformity, in late cases of gout, has undergone pleasing if limited improvement in the majority of those having it previously.

Radiography has revealed no new lesions suggestive of gout during periods of up to 30 months of benemid therapy, which is regarded as significant for at least some of those who already displayed considerable abnormalities. A small number of patients, moreover, showed radiographic changes believed to represent slow absorption of bone tophi.

The handful of possible side effects occurring during prolonged administration of benemid were temporary, never related with certainty to the drug itself, and never required cessation of therapy. This finding is in prominent contrast to other established uricosuric agents, of which even the most harmless - salicylate - is not devoid of some unpleasant effects in the dosage used, especially in patients with substantial renal disease<sup>89</sup>. Benemid is especially pleasing in view of its relative biochemical and clinical effectiveness, and lack of increased toxicity, in the presence of renal impairment.

No appreciable changes occurred, during this study, in patients' renal, hypertensive or vascular conditions that were not explicable by their natural course.

The degrees of clinical improvement recounted above all began at varying intervals after the onset of benemid therapy, relief of chronic active symptoms usually taking a month or two, shrinkage of tophi half a year or longer, and x-ray improvement (if such is their interpretation) at least one or two years. Such delays are compatible with the mechanism by which benemid is believed to produce its effects, and for that reason more than passing attention has been paid to a feeling of improved well-being warmly claimed by a third of the patients, with or without synchronous relief of gout symptoms, after a similar lag interval. If not due to an addition action of the drug on tissues or on pituitary-adrenal functions (as is the case for some uricosuric agents), the thought is posed whether the hyperuricaemic state - which benemid corrects - may possibly be detrimental not only to joints, and perhaps to blood vessels and kidneys, but to the subject's ordinary sensation of active health.

E. BENEMID THERAPY COMBINED WITH SMALL DOSES OF CORTISONE

1. Premises of treatment

Seven of the 50 gout patients in whom the effects of benemid were followed received, in addition, 25-50 mg. daily of orally administered cortisone acetate. This measure was based on the combination of the following properties of cortisone:

(a) It has a mildly uricosuric action in company with the group of 11-oxysteroids<sup>124</sup> which is less pronounced than that of ACTH but might theoretically be of slight additional value in the management of gout.

(b) It has a powerful non-specific antiphlogistic action<sup>121</sup>, inhibiting the manifestations of many inflammatory processes and the cellular and humoral reactions to many irritants. Despite the intensive use, through the years, of various drugs such as salicylate, cinchophen and colchicine for preventing the occurrence of acute gout and the prominent interval symptoms of long-standing cases, no completely satisfactory measure is available for inhibiting acute or chronic gouty activity in certain severe cases with a high-frequency pattern and little freedom between. The best of the available anti-inflammatory measures in gout, in terms of relative safety and effectiveness, has been colchicine, and several authorities testify to the success which crowns its persistent, judicious use<sup>59, 118</sup>. There is no doubt, however, from the literature and from personal experience, that colchicine alone is not the complete answer to the problem of suppressing gouty inflammation.

The use of continuous colchicine medication together with benemid held promise, even before these studies began, of being more effective than either alone in the over-all management of gout, and Gutman and Yü do in fact pursue this regime with considerable success<sup>59</sup>. In deciding to combine benemid with maintenance doses of cortisone, however, the possible significance of the following premises was taken into account:

(c) Implication of the adrenal cortex in gout. Evidence

that adrenal cortical function was disturbed in patients with gout has come from two main directions. Talbott, Jacobson and Oberg<sup>119</sup> had some years ago described what they believed to be a characteristic pattern of adrenocortical disturbance before, during and after an attack of gout, in which spontaneous changes of electrolyte metabolism, reminiscent of Addison's disease, occurred briefly before the clinical flare-up. More recently, Wolfson and others<sup>124, 100</sup> have postulated two other disturbances: (i) An abnormal 'gouty' androgen is believed to originate in the adrenal cortex and give rise to the hyperuricaemia of gout by influencing urate metabolism; (ii) the gout patient is visualised, on the basis of various quantitative indices, as being unable to sustain stressful stimuli (among which may be included some of the precipitants of an attack) by an adequate response of pituitary-adrenal secretions. During the temporary phase that follows, in which there is relative deficiency of adrenocortical function, the phenomena of acute gout are thought to be released. Those attacks which occur spontaneously are explained, in this hypothesis, as resulting from a tendency of the adrenal cortex in gout to undergo spontaneous phases of temporary hypofunction; this ties up with Talbott's demonstration of a metabolic 'gout cycle' with recurrent 'Addisonian' episodes introducing acute gout.

While not entirely convincing, these reports, at the time that investigations began locally, were attractive evidence of endocrine abnormality in gout. Since then, evidence no less sound has appeared<sup>81, 82, 59</sup> tending to refute both the electrolyte and hormonal disturbances previously described in association with episodic gout. In deciding originally to combine cortisone with benemid for the worst cases of gout, who were having innumerable attacks and disabling interval activity, it was intended to suppress the supposed cyclical fluctuations of the patient's own adrenal cortex by continuously administering cortisone in daily dosage of 25-50 mg., an amount able to produce 'functional atrophy' of the gland by depressing its pituitary control. Dosage of this order is considerably less than that used in the empiric treatment of rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus and other acute and chronic illnesses in which no specific deficiency of adrenal function exists. It is comparable, on the other hand, to the amounts used in substitution therapy in Addison's disease or for suppression of the hyperfunctioning gland in the adrenogenital syndrome of young girls.

## 2. Results of treatment with benemid and auxiliary cortisone.

The patients (who are depicted in Fig. 66) included one woman (case 2) and one African native (case 44). Their average age when first seen was 49 years (38-62), and the average duration of clinical gout among them was 16 years (10-40). All were severely incapacitated by a varying mixture of crippling tophaceous deformities, unremitting chronic active gout, and recurrent acute attacks which were usually polyarticular, and - in 5 of the seven - of exceptionally high frequency. Only one patient (case 36) had no structural joint damage clinically, and only one - the woman - no external tophi. Radiographic signs of gout were present in all, and all had unequivocal hyperuricaemia except case 5, who displayed the unprecedented anomaly of proven tophaceous gout with consistently normal serum urate levels. Six of the seven patients had impaired renal function, two of whom were frankly uraemic (cases 2 and 8). Diabetes mellitus was present in the Native patient, requiring daily insulin injections.

The administration of cortisone was begun 2-3 months after benemid in three patients, and together with or just before it in the other four (Fig. 66). The initial dosage was 50 mg. daily (2 tablets) by mouth in each, which was reduced after a variable number of months to 37 and ultimately 25 mg. daily.

(a) Metabolic results. Cortisone as used in these patients had no detectable uricosuric action. For the three who were already on benemid, no further reduction in serum urate occurred, nor was the urate/creatinine clearance ratio further enhanced. Serum urate levels, before and after the addition of cortisone to their programme, are shown in Table 15, using, as was done previously for benemid, the mean of the 3 lowest values in the month before cortisone, and the mean of the 3 highest values in the first month of cortisone administration.

Patient	Serum urate level (mg./100 ml.)	
	Benemid alone	Benemid + cortisone
Case 4	6.5	6.9
Case 5	2.7	2.8
Case 8	5.1	5.7

Table 15. Serum urate levels in 3 gout patients receiving benemid, before and after the addition of cortisone 50 mg./ day.

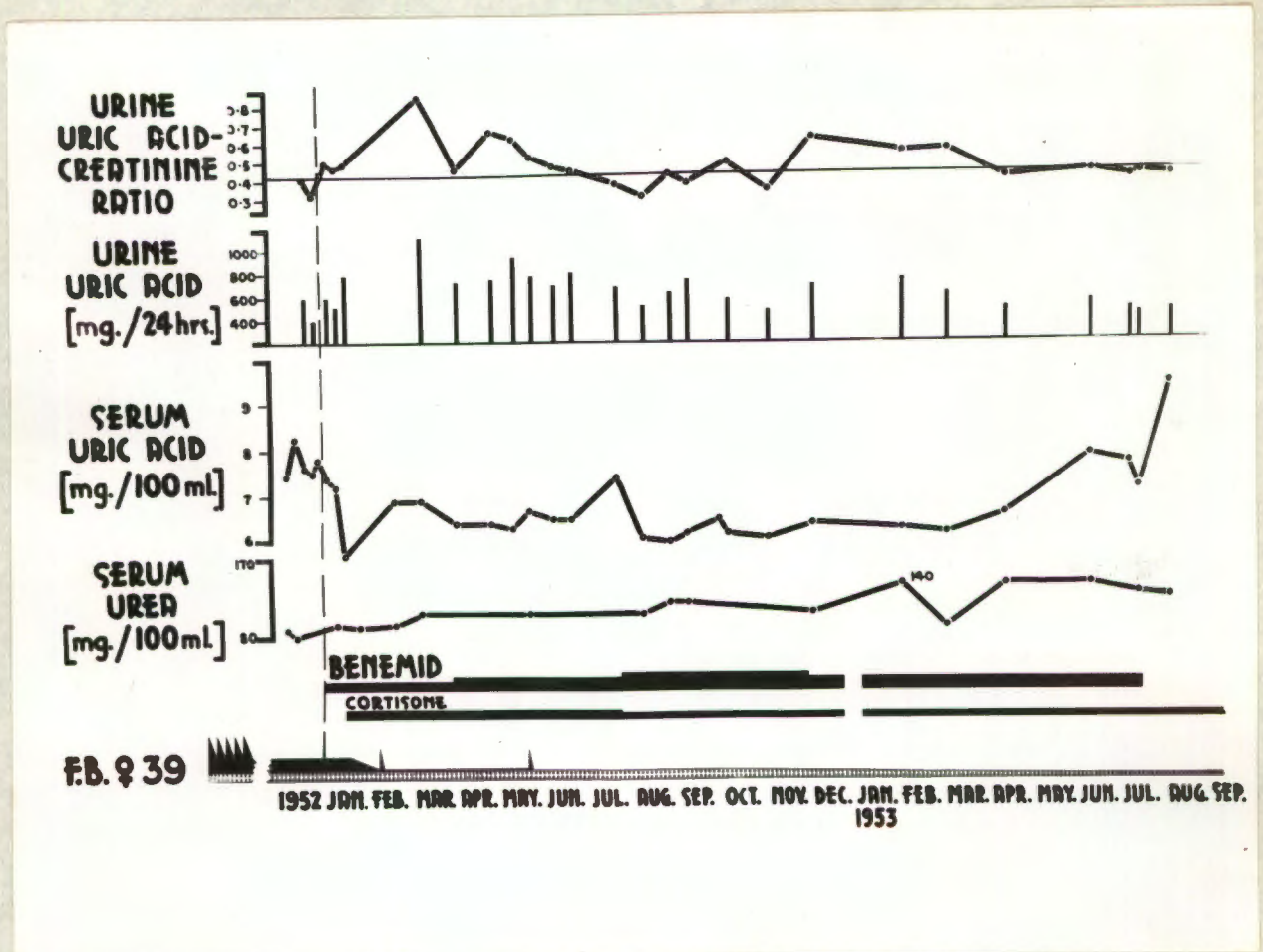


Fig. 65. (Case 2). Clinical and biochemical changes in a woman with gout and chronic, progressive, renal failure, during 18 months of combined benemid and cortisone administration (1 - 2 G. and 37-50 mg. daily, respectively).

- Note
- (a) Definite uricosuric response in a uraemic patient;
  - (b) Relative maintenance of serum urate level while serum urea increases;
  - (c) Steep increase in serum urate on withdrawing benemid (July 1953);
  - (d) Failure of cortisone alone (a weak uricosuric) to prevent rise of serum urate.

The combination of the two drugs from the beginning produced, if anything, a less than average effect compared with the main group of patients who started treatment with benemid alone (for example, cases 2 and 36 in Figs. 45 and 46), but this is attributable to the presence of substantial renal disease and does not necessarily signify mutual interference by benemid and cortisone with each other.

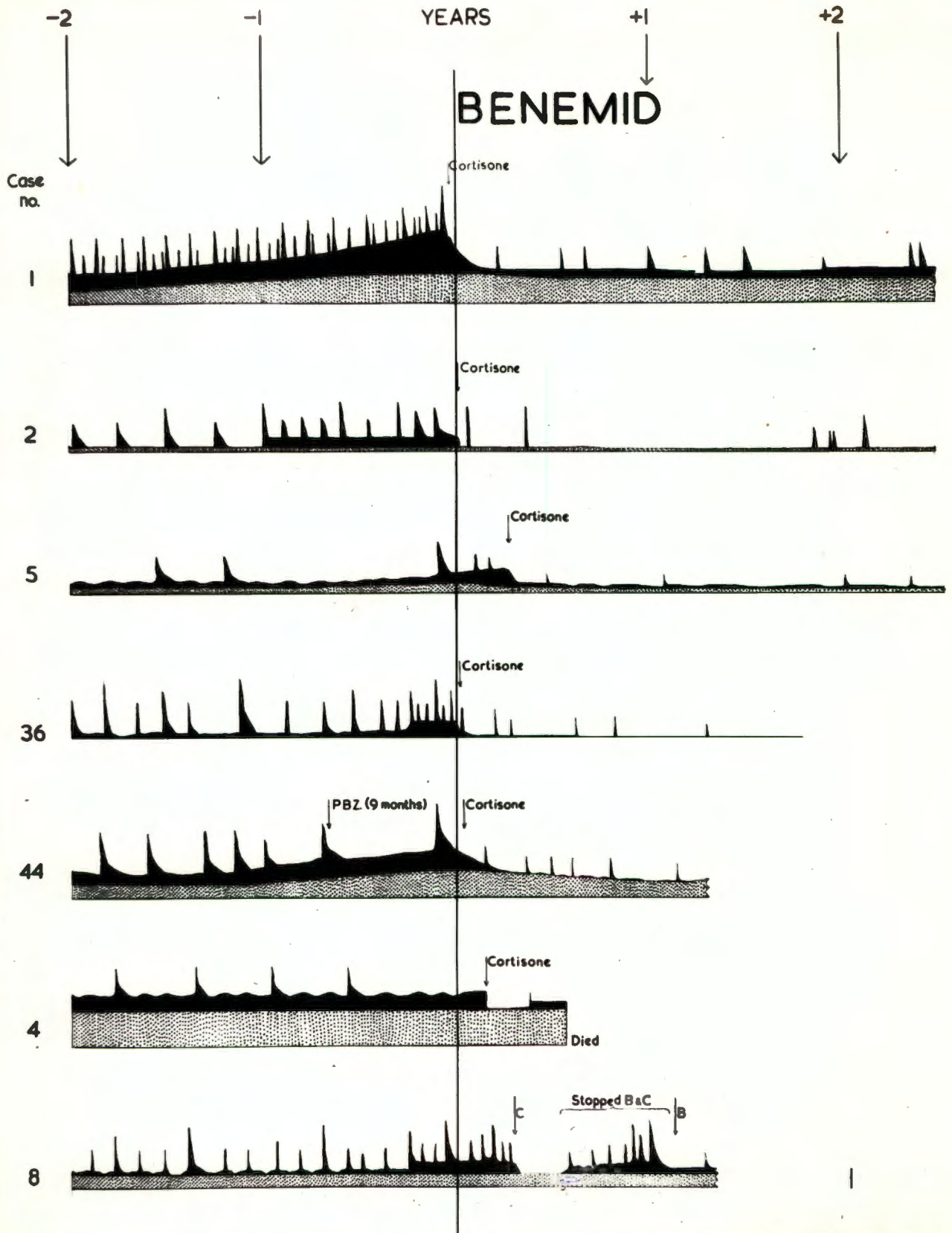
In several of the group, tests of adrenocortical function (eosinopenic response to ACTH) were done before and during the administration of cortisone, but attempts to discover an inhibition of activity as a result of treatment were vitiated by impaired responses in a few before starting (those with uraemia), and equivocal results in the others by the technique used.

Metabolic complications in the form of mild diabetes mellitus, occurred 27 months after starting cortisone in case 1, and after 22 months in case 36. Both have family histories of diabetes. The condition has been controlled by further reduction of cortisone dosage and attention to diet.

(b) Clinical results. Improvement in this group of patients was uniformly striking (Fig. 66).

(i) Acute attacks. The previous pattern in five of the seven patients had been one of high frequency. All of them, except one whose attacks had diminished on recent phenylbutazone therapy, experienced a prompt reduction in the incidence of acute gout following the use of cortisone in combination with benemid.

Gout in its most agonizing form had progressively developed in a 52-year old company director (case 1) since his first attack as a schoolboy of twelve. He had recently become maximally disabled by constant polyarticular pain, swelling and stiffness in damaged joints and subjected to incessant episodes of more acute gout. He was taking colchicine daily to the point of constant nausea, in addition to measures gathered in a worldwide search for relief. After termination of a severe attack with ACTH plus colchicine, and the institution of 50 mg. cortisone with 1.0-1.5 G. benemid daily, increasing improvement of an unprecedented degree rapidly ensued. Initially no longer able to dress himself or sign company cheques, and in recurrent agony from attacks, he made a satisfactory return to business and



**Fig. 66.** (Seven patients receiving benemid combined with small doses of cortisone). Diagram of clinical course during 24 month period before starting benemid, and during subsequent period of treatment with both drugs.

Note universal improvement in (a) frequency of attacks and (b) chronic active arthritis. (c) Mechanical disability has diminished significantly in some.

social activities. Structural features of gout, which were difficult to distinguish in his case from chronic activity, underwent slight improvement in terms of joint mobility, but the degree of damage in feet and hands (Fig. 61) militated against significant change. In the third year of treatment rupture of a large superficial tophus took place, without having increased in size while on uricosuric therapy. The recent appearance of mild diabetes and progressive renal damage have begun to offset his earlier improvement.

In two other cases (2 and 36) relief from high-frequency gout enabled the patients to engage once more in full-time work, the improvement being most remarkable in the former, a young woman with steadily advancing uraemia and a 12-year story of undiagnosed gout, whose life had been 'sheer hell' for the past 12 months. In case 8, the other patient with chronic renal failure, the use for three months of benemid alone produced a moderate uricosuric and no clinical response; attacks and interval symptoms disappeared for as long as cortisone was taken as well.

(ii) Chronic active arthritis. A prominent feature in all cases, this cause of disability had already failed to improve in cases 5 and 4 on 2-3 months of benemid only. In the latter patient the explanation may have been the presence of colossal tophaceous deposits (Chapter 1) which delayed the customary response of this particular clinical feature to uricosuric treatment with benemid alone. The addition of 50 mg. daily of cortisone wrought remarkable symptomatic improvement in each, especially impressive in the comfort and agility it conferred on the much deformed patient (case 4), whose further progress, unfortunately, was interrupted by fatal coronary artery disease.

Diminution or disappearance of chronic pain and stiffness formed the main contribution to the over-all improvement of each of the other members of this severely affected group.

(iii) Tophi and rigidity. While appreciable loosening of previously rigid or impaired foot and hand joints occurred in cases 1, 2 and 44, the degree of improvement was limited, and tophi showed no appreciable change during the time

of observation. Recalling the poorer biochemical response to benemid in this group as a whole, and the tophaceous damage already present in most, this result is perhaps not surprising, and gives cause for regret that earlier measures could not be instituted to prevent the clinical and radiographic features of advanced gout. The discharging of a tophus, already 'out of control' in terms of sheer bulk, has been mentioned in case 1, and surgical decompression of a similar mass was timeously performed in case 44. Evidence of definite expansion of urate lesions in this group, as in the 43 taking only benemid, was uniformly absent.

(iv) Conclusions. Cortisone in relatively small doses of 50-25 mg. daily appeared to be a potent antiphlogistic auxiliary to uricosuric therapy with benemid in a group of 7 patients with unusually severe gout. In only one, however (case 1), had full prior use been made of colchicine, (with complete failure), and there is no reason to think that substantial - if not equal - relief would have followed the combined use of benemid and colchicine in the other patients. Even dosage of this order was not devoid of complications (diabetes in two), although no trace of hypercorticism appeared. It is felt that useful evidence has been offered (in contrast with the presumptive views of some modern authorities<sup>59, 118</sup>) that continuous small doses of cortisone as an auxiliary to uricosuric therapy may, in cases of unremitting gout not adequately relieved by colchicine and benemid, offer a welcome improvement in the clinical management of the disease.

SECTION IV

SUMMARY AND CONCLUSIONS

REFERENCES

ACKNOWLEDGMENT

## SUMMARY AND CONCLUSIONS

Gout is a common disease and uric acid accumulation its most tangible feature. This thesis deals with several aspects of the clinical entity and of the metabolic abnormality characterizing it, stressing the closeness of their relationship and the practical importance of a biochemical approach to the understanding and successful treatment of gout.

The objects of the thesis which are outlined in the preface are:

(A) To demonstrate the local prevalence of gout, to emphasise the need for its correct diagnosis and treatment, and to re-evaluate certain aspects of its natural history, notably the common association with renal disease;

(B) To study the possible therapeutic value of a potent new uricosuric agent, benemid, after reviewing the evidence which justifies the use of therapy based on urate elimination;

(C) To describe for the first time the potent uricosuric action (confirmed by investigation in humans and animals) of the anti-coagulant drug, tromexan, and to discuss the chemical, biological and therapeutic implications of this discovery.

A. The prevalence of gout in Cape Town is indicated by a presentation of clinical and diagnostic data on 140 patients with unequivocal gout, encountered by the writer in 2½ years of hospital study. (Chapter 6).

No explanation is available for the high local incidence of the disease. White and coloured members of the population are comparably affected, but African patients (like negroes elsewhere) are rarely seen. The proportion of males in the series was 92%. No special social or occupational factors were apparent in the case distribution, and, although alcohol is no longer blamed as a fundamental cause of gout, 28% of the patients drank excessively. The propensity of gout to affect heavily-built men of full-blooded appearance was substantiated.

Among the diagnostic criteria which are displayed for each patient in detailed clinical tables, only one -urate deposition - is pathognomonic. Chief among the others are (i) the clinical details of the typical acute attacks, (ii) a convincing response to colchicine at the height of an acute episode, and (iii) hyperuricaemia greater than 6.0 mg./100 ml. serum by the method used. Control values in 110 non-gouty males averaged 4.30 mgm./100 ml. and in 83 females, 3.82 mg./100 ml. Significant associated features

include acute or chronic olecronon bursitis, the latter not necessarily tophaceous.

Of all diseases liable to be associated with gout, hypertension and renal disease rank highest. By criteria carefully defined, at least 33% of the patients were hypertensive, 40% had proteinuria and 35% had significant impairment of renal function.

An analysis is presented aimed at correlating the known pathological changes in kidneys of gout patients with the clinical and laboratory features displayed at different stages of the diseases in life. Apart from their academic interest, the potential importance of these results in determining the advisability of uricosuric therapy in gout is pointed out. One renal syndrome, characterized by severe ursemia, and occurring disproportionately early in relation to joint symptoms, is thought likely to precede gout in its pathogenesis. Others, chiefly in older patients, are attributable to the kidney lesions usually found at autopsy, namely, nephrosclerosis, interstitial urate deposition, secondary infection and calculus. A final important clinical group with features resembling silent glomerulo-nephritis is found in whom gout is not necessarily far advanced, and remains unexplained in terms of the writer's clinical and laboratory analysis. The problems in this field well merit planned study for a long period.

The diversity of renal lesions which may be found associated with gout is illustrated by annotated photographs.

B. Before embarking on a long-term study of uricosuric therapy in gout, it is necessary to consider the clinical and pathological relationship between uric acid and the features of the disease. The extent to which such measures are logical, and the benefits likely to result from their use, may then be assessed. (Chapter 1 and Introduction to Chapter 7).

A brief review is presented of recent advances in the understanding of hyperuricemia in gout. Genetic studies and the use of isotopes have emphasized the hereditary nature of the biochemical trait, and its probable underlying mechanism as one of excessive urate production. Although no tangible renal defect is usually present early in the disease to explain the hyperuricemia, some authorities do not exclude the possibility that the kidney function in gout is inadequate relative to the need for greater urate excretion.

Of the clinical manifestations of gout, those most obviously directly due to uric acid are found at the stage of chronic tophaceous arthritis. There is no evidence to implicate urate

itself in the pathogenesis of acute gouty episodes, the mechanism of which remain a puzzle. Vascular degeneration has been the subject in recent studies of interesting correlation with hyperuricemia, and the extent to which uric acid may be blamed for the renal and vascular - as well as joint - abnormalities in gout patients is considered.

It is concluded that uricosuric therapy is appropriate in gout at least to prevent or modify structural damage due to continuous urate deposition. The possibility exists that prolonged study may demonstrate associated benefits among some of the other features of the disease.

As a prelude to the clinical (and subsequent experimental) investigation of uricosuric agents, the biochemical basis of their activity is reviewed, and certain laboratory studies presented illustrating the principles of action of benemid. (Chapters 2 & 3).

The renal mechanism for urate excretion has recently been shown to involve total glomerular filtration with partial tubular reabsorption. The relative abilities of known urate diuretics to impair the process of tubular reabsorption is discussed, and an analysis is presented - based on the experimental literature - of the biochemical relationships between tubular reabsorption of urate, and tubular secretion of certain other organic molecules, such as PAH and penicillin. The concept of intracellular transport systems, each serving a group of organic compounds traversing the tubule, enzymatically activated and capable of inhibition by certain agents, is critically discussed.

The uricosuric activity of benemid - therapeutic assessment of which constitutes one of the three objects of the thesis - is exemplified by a short account of the results following its use in normal and gouty subjects, and in various renal diseases. Biochemical methods used are described, and the great effectiveness of the drug in enhancing urate elimination is illustrated in terms of lowered serum urate levels, increased urate clearance (and urate/creatinine clearance ratio), and augmentation of daily urinary urate excretion. The new metabolic concept of a large 'miscible urate pool' characterizing the disturbance in gout is discussed with reference to the biochemical results of benemid administration.

In Chapter 7, having thus reviewed the uric acid problem etiologically and biochemically, and considered the premises for uricosuric therapy, a clinical and laboratory appraisal is presented of the prolonged use of benemid in 50 patients with gout.

The shortcomings of other uricosuric drugs are discussed and the need for improvement, even respecting salicylate, in the balance between

effectiveness and toxicity is pointed out. Benemid, which became available here early in 1952, was new and imperfectly tried, but held initial promise of fulfilling the requirements of an ideal uricosuric. Its continuous use has been studied for periods of 6 to 30 months in patients whose average severity of gout was rather above the average for the whole series. Of the 50 patients treated, 43 received daily amounts of 1.5 G. of benemid alone with no other measures except the prompt alleviation of intercurrent attacks (the modern treatment of which is recounted). The remaining seven, chosen for their unusual frequency of acute episodes and severity of chronic gouty symptoms, were given small maintenance doses of cortisone (50-25 mg. daily) in addition to benemid, on the premises that it was mildly uricosuric, a potent non-specific inhibitor of inflammatory processes, and able to suppress endogenous adrenocortical activity (a disturbance of which has been blamed for many of the features of clinical gout).

The biochemical results of benemid therapy (which were uninfluenced by cortisone) are detailed in a series of graphs, tables and descriptions. Specially note-worthy were the following:-

- (i) Initial lowering of serum urate levels by amounts up to 52% of the initial value, with an average for all of 33%. By taking the highest figures of all patients (with and without renal disease) in the month after starting benemid therapy, a mean reduction of at least 28% was demonstrated.
- (ii) No signs of biochemical escape from the uricosuric effect of benemid were observed at any later time in the study.
- (iii) Urinary urate excretion was greatly enhanced, (to significant degrees even in those with renal impairment), with evidence of slow return to a normal output as the large metabolic pool of urate was progressively depleted. The results indicate, as previously demonstrated in Chapter 3, that gout patients with tophi have great reserves of urate which are at least partly mobilizable by persistent uricosuric therapy, auguring well for future clinical progress.
- (iv) Only the worst grades of renal failure markedly impair the uricosuric action of benemid on the renal tubules, as measured by urate clearances and total excretion. Patients with gout and moderate renal disease - a common combination - stand to benefit as much as others from the use of the drug.
- (v) Conversely no significant evidence emerged of benemid directly aggravating - or improving - the laboratory indices of renal function.

The clinical results of prolonged benemid administration illustrate the success which may accompany effective uricosuric therapy in all grades of clinical gout. Special attention, however, is paid to the difficulties of clinical interpretation in some cases.

Of the criteria used in assessing results, chronic active gouty arthritis showed the most satisfactory response, improvement occurring in 22 of the 28 patients who had this feature and were treated with benemid alone. The seven receiving auxiliary cortisone experienced even more impressive and rapid relief, which would characteristically be delayed by several weeks in those only taking benemid.

Frequency of attacks were less certainly altered during the period of benemid therapy in 43 patients. A small proportion with previously frequent episodes showed definite improvement not attributable to other medication. Another few have plainly had as many or more attacks, while in the biggest group a longer period of observation will be required to confirm an apparent slight reduction in frequency. The seven patients treated with cortisone in addition to benemid demonstrated its potential value in those not controllable by benemid and colchicine, for suppressing much of the distress of incessant gouty inflammation.

Urate deposition was apparently arrested in all cases, and varying degrees of diminution resulted in tophi and joint rigidity. Radiographic lesions were arrested, and in 2 or 3 cases appear to have partially healed. It is felt that a longer follow-up will be needed to decide whether the kidney lesions in gout, especially those resulting from renal urate deposition and its complications, will ultimately be benefited by benemid therapy or not.

Among the particular advantages of benemid and its unusual potency and its virtual absence of toxic effects in the dosage used, even in those with considerable renal damage.

It is believed that benemid is, to-day, the ideal uricosuric agent for the long-term management of gout, and together with the use of colchicine to minimize or treat acute attacks, holds promise of changing the outlook for many patients with the disease. Biochemical and clinical evidence of urate depletion is so convincing that serious thought should be given to the use of benemid in small or intermittent dosage, by those in even the earliest phase of clinical gout.

C. The major part of the experimental work in this thesis concerns the discovery of the potent uricosuric action of tromexan. (Chapter 4).

Studies in man confirmed its renal inhibition of urate reabsorption, and, on the basis of fewer observations, its probable interference with the secretion of PAH, phenol red and, possibly, of penicillin.

Animal experiments further substantiated the uricosuric action, and special attention was paid to its effects in the Dalmatian coach hound. The anomalous urate excretion of that breed was reviewed, and confirmation offered of their active tubular secretion of urate. Tromexan, as well as benemid, thus reduced urate clearance in the Dalmatian, in contrast to enhancing it in an ordinary dog.

A detailed consideration is presented of the implications of this discovery. (Chapter 5).

An attempt has been made to identify the chemical structures relating uricosuric, anticoagulant and anti-rheumatic drugs, and limited conclusions are drawn. The therapeutic benefit which may possibly be derived from the uricosuric function of tromexan are, finally, tentatively discussed.

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