MODERN MEDICAL MONOGRAPHS

7

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By JOHN H. TALBOTT, M.D.

Professor of Medicine, The University of Buffalo School of Medicine;
Physician-in-Chief, Buffalo General Hospital, Buffalo, New York

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Preface

APPROXIMATELY TEN YEARS have passed since previous efforts were made by the author to assemble in a comprehensive treatise pertinent laboratory data on uric acid metabolism and clinical impressions of the dyscrasia known as gout. A decade is a considerable span of time as measured by progress in some phases of medicine. Gout has not been an exception to this generalization. In spite of the critical war years, which consumed a portion of the period and necessitated curtailing of research activities on subjects of little military significance, advances have been recorded which further the understanding of the metabolic dyscrasia as well as enhance the therapeutic armamentarium of the regimen for the sufferer from articular gout. Furthermore, gouty arthritis, as one type of joint disease, has shared in the remarkable progress that has encompassed broad aspects of articular disorders in recent years. In this category, gout has received increasing attention as a biochemical and medical enigma and has posed a challenge to the clinical chemist in the laboratory and to the clinical investigator at the bedside.

An attempt will be made in this small volume to document significant advances in the understanding of the gouty dyscrasia and gouty arthritis. The emphasis, however, will be upon the phases of this malady which we believe to be of interest to the clinician, since the goal of clinical research is not reached until the patient reaps the gain.

Gout is not a rare malady and because of its incidence deserves more consideration than is frequently afforded to it in the practice of medicine. The clinical recognition of gout and gouty arthritis by many physicians leaves much to be desired. A similar statement is applicable concerning therapy. If the physician who peruses these words considers gout as a diagnostic possibility more often in the future than he has in the past and derives assurance not discouragement from the suggestions regarding treatment, these efforts will not have been in vain.

A great many of the clinical impressions, many orthodox, others unorthodox, advanced in this tract, are derived from two series of

patients. The first group was seen at the Massachusetts General Hospital between 1933 and 1941. The second series was seen at the Buffalo General Hospital between 1946 and 1952. There were no significant differences in the clinical findings between the two series.

The investigative labors have been pursued in the clinical laboratories in the respective hospitals and in addition, since 1951, at the University of Buffalo Chronic Disease Research Institute.

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Important as finances are in supporting research, they would fall on fallow soil without the stimulus and perspiration provided by research associates. At the Massachusetts General Hospital, Frederick S. Coombs, William V. Consolazio and Louis J. Pecora contributed heavily either in the clinic or the laboratory to the studies described herein. At the Buffalo General Hospital, Charles Bishop, James Buzard, Royden Rand, William Garner, Donald Wilson, George Miller and Warren Montgomery assumed one of several assignments, each with skill and interest. Lastly the several members of the Arthritis Clinic at the Buffalo General Hospital, especially Maxwell Lockie, Harold Robins and Bernard M. Norcross, deserve special mention for the cooperation offered since 1946.

"*I hold every man a debtor to his profession.*"—Francis Bacon, 1630

J.H.T.

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Gout and Gouty Arthritis

Definition

THE ENGLISH TERM gout has been adapted from the Latin, *gutta*, which refers to a drop caused by a "defluxion of the humours." Although Pepper[56] considers the term a curious one, there is adequate biochemical and pathological basis for the appellation. The visible tophus is a massive precipitate of salts of uric acid, a macroscopic "drop." Undoubtedly it had its beginning as a microscopic "drop," or precipitation from body fluids overloaded with urates.

Confusion concerning the differentiation between gout and gouty arthritis continues to be prevalent. Frequently the terms are used interchangeably. This offends particularly the literary purist. Such an individual most likely would prefer that the term gout be restricted to the metabolic dyscrasia associated with an increased concentration of uric acid in blood and body fluids. No particular implications concerning arthritis or rheumatism need accompany this restricted use of the word. Gouty arthritis, on the other hand, refers to the articular manifestations, acute or chronic, caused by the metabolic disturbance. Podagra is a Greek derivation from *pous* foot and *agra* attack. The term is neither specific nor factual. Since gouty arthritis encompasses many joints of the body other than those distal to the ankle, podagra is thought to be obsolete.

Gouty arthritis may be observed as one of three clinical phenomena: (1) *Acute gouty arthritis* or *an acute attack of gouty arthritis* usually is the cause of the afflicted person seeking medical counsel. These are synonomous clinical events and are highly susceptible to therapeutic agents. Most patients with gout should suffer from acute attacks of gouty arthritis but a small portion of the time during the natural history of the disease. (2) The *intercritical period* is the interval between the acute attacks. In all patients during the earlier years following the first attack of acute gouty arthritis and in most patients throughout the natural course of the disease, the afflicted should be free from joint symptoms in the intercritical periods. In other words, many patients with the metabolic dyscrasia experience an acute attack from

time to time but between the attacks no articular symptoms are present and chronic deforming arthritis caused by prolonged insult from the uric acid diathesis has not had sufficient time to develop. The intercritical period likewise is susceptible to therapeutic agents. (3) *Chronic deforming gouty arthritis* is the fate of only a small number of patients afflicted with gout. This is a late manifestation of the disease and several decades usually elapse following the first attack of arthritis before this stage is reached. The earlier in life the first attack of acute gout appears, the greater is the tendency to develop chronic deforming gouty arthritis. Inadequate treatment undoubtedly contributes also in some individuals to the earlier development of this stage. Repetition is desirable regarding the incidence of this clinical phase of the disease. Chronic deforming gouty arthritis with partial or extensive incapacity constitutes a negligible percentage of the total population afflicted with gout.

The terms *urate* and *uric acid* are used interchangeably in this discussion. The former is preferred just as chloride is preferred to hydrochloric acid in any discussion of the Cl radical in electrolyte metabolism. Urate refers to the anion salt of uric acid and as such constitutes the principal form of the degradation product in the body.

The designation *gouty diathesis* recurs frequently in the literature of the Nineteenth century, but is used in some instances in contemporary writings also. A predisposition to gout undoubtedly exists in some individuals as will be discussed under HEREDITY. On the other hand, there is some tendency to employ the expression gouty diathesis in order to explain atypical or typical sclerosis of the coronary arteries, gastrointestinal disturbances, skin eruptions and other unrelated maladies in individuals who do not suffer from the characteristic disturbance of uric acid metabolism or typical gouty arthritis. Hence, it is believed that the term gouty diathesis has no place in the clinical description of the disease under consideration. When the adjective *gouty* is used in this discussion, it implies an intimate relationship to a disturbance of uric acid metabolism and will not be used as an impure term to mean gout-like or simulating gout.

Heredity

The recognition of the hereditary nature of gout has been attributed to Gallium in the second century A.D.[25] One of the first statistical

tabulations was reported by Scudamore,[64] who noted a familial incidence of 64 per cent in a series of 522 patients. In the series of patients seen by the writer, the familial incidence is somewhat higher.

The success in detecting a significant familial incidence of gout is related partially to the interest manifest by the attending physician in investigating the family tree. The greater the interest, the higher percentage of positive family histories. In 1907 Luff[50] summarized succinctly the prevailing impression: "It is doubtful, however, whether, true atavism occurs in connection with gout; that is, whether gout entirely misses a generation. . . . The diathesis, the inborn tendency to acquire the disease under certain conditions, is transmissible; but there is no evidence that parental high living increases that tendency in the child."

The familial incidence of gout is accepted currently although statistical observations of a series of patients as large as that of Scudamore or Luff has not been published in this generation. On the other hand, a logical extension of the familial aspects of gouty arthritis has been a geneologic study of the disturbance of uric acid metabolism. This has been made possible by the development of relatively satisfactory methods for the determination of uric acid in serum and urine and more recently by the development of a technique for the determination of the metabolic pool as measured by the exchange of uric acid labeled with isotopic nitrogen.

Folin and Lyman[22] observed an increased concentration of uric acid in the serum in a nonarthritic relative of a gouty individual. Twenty-five years later Jacobson[42] noted a similar abnormality in 3 nonaffected relatives of gouty persons. A study subsequently of a larger number of individuals was reported by the author in relatives of 27 patients with gout.[76] A total of 136 relatives not affected with gout were interviewed and included in the investigation.[77] The criterion for inclusion as a "nonaffected" relative was the absence of stigmata usually associated with acute or chronic gouty arthritis. The ages of the nonaffected relatives varied from 6 to 86 years. Most of them were between the ages of 30 and 60. Fifty-eight per cent were males. A diagnosis of gouty arthritis was excluded upon examination of the clinical findings and laboratory data in each instance.

The concentration of serum uric acid was determined one or more times in each nonaffected relative. One hundred and two had a con-

centration less than 6.0 mg. per 100 ml. In several instances the determinations were repeated and the normal values checked. The average for the 102 subjects was 4.6 mg. per 100 ml. This is slightly higher than the average for a similar number of nongouty subjects.[78] The remaining 34 nonaffected relatives had a serum urate greater than 6.0 mg. The values ranged from 6.1 to 10.8 mg. per 100 ml. The average was 7.3 mg. This may be compared with the average value of 8.8 mg. for a series of 100 gouty patients. The ages of the 34 relatives with an increased uric acid concentration ranged from 14 to 86. Eighty per cent were males. Three patients in the series with an elevated uric acid developed an acute attack of arthritis within a five year period. Approximately 50 per cent of the relatives have been contacted by letter or seen in person subsequently. No new instances of acute gout have been observed or reported in addition to the three identified above.[79]

Since the ages of the nonaffected relatives covered a span of approximately eight decades, it is believed that these data lend support to the presumption that the observed disturbance in uric acid metabolism may be present many years before the onset of acute gouty arthritis; in fact, it is believed to be theoretically possible for the metabolic disturbance to be present throughout life without the appearance of clinical manifestations of gouty arthritis. If this presumption is considered from one viewpoint, the hereditary predisposition is the dominant factor in the causation of gout while dietary indiscretion, social factors, bacchanalian fiestas, etc., are of secondary importance only. On the other hand, it cannot be denied that dietary indiscretion as well as other ill-defined factors may augment the tendency to articular distress in a predisposed individual who without these extraneous factors might escape clinical gouty arthritis. This will be referred to again under PATHOGENESIS.

An extensive investigation into the familial aspect of gout and hyperuricemia has been reported by Smyth, Cotterman and Freyberg.[69, 70] Data for 87 relatives of 19 patients with gout are presented by them. It was concluded that hyperuricemia was apparently due to a single autosomal dominant gene, while only a portion of the heterozygotes for this factor develop clinical gouty arthritis. The lower incidence of gout in females was attributed to the lower con-

centration of serum urate and to a lessened effect of the pathological gene in this sex.

The gene for essential hyperuricemia must be considerably more common than one might suspect from the incidence of clinical gout and the homozygote for this gene should, therefore, be observed occasionally. Stecher, Hersh and Solomon[74] in a larger study confirmed these observations but discovered no affected female below the age of 50 in a group of 201 members of 44 families with gout. They postulated that the normal menstrual function inhibits hyperuricemia. While Smyth and associates concluded from their observations that hyperuricemia was apparently due to a single autosomal dominant, Stecher et al. noted that in some families included in their study, it resembled an autosomal recessive, whereas in others it appeared as an autosomal dominant.

Since most of the studies of uric acid levels in the serum have been conducted upon clinic or hospital patients and particularly upon patients or relatives of gouty patients, the incidence of hyperuricemia in the general population remains to be determined. Systematic sampling of serum urate levels of "normal" persons such as is pursued in selected areas in regard to the detection of latent or undiagnosed diabetes mellitus is a challenge in preventive medicine but has not been applied to the gout problem. When this becomes a fact, it may prove to be a profitable line of approach in the prevention of articular distress in predisposed individuals. If nonaffected persons with an elevated uric acid were recognized and an intelligent understanding of the possibility of gouty arthritis developing subsequently could be assumed, one might even be justified in treating a nonaffected hyperuricemic young individual as a gouty patient in the intercritical period.

Incidence

Gouty arthritis is not a rare malady although the recognition of it leaves much to be desired. If the presumption is correct that gout is a familial disorder, one should not anticipate any significant diminution in incidence from generation to generation. The statement frequently is made that gout is a forgotten disorder, that it is dying out and no longer seen in the practice of medicine in sufficient numbers

to keep alive interest and awareness of its recognition. This opinion is voiced particularly by our associates in England. Gout may be forgotten but it is not a nonexistent malady.

There are several reasons for the failure of physicians to make a correct diagnosis of gouty arthritis or to consider this malady in the differential diagnosis of a patient with unexplained joint disease. Instruction in arthritis in medical schools is inadequate in many instances. If the physician has only a casual interest in arthritis, the percentage of correct diagnoses of gouty arthritis in the early years of the disease will be relatively small. Another reason for the discrepancy between incidence and clinical recognition is a common failing among physicians to disregard the possibility of gouty arthritis in the absence of advanced tophaceous changes, changes which are typical of the well developed stage of the malady only. Also there is a tendency to place too much reliance upon the significance of the concentration of uric acid in the serum as determined by the biochemical technician in the routine clinical laboratory. Such an individual may have only a sporadic interest in the procedure which is a difficult one to perform even in enthusiastic and competent technical hands.

There are no satisfactory data regarding the incidence of gout in this country or in other countries. The statement by Hench[39] that at least five per cent of all patients suffering from arthritis seen at the Mayo Clinic had gouty arthritis has been used as a standard reference datum. Under any circumstance, the potential incidence of gout is not generally appreciated and because of this, the diagnosis frequently is overlooked in the early years of the disease or in the mild form.

Sex

This is a disease of the male; less than five per cent of those afflicted are female. Particular care should be exercised in confirming a presumptive diagnosis in a female. In the early stages of the disease in females, each of the diagnostic criteria should be applied critically before a commitment is made. The development of urate tophi is conclusive proof but it is the author's experience that the recognition of tophaceous gout in a female is a rather uncommon encounter.

Hippocrates did not observe gouty arthritis in the female until after the menopause. Although females have been observed with gouty arthritis before the menopause, this circumstance is the excep-

tion (see HEREDITY). Another observation in the author's series is the low fertility rate among married gouty women. I have not seen a well developed instance of tophaceous gout in a female with young offspring.

Age

Most patients with gout experience the first attack of arthritis in the middle decades of life. However, there are a few documented instances of the first acute attack appearing before the age of ten[31] or as late as the tenth decade.[27] It appears that no susceptible child is too young to have gouty arthritis and no susceptible adult is too old. One of the significant differences in the age of onset of the first attack is the severity of the affliction. The later in life that initial articular symptoms appear, the milder the disease and the less the tendency to the development of chronic deforming changes.

Social Status

There is meager support for the presumption that gout is one price to be paid for good food, good wine and leisure living. This is an old wives' tale that should be relegated to the discard. Prolonged starvation or other indigent conditions may inhibit the development of articular attacks,[32] but they do not prevent gouty arthritis in a susceptible individual. Standards of living above inadequate subsistence neither augment nor inhibit the development of gouty arthritis in the person endowed with a constitutional predisposition for the dyscrasia.

Race

Gout shows no particular preference for the white man. It is widely distributed throughout countries that support medical periodicals and hence, provide documentary evidence of the prevalence of the malady. Members of the yellow and brown race have been described with attacks of acute gout. The exception appears to be the Negro who is reported to be highly immune to the disorder. Cohen[16] has published a report of two cases of proved gout in Negro brothers with a genealogical tree of four generations of one family and notes the unusual features of this circumstance.

Etiology

The etiology of gout remains an enigma. The author has supported one etiologic mechanism for almost two decades but this is not accepted unanimously by any optimistic appraisal. More and more of the evidence, however that is accumulating slowly in the laboratory, is believed to be in support of the favored theory rather than opposed to it.

There are three items concerning the disease that are believed to be pertinent to the preferred explanation of the etiology:

1. The malady is a familial one.
2. There is an increased concentration of uric acid in serum and body fluids of patients with gout.
3. The increased concentration of serum urate probably precedes the first attack of gouty arthritis.

Following an increased concentration of urate in body fluids, deposition in articular and periarticular structures occurs. A satisfactory explanation of gouty arthritis, therefore, should account for the increased concentration of urate in the body fluids and selective deposition in structures as noted above.

An increased concentration of urate in the body might be caused by external factors or by internal derangement. Improper diet, excessive intake of alcoholic beverages and exposure to lead, among other items, have been implicated as external noxious forces. Except for an abnormally high purine intake, there is little evidence in support of any one of these factors or a combination as responsible for the metabolic dyscrasia in most afflicted persons.

Endogenous factors may be presumed to be concerned with the intermediary metabolism of purine substances and other precursors of uric acid or with the urinary excretion of urates. There are at least three possible endogenous disturbances which might give rise to an increased concentration of urate in body fluid. These are:

1. Diminished destruction of urate in the tissues.
2. Diminished excretion by the kidney.
3. Increased formation by the body.

The third formulation is believed to fit more closely with experimental observations.

Destruction by the human organism of significant quantities of uric acid utilizing an enzyme system comprising uricase has not been proved. The concentration of uricolytic ferments in human tissues, except in the liver and intestine, is not high when comparison is made with certain lower animals. The degradation product of uric acid in such animals is allantoin and presumably the action of uricase in man would produce the same end-product. Since only a few milligrams of allantoin are excreted by nongouty humans daily, a deficiency of uricase in gouty persons seems unlikely. There are no strong proponents of this explanation if one bases this opinion upon perusal of contemporary writings.

Diminished excretion of urate by the kidneys has enjoyed certain popularity as an explanation of the increased concentration in body fluids. Garrod[26] advanced this hypothesis which found a strong supporter in Thannhauser.[84] According to this theory a specific impairment of the kidney in regard to the excretion of uric acid is responsible, without impairment necessarily of other quantitative functions of the kidney. It is generally agreed that many gouty subjects in the earlier years of the disease, particularly those who have the malady in a mild form, have normal renal function as shown by routine clinical tests. Likewise, the determinations of glomerular filtration rate and renal blood flow in selected study cases have led to similar conclusions.[26] As acute articular attacks recur and the disease progresses, one or more indices of renal efficiency not infrequently show evidence of deterioration. A small amount of albumin in the urine, cylindruria, an inability to concentrate solids maximally, or a persistent decrease in rate of formation of glomerular filtrate may produce no clinical symptoms but if so pursued by laboratory procedures, one or more of these stigmata of kidney dysfunction may be recognized. The identification of any one of these disturbances is believed to be indicative of irreparable kidney damage in the gouty patient. Late in the course of renal impairment in the afflicted person the specific gravity is fixed, excretion of phenosulfonaphthalein dye is markedly delayed, glomerular filtration rate is reduced to a critical level and the concentration of nonprotein nitrogen of the serum is elevated. These represent late manifestations of the kidney dysfunction in gouty persons. The point to be stressed is that kidney function in patients with gout should not be called normal if any one of the

above mentioned findings, minimum, moderate or severe, is observed. Moreover, the kidney in gouty persons should be investigated with as many independent procedures as possible since the early evidence of insult to the kidney may be singular and not multiple.

Urinary excretion studies reveal that a significant number of gouty patients are able to concentrate uric acid in the urine above 50 mg. per 100 cc. This value is the dividing datum according to Thannhauser[84] which differentiates gouty from nongouty individuals. In our laboratory it has been noted that there is no inability of the gouty kidney to concentrate urate except in those patients with damaged kidneys as measured by one of the several routine or precise tests of renal function. Furthermore, urate clearance and urate reabsorption (see RENAL EXCHANGE OF URATE) observations confirm the assumption that no differential impairment of the kidney in regard to urate excretion exists. There appears to be little difference between gouty and nongouty persons in renal exchange of urate. Likewise, when urate reabsorption is altered by the action of uricosuric drugs such as diodrast, cinchophen, and Benemid, gouty and nongouty persons respond in a similar manner if kidney damage is absent.

The faculty of the kidney to maintain urate clearance with a decreasing glomerular activity bespeaks for a superior rather than an inferior ability of the excretory apparatus to handle urate. This adjustment continues into the preterminal stages of renal insufficiency in gouty patients who suffer from advanced kidney disease. Gouty patients with azotemia may have a urate clearance that is essentially normal but a urate reabsorption mechanism that is depressed 30 or 40 per cent. Urate clearance approaches zero in the terminal stages of renal impairment because of the critical depression in glomerular filtration. It is concluded that no constitutional inferiority of the kidneys of gouty patients to excrete urate has been demonstrated and that renal changes in patients with gout are the result of gouty and secondary nongouty processes and are not the cause of the metabolic dyscrasia.

Increased formation of urate by the body as manifested by an increase in the size of the metabolic pool is believed to be the most satisfactory explanation for the metabolic disturbance. An increased metabolism of purine bodies and a concomitant increase in urate content of body fluids need be slight to account quantitatively for

the phenomenon of gout. Furthermore, in selected gouty patients a significant increase in the 24-hour excretion of urate has been observed on a control diet when comparison is made with nongouty normals. The clinical effects of Benemid, a powerful uricosuric agent, are additional new data in support of this hypothesis.

These collected observations are interpreted as favoring the explanation of an increased formation of urate by the body as the etiologic mechanism and as lending meager support to the other possibilities.

During the past five years there have been isolated attempts to identify gout as an "endocrine" disorder. To be sure, Hippocrates noted that females do not suffer from acute gouty arthritis until after the cessation of the menses but only recently has an endocrine etiology been championed. In 1949, Hellman[38] noted that acute articular gout might be precipitated by the intramuscular injection of ACTH. In the same year Wolfson et al.[87] reported a decreased excretion of 17-ketosteroids in the urine of gouty patients with normal biologic androgen activity. He postulated the formation of an abnormal androgen in gouty patients. This postulate has not been confirmed nor has a consistent decrease in 17-ketosteroid excretion in gouty subjects been observed by other investigators.[44] Until further evidence is forthcoming, it must be concluded that gout is no more a disease of the endocrine glands than is rheumatoid arthritis.

Nor is there any better evidence that gout is an allergic disease. Harkavy[37] reported studies on three patients with gout whose attacks were precipitated by sensitizing agents. Antiallergic measures were effective in controlling acute symptoms. I do not subscribe to this mechanism generally and in no patient have stubborn attacks of gout responded to antihistaminic drugs in the instances where they have been subjected to clinical trial.

Intermediary Metabolism of Uric Acid

Precursors of Uric Acid

The chemical formula of uric acid has been shown by Fischer[21] to be 2-6-8 trioxypurine with the "lactam" formula. Uric acid is the end-product of purine metabolism in humans while urea is the end-product of the nitrogenous substances of amino acid and pyrimidin origin. Most other mammals convert uric acid to allantoin and excrete only small amounts of the former substance. Birds and reptiles ex-