Hyperuricemia, Acute Gout, Renal Insufficiency and Urate Nephrolithiasis Due to Starvation

By ERNST J. DRENICK

The levels of uric acid in the serum and the excretion in the urine was measured in a group of 43 obese individuals who starved for prolonged periods and were then fed low calorie diets. Many obese patients were noted to have abnormally high serum uric acid levels initially. With starvation, marked hyperuricemia occurred due to impaired renal clearance. Four patients developed gout. Renal clearance was improved with the administration of probenecid and gout did not occur in the treated patients. The sudden excretion of large amounts of uric acid when hyperuricemic patients were given probenecid led to the development of uric acid calculi in one subject. Feeding of protein or carbohydrate resulted in a reduction of starvation ketosis and serum uric acid levels while improving renal uric acid clearance.

Le nivellos seral de acido uric e le excretion urinari de illo esseva mesurate in un gruppo de 43 subjectos obese qui jejunava durante prolongate periodos de tempore sequite del institution de un programma dietari a basse contento caloric. Esseva notate initialmente que multes de iste patientes obese habeva anormalmente alte nivellos seral de acido uric. Con le jejuno, marcate grados de hyperuricemia se manifestava in consequentia de un defective clearance renal. Quatro del patientes disveloppava gutta. Le clearance renal esseva meliorate per le administration de probenecido, e nulle gutta occurreva in patientes assi tractate. Le subite excretion de grande quantitates de acido uric occurrente in patientes hyperuricemic quando illes esseva tractate con probenecido resultava in le disveloppamento de calculos de acido uric in un del subjectos. Alimentation a proteina o hydrato de carbon resultava in un reduction del cetosis de affamation e del nivellos seral de acido uric e simultaneemente in un melioration del clearance renal de acido uric.

ELEVATED SERUM URIC ACID levels during fasting were first observed by Cathcart[1] in 1907. Lennox[2] suggested a decrease in renal uric acid clearance as the primary reason in 1924. Murphy[3] studied obese patients during short-term starvation and felt that several elements of renal function are impaired and discussed the possibility that the ketonemia of starvation may be one factor in this disturbance. Cristofori[4] demonstrated the effects of the adminstration of glucose, glycine and probenecid on serum uric acid levels and uric acid clearance. Lecocq[5] and Scott[6] recently corroborated the correlation of ketone levels to renal uric acid clearance by demonstrating that an infusion of beta-hydroxybutyric acid in humans resulted in the simultaneous decrease of urinary uric acid and a further increase of serum uric acid.

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Over the last two years data were collected during weight reduction of obese patients to evaluate the various abnormalities in uric acid metabolism and the effects of probenecid during prolonged periods of starvation. The resulting clinical complications, briefly described previously,[7] were correlated with the changes in blood and urinary chemistry.

Methods

Thirty-six male and seven female obese individuals hospitalized on a metabolic ward were studied before and during weight reduction with a variety of regimens: 1) Total starvation up to four months' duration, 2) A 500 calorie diet containing 60 gm. of protein, 4 gm. of carbohydrate and 30 gm. of fat, 3) A 300 calorie diet containing 30 gm. of protein, 3.6 gm. of carbohydrate and 20 gm. of fat.

A uricosuric agent (probenecid 1.0 gm. per day) was administered to one group of patients from the start of starvation and to a second group after several weeks of starvation and after hyperuricemia had developed. In a third group no uricosuric agent was given.

Urine collections were carried out on the Metabolic Balance Ward in 24 hour or 5 day periods. Urinary uric acid was measured quantitatively daily.[8] Urinary nitrogen was determined quantitatively in 5 day periods throughout hospitalization using the macro Kjeldahl method. Urinary acetone was determined at intervals.[9] Serum uric acid levels were determined at weekly intervals.[8] In selected subjects, with termination of the fast, the effect of 250 gm. of glucose per day orally or of a 300-calorie, high protein diet was determined on serum uric acid, serum acetone[9] and urinary uric acid excretion.

Results

Hyperuricemia and Urinary Uric Acid

Among 36 male patients, weighing in excess of 220 pounds (100 Kg.), serum uric acid levels ranged from 5.4 to 10.2 mg. per cent with a mean average of 8.7 mg. per cent. For a group of 7 females, weighing 250 pounds (114 Kg.) or more, the range was from 3.6 to 8.1 mg. per cent with a mean average of 5.2 mg. per cent. In comparison with a normal male hospital population[10] uric acid levels in the obese were found to be concentrated in the high ranges (fig. 1). These patients had no prior history of gouty arthritis, nor a family history of gout. There was no consistent correlation between serum uric acid levels and degrees of obesity (fig. 2).

Progressive hyperuricemia occurred in every individual who maintained a complete fast. The rate of increase in serum uric acid levels, as well as maximal concentrations, varied. Figure 3 demonstrates the ranges of serum uric acid levels measured at weekly intervals during starvation periods up to 50 days in two groups of patients, one receiving 1 Gm. of probenecid daily (lower shaded area). The untreated group consisted of the first 14 consecutive patients who were maintained without food for at least 50 days. Subsequently, 13 patients subjected to prolonged fasting were given probenecid and these made up the second group. The solid line indicates serum uric acid levels in one patient with a history of gout who was given probenecid and colchicine during the entire period.

With few exceptions the probenecid-treated group maintained serum uric acid levels of the prestarvation period. In four patients who starved longer than two months, uric acid levels gradually climbed to 18 mg. per cent,

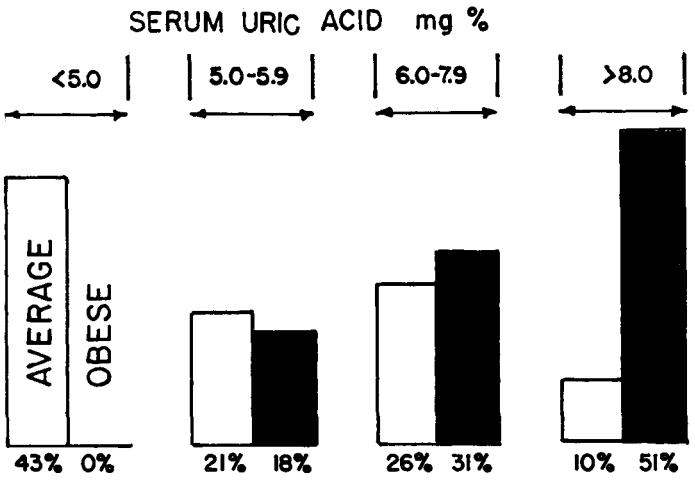

Fig. 1.—Distribution of serum uric acid concentrations in an average male hospital population compared to obese males.

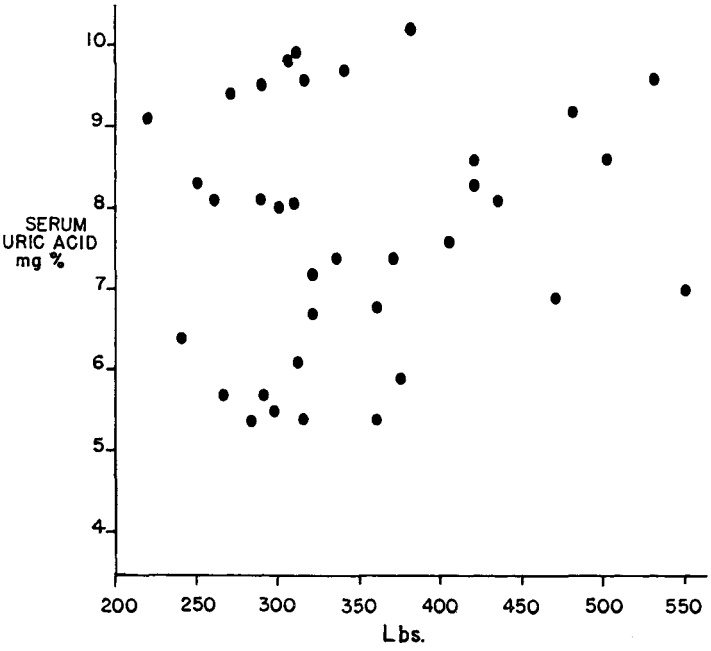

Fig. 2.—Serum uric acid levels in 36 obese males fail to show a discernible correlation to degree of overweight.

despite probenecid therapy, and remained elevated as long as starvation was continued. In the untreated starving group serum uric rose progressively for the first 15 to 20 days to levels of 12 to 18 mg. per cent, and with the starvation period extended past two months a maximal level of 21.8 mg. per cent was noted. When these patients were given probenecid while continuing to fast, serum uric acid fell gradually over a period of 10–15 days to near prestarvation levels.

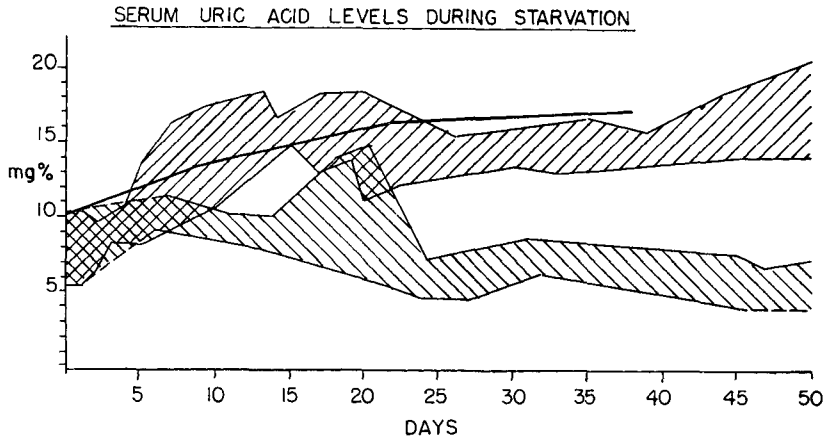

Fig. 3.—Weekly serum uric acid determinations in two groups of starving patients. The patients represented in the lower shaded area received probenecid; those in the upper area did not. The solid line represents serum uric acid levels in a fasting gouty patient who was given probenecid.

In the untreated, as well as in the probenecid-treated group, urinary uric acid excretion varied from day to day and from one patient to the next. In the group of patients who took probenecid from the beginning of starvation, 24 hour urinary uric acid averaged 352 mg. during the first 5 days, compared to 283 in the untreated patients. Nine patients, who were not given probenecid until after an initial prolonged fasting period, showed a drastic increase in urinary uric acid with wide daily variations for a period of five to ten days immediately after institution of probenecid (fig. 4). Subsequently, excretion of uric acid decreased gradually, and the quantities found in the untreated group were slightly lower (190 mg. in 24 hours) than in the probenecid treated group (220 mg. in 24 hours) (fig. 5).

In patients on a semi-starvation diet of 300 or 500 calories, serum uric acid levels increased to levels of 10–14 mg. per cent. The increase was accompanied by ketonemia and ketonuria while urinary uric acid excretion ranged from 350 to 500 mg. per day. If a uricosuric agent was given in conjunction with the hypocaloric diet, the serum uric acid levels remained in the range of the pre-treatment period.

In three patients 250 gm. of glucose were given daily for one week at the end of the starvation period. This was accompanied by a prompt increase of urinary uric acid excretion of 30 to 50 per cent for a period of eight to ten days. Concurrently, the serum uric acid tended to return to prestarvation levels. A similar though less drastic response was noted when a group of five patients were re-fed with a milk powder containing 60 per cent protein, but only 7 per cent carbohydrate, providing 320 calories a day. With the administration of glucose or protein powder, serum ketones decreased simultaneously with the serum uric acid. Urinary ketones disappeared within three days. The response to glucose in one representative obese subject is shown in figure 6.

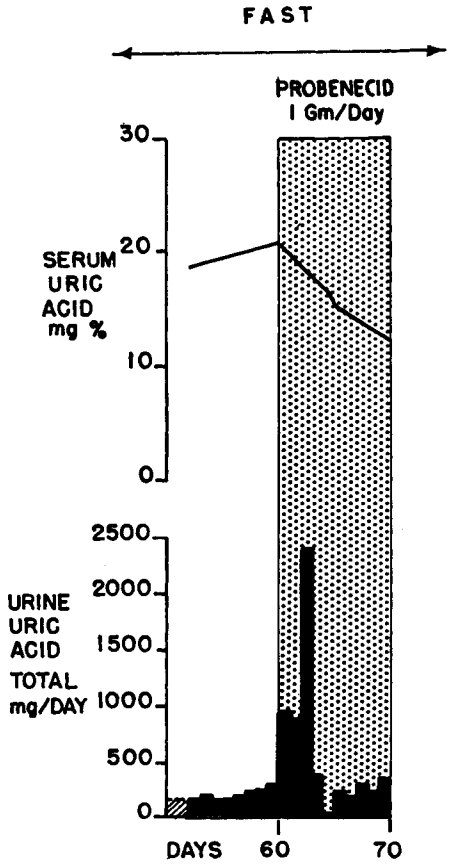

Fig. 4.—With administration of probenecid to a starving individual, urinary uric acid clearance rises with a simultaneous decrease in serum uric acid.

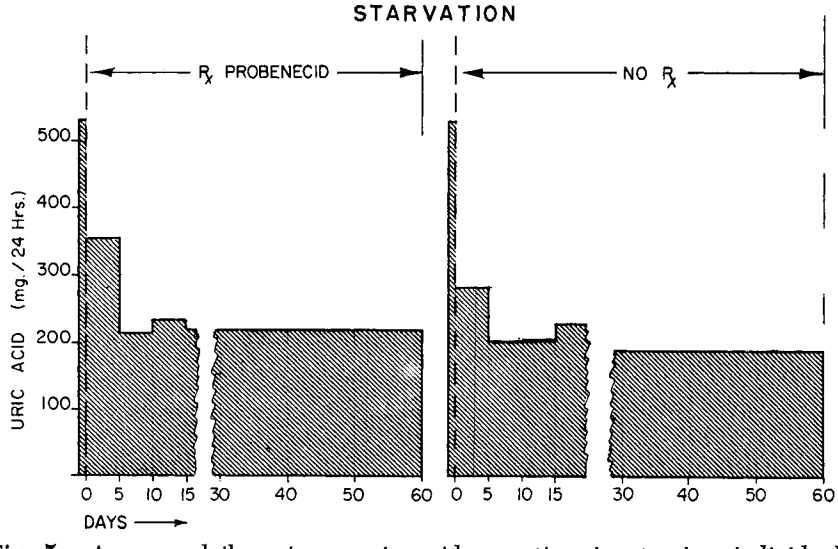

Fig. 5.—Average daily urinary uric acid excretion in starving individuals is slightly higher in the probenecid treated group. (5 patients in each group).

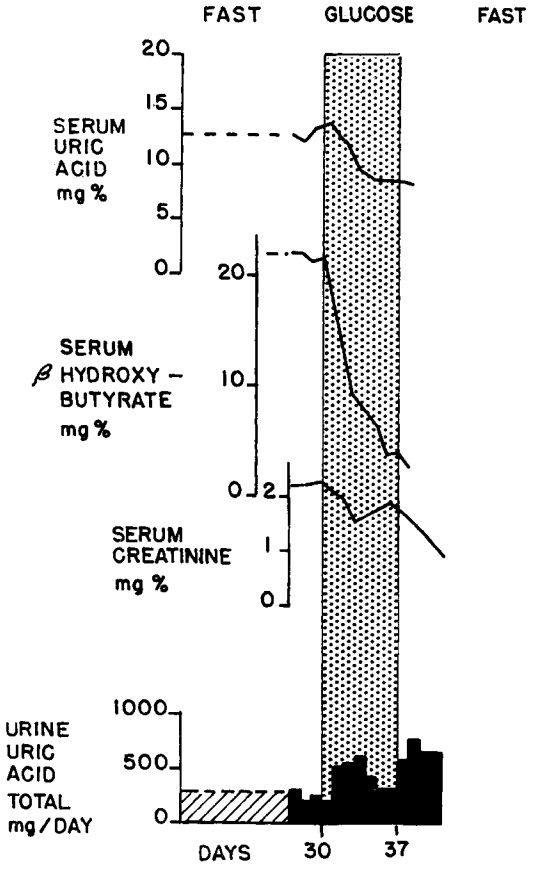

Fig. 6.—Urinary uric acid excretion rises following administration of glucose to a starving individual while serum uric acid, ketones and creatinine decrease.

Gout

Four patients, who had never had gout and whose family history was negative, developed a total of seven gouty attacks (table 1). The first patient was treated only with rest, warm compresses and codeine and continued to fast. The acute episode subsided temporarily but flared up soon after commencing ambulation. Subsequently an 800 calorie, high-protein diet was given, and the gouty arthritis slowly subsided with gradual restoration of a normal serum uric acid level. The second patient with gouty arthritis was treated with colchicine and responded promptly. He was then given a 500 calorie, high-protein diet. Colchicine was discontinued and within ten days the patient experienced a recurrence of the arthritis. At that time the patient had a negative nitrogen balance, and serum, as well as urine, were positive for acetone. The third patient was started on probenecid when his serum uric acid had risen to 20.4 mg. per cent, and he developed acute gout four days later. Treated with colchicine he had prompt relief, even though the fast was not interrupted. When colchicine was stopped, gout recurred within two weeks.

Table 1.—*Acute Gouty Arthritis*

Patient	Initial Weight Pounds	Weight Loss Prior to Gout Pounds	Days Fasted Prior to Gout	Initial Serum Uric Acid mg.%	Maximum Serum Uric Acid mg.%
1	315	91	97	6.8	17.7
2	550	77	42	7.0	18.2
3	370	64	77	7.4	13.0
4	404	66	74	7.6	21.8

In all four patients ankles or metatarsal-phalangeal joints were involved. Joint fluid was aspirated from three of these patients. Characteristic needle-shaped uric acid crystals appeared in the aspirate after evaporation of the joint fluid. After resumption of a regular diet, serum uric acid in these patients remained normal, the joints were free of residuals, and renal uric acid excretion was within normal limits.

None of the patients who were given probenecid from the start of starvation developed gout, even though in four subjects a significant hyperuricemia persisted for many weeks.

Urate Nephrolithiasis and Renal Insufficiency

One patient, who had maintained a severe hyperuricemia for over two months and had experienced two episodes of gout, developed symptoms and signs of a ureteral calculus. He had had two relatively short courses of probenecid. On each occasion, with the institution of this medication, he had a drastic rise in urinary uric acid excretion, reaching 2400 mg. in one 24-hour period. Urinary volume occasionally decreased to as low as 180 ml. per day with an average of 400–500 ml. daily. The reaction of the urine was always acid, and on standing a brownish sediment settled out which contained uric acid crystals. Two weeks after onset of symptoms, the patient spontaneously passed a brownish urinary calculus, which was found to be a urate stone. Two months later, after discharge from the hospital, a second stone was passed, but it was not submitted for examination. Renal function was unimpaired following resumption of a normal diet.

An interesting experience involved a very obese male patient with known gout who was starved for 27 days while on prophylactic probenecid and colchicine from the first day. His uric acid was elevated on admission and rose steadily to 17.2 mg. per cent. After 24 days the serum creatinine started to rise suddenly over a three-day period and reached 5.4 mg. per cent. Urinary uric acid excretion had fallen to less than 100 mg. daily. With refeeding, renal clearance of uric acid and creatinine returned promptly to normal, and serum creatinine and serum uric acid were restored to prestarvation levels.

Discussion

Starvation for prolonged periods is being used with increasing frequency in the treatment of obesity. The well-known abnormalities in uric acid excretion have been investigated and some explanations have been offered by various authors. These abnormalities deserve the attention of physicians

who employ starvation in the treatment of obesity because dramatic and potentially serious complications may arise.

Several manifestations remain unclear or are only partially explained. Why serum uric acid levels are frequently higher in obese than in normal individuals is unknown. The observation that serum uric acid levels seem to be proportional to body surface[10] was not evident in this group of patients with a sizeable incidence of high concentrations in the relatively less obese subjects (fig. 2). Uric acid levels tended to decrease promptly in some patients who spontaneously reduced their caloric intake after admission to the hospital. It seems that in some subjects hyperuricemia is associated with a large intake of dietary protein rather than with obesity, itself.

The rising uric acid levels in the serum during starvation and the lowered urinary uric acid output have been explained in different ways. The theory that ketones compete with uric acid[5,6] for excretion by tubular cells appears likely, but the precise mechanism is difficult to establish. The parallel increase of serum uric acid and ketones and the inverse relationship to urate excretion could also be explained by starvation in itself bringing about deranged enzymatic mechanisms in the tubules with impairment of tubular transport.[12] Thus, retention of a number of organic acids, as well as other metabolites, such as creatinine, occurs. Moderate increases in serum creatinine to levels in excess of 2 mg. per cent have been observed. Lactic acid levels also increase progressively though physiologically abnormal concentrations have not been noted.[13] The marked increase of serum creatinine in a starving gouty patient with ketonemia and hyperuricemia indicates that renal function can become compromised to the point of insufficiency if starvation is permitted to exert its harmful effects for too long. Thus, it is not surprising that during starvation the experimental infusion into the blood stream of a load of beta-hydroxybutyric acid, or any other derivative of fat metabolism, causes a further proportionate decrease in the clearance of competing metabolites. However, this finding does not necessarily define the primary cause of hyperuricemia, nor exclude other etiologic factors.

The hypothesis has been advanced that starvation hypoglycemia leads to a lower filtered glucose load, and, secondarily, because of lessened competition to an increased urate reabsorption in the proximal tubule.[4] However, this is open to some question. First, we have observed hyperuricemia in fasting patients who had entirely normal serum glucose levels; and secondly, hyperuricemia is known to occur in diabetic acidosis where the serum glucose, as well as urinary sugar, rise to high concentrations.[14] In two large series of gouty patients the incidence of diabetes was twice the expected number.[15] If hyperglycemia and glycosuria indeed promoted uric acid excretion, this combination of diseases should be expected to occur with less than chance frequency. The uricosuric effect of orally-administered amino acids, such as glycine, need not necessarily be interpreted as the result of competition of glycine for the reabsorptive capacity of the proximal renal tubule. It seems quite possible that amino acids are converted to glucose and thus facilitate a lowering of the concentration of ketones, which in turn may effect a decrease

in uric acid levels. In this connection it may be pointed out that serum glycine levels during a 30 day fast have been found to increase gradually and progressively from an average of 18 micromoles per 100 ml. to as high as 40 micromoles per 100 ml. in eight out of ten patients.[16]

The use of 1 Gm. of probenecid daily in prolonged starvation was effective in maintaining fairly normal serum uric acid levels in nearly all patients. This dosage did not prevent a persistent hyperuricemia in one patient with known gout and in four others in whom hyperuricemia finally supervened after more than two month's starvation. In two patients, 1.5 Gm. and 2.0 Gm. of probenecid have proved more effective. Unless the medication was given from the start, rather than after hyperuricemia had developed, the sudden flushing out of urates in great quantities through the kidneys and ureters produced urate sludge and urate stones. Refeeding in the presence of severe hyperuricemia of long standing brought about similar results. Figure 4 shows the drastic increase in urate excretion with the administration of probenecid.

The episodes of gouty arthritis were typical and indistinguishable in course and drug response from the metabolic type of gout. Why some patients develop this complication, and others with equally high or higher uric acid levels do not, is unknown. The four patients who developed gout (table 1) were extremely obese. They had fasted for periods of 42 to 97 days, but neither total nitrogen excretion, nor total urinary uric acid excretion during the entire starvation period prior to the onset of gout, was distinctly different from other patients who did not develop gout after fasting equally long periods.

While the hyperuricemia of the obese is in most cases a sequel of excess protein intake, the high serum levels in the starving obese patient cannot be explained on the basis of high protein catabolism. Urinary nitrogen measurements during prolonged starvation indicates that less than 30 Gm. of protein per day are utilized.[7] Prolonged starvation of obese patients has to be included in the list of iatrogenic gout which is primarily renal in origin.

Summary

Serum uric acid levels tended to be higher in obese than in normal weight individuals. Hyperuricemia with serum uric acid concentrations up to 21.8 mg. per cent resulted from prolonged starvation and lesser degrees of uric acid retention accompanied semi-starvation. Nearly normal levels of uric acid could be maintained with administration of probenecid. Ketonemia and ketonuria accompanied the urate retention and glucose or protein administration resulted in improved urate clearance and ketone metabolism.

Four patients experienced a total of seven attacks of gouty arthritis, and one of these subjects developed renal colic due to a urate stone. Despite medication, the development of renal insufficiency in a starving gouty patient makes it inadvisable to resort to drastic reducing regimens in such individuals.

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