

# A Familial Disorder of Uric Acid Metabolism and Central Nervous System Function\*

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PRIMARY GOUT is a metabolic disease which occurs predominantly in the adult man in whom it usually does not become manifest until after the third decade of life. It has been described in children [7], but hyperuricemia in children less than ten years of age is extremely rare. It is the purpose of this report to describe two brothers, aged five and eight years, in whom hyperuricemia, choreoathetosis and mental retardation appear to constitute a syndrome.

## CASE REPORTS

**PATIENT M. W. (JHH 857202).** At the age of four and a half years this boy was admitted to the Harriet Lane Home because of hematuria. He had been born after uneventful gestation and delivery, but by three months of age it was apparent that his development was slow. He was first seen in this clinic at the age of eight months at which time he was found to have marked spasticity, a double hemiparesis and choreoathetosis. His subsequent development was markedly retarded, and at the age of four and a half years he could not sit unassisted.

His first episode of hematuria was accompanied by fever and occurred five months prior to admission. A diagnosis of hemorrhagic cystitis was made and antibiotic treatment initiated. Fever and hematuria subsided within three days on this regimen. Thereafter he was well until two days prior to admission when fever and vomiting developed. Fluid intake and urinary output were decreased. On the day prior to admission he experienced hematuria. When examined in the outpatient department, he was found to have marked crystalluria and was admitted with a diagnosis of cystinuria. It soon became apparent that there was no cystine in the urine and that the crystals were of uric acid.

Both the mother and the father were twenty-five years old and well. Each had had febrile convulsions as children. An older brother is described as Patient

E. W. The family history was negative for gout and disease of the central nervous system. Past and family history were otherwise negative.

The patient was a well developed, rather thin white boy with advanced cerebral palsy. (Fig. 1.) Temperature was 39.2°C., pulse 140 beats per minute, respirations 40 per minute and blood pressure 110/70 mm. Hg. His weight was 14.3 kg. Choreoathetosis was marked. Muscle tone was greatly increased; the legs were kept in a scissor position with the feet and toes plantar flexed. Deep tendon reflexes were increased throughout, and sustained ankle clonus was elicited. Plantar reflexes were flexor. Developmentally he appeared retarded, although the severity of the motor defect precluded adequate evaluation. He could not walk, stand or sit without assistance. He spoke little, although he appeared to comprehend better than communicate. His most striking behavioral characteristic was destructive biting of the fingers and lips. His behavior clearly indicated that there was no sensory anesthesia; he appeared terrified and screamed as if in pain during the process and appeared happy only when restrained securely. There was no evidence of joint disease or tophi. The remainder of the physical examination was within normal limits.

The hematocrit was 40 per cent, the erythrocyte sedimentation rate 15 mm., corrected, and the leukocyte count 17,200 per cu. mm. with 85 per cent neutrophils, 11 per cent lymphocytes and 4 per cent monocytes. Urinalysis showed gross hematuria, 1 plus proteinuria and many hexagonal crystals that dissolved in alkali. Chemical analysis of the serum revealed sodium 146, potassium 3.9, chloride 104 and carbon dioxide 21.6 mEq. per L., calcium 10.6, phosphorus 4.0 and serum urea nitrogen 31 mg. per 100 ml. On the fifth hospital day the uric acid concentration of the serum was found to be 16.8 mg. per 100 ml., when the serum urea nitrogen was 30 mg. per 100 ml. An intravenous pyelogram demonstrated slightly decreased function bilaterally and a nephrogram effect suggesting distal obstruction. On cystoscopy the bladder was coated with fine yellow

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† Work carried out during the tenure of a Medical Student Research Fellowship (U. S. Public Health Service Experimental Training Grants 2-R-9(C4) and 2T5-GM9-06).

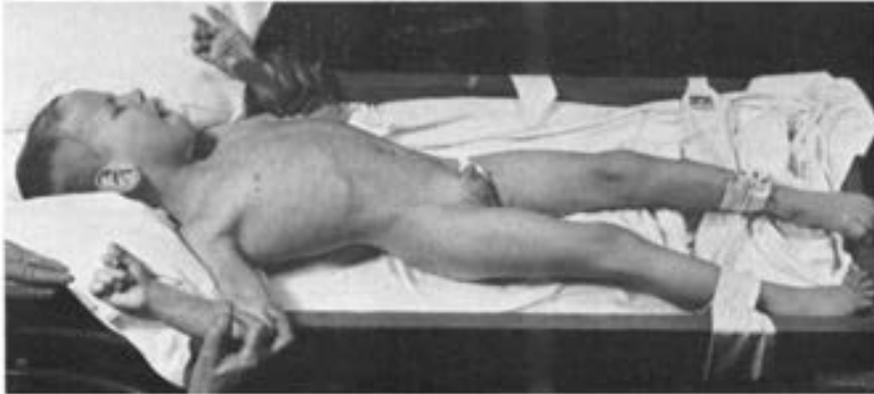


FIG. 1. Patient M. W. at four and a half years of age. The legs are in the characteristic position.

crystals. Roentgenographic survey of the chest, abdomen and bones was normal except for bilateral coxa valga deformities of the hip.

With the diagnosis of hyperuricemia, alkali therapy was initiated using Polycitra.<sup>®</sup> Within three days the serum urea nitrogen was 13 mg. per 100 ml.; four days later it was 5 mg. per 100 ml., at which level it remained. Phenolsulfonphthalein excretion was 60 per cent in eighty minutes. Repeat cystoscopy and intravenous pycnography yielded normal findings. The concentration of uric acid in the serum varied from 8.9 to 10.3 mg. per 100 ml. The concentrations of sugar and cholesterol were 86 and 160 mg. per 100 ml., respectively. The serum total lipids were 0.74, total proteins 7.4, albumin 4.5 and globulin 2.9 gm. per 100 ml. The concentration of glycine in the plasma was 1.7 mg. per 100 ml.; the concentration of uric acid in the cerebrospinal fluid was 0.4 mg. per 100 ml. Studies of the chromosomes revealed no abnormality in number or structure.

The patient was discharged and maintained on alkali therapy until he could be admitted to the Pediatric Clinical Research Unit for the studies to be described. On completion of the studies treatment was initiated with probenecid. He was given 15 mg. per kg. per day for four weeks and then 25 mg. per kg. per day; Polycitra therapy was resumed as well. In four months his serum uric acid level decreased to 4.8 mg. per 100 ml. During this period his weight increased 1.5 kg., and his behavior appeared to improve. The primary incisors and canines have been extracted in order to inhibit the biting of lips and fingers. No attacks of acute arthritis or of renal colic occurred throughout the course.

**PATIENT E. W. (JHH 857203).** The eight year old brother of Patient M. W. was found to have increased levels of uric acid in his serum and was admitted for studies of uric acid metabolism. The patient was first noted to be retarded at five months of age when he did not grasp or sit. He was first seen at the Harriet Lane

Home at seventeen months of age, at which time he could not sit without support. Deep tendon reflexes were hyperactive, and plantar reflexes were extensor. At the age of five years he was admitted for diagnostic studies. At this time double hemiparesis with marked hypertonicity and athetoid movements were noted. The patient appeared mentally retarded. He had begun to bite his hands and lips at four years of age. Investigation during this admission included negative ferric chloride test results and a normal cerebrospinal fluid with glutamic oxaloacetic transaminase of 15 units, glutamic pyruvate transaminase 0 and protein 14 mg. per 100 ml. An electroencephalogram appeared to be disorganized, but there were no seizure discharges. A pneumoencephalogram revealed minimal cerebral atrophy bilaterally as indicated by somewhat dilated lateral ventricles. Shortly after discharge the patient was institutionalized. One month prior to admission he had an episode of severe pain in the right knee. The joint was described as hot, tender, somewhat violaceous and with limited active and passive motion. Roentgenograms of the knees were negative. No history of renal colic was elicited.

On admission, the patient was a fairly well developed and well nourished white boy with cerebral palsy. (Fig. 2.) The weight was 16.3 kg. and the height 110 cm. He was active in bed but could not sit or crawl. There was marked hypertonia with scissoring of the legs. The arms were usually extended and abducted. There was, however, no limitation to active motion, and the patient could make purposeful movements well. The severity of the motor defect precluded precise evaluation of his mental function. However, it was apparent that he was severely retarded. Biting of the hands and lips followed the pattern described in the younger brother. This patient had partially amputated the distal phalanx of one finger and had completely chewed away his lower lip, so that it was no longer accessible to his teeth. Deep tendon reflexes were symmetrically

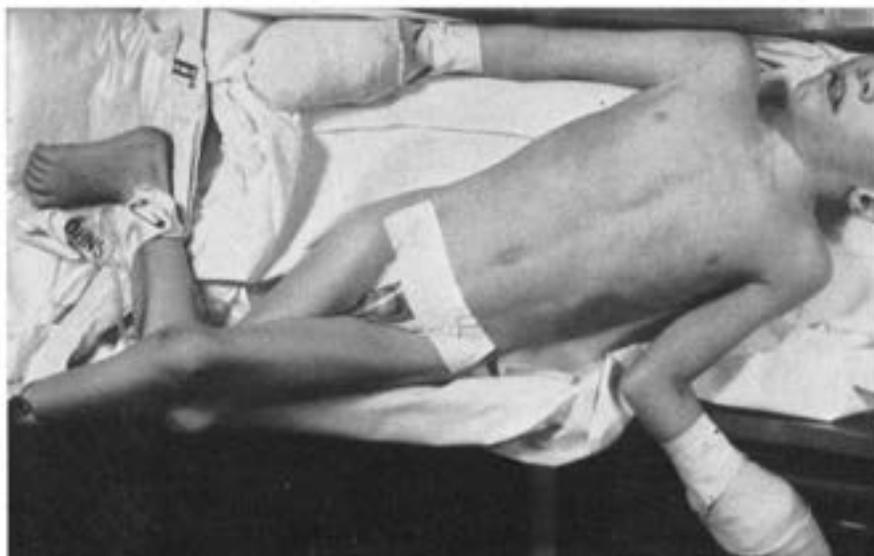


FIG. 2. Patient E. W. at the age of eight years. The mittens on the hands are to protect the child from biting his fingers. The lower lip has been chewed away and is no longer accessible to the central incisors. The marked hypertonia is suggested by the position of the legs.

hyperactive. There were bilateral Babinski responses. Careful examination revealed no evidence of tophi. The remainder of the examination was negative.

The hematocrit was 36 per cent, the leukocyte count 11,000 per cu. mm. with 66 per cent neutrophils, 25 per cent lymphocytes, 2 per cent eosinophils and 8 per cent monocytes. Urinalysis was negative. Examination of the blood revealed concentrations of uric acid of 9.9 to 11.2 mg. per 100 ml. The serum urea nitrogen was 12, glucose 58 and cholesterol 210 mg. per 100 ml., carbon dioxide 22.5, sodium 157, potassium 4.4 and chloride 111 mEq. per L. Serum total lipids were 0.82 gm. per 100 ml., total protein 7.4, albumin 4.7 and globulin 2.7 gm. per 100 ml. The serum lactic acid was 8.5 and the pyruvic acid 1.0 mg. per 100 ml. The plasma concentration of glycine was 0.7 mg. per 100 ml. Inulin clearance was 118 ml. per minute per 1.72 M<sup>2</sup>. The uric acid concentration of the cerebrospinal fluid was 0.9 mg. per 100 ml. Roentgenograms of the skeleton revealed coxa valga deformities of both hips, and the right femoral head was displaced laterally, changes which appeared to be secondary to the cerebral palsy. On the left hand there was an abnormality of the distal phalanx of the fourth finger with truncation of the distal ungual tuft and irregularity of soft tissues, which appeared to be a traumatic amputation. Otherwise, examination of the bones was normal.

#### MATERIALS AND METHODS

The two children described (M. W. and E. W.) and three control patients (B. S., E. S. and W. H.) were admitted to the Pediatric Research Unit of the Harriet Lane Home for the duration of study. Two of the control patients (B. S. and E. S.) were brothers

aged five and eight years, respectively, with non-specific mental retardation. Their IQ's were estimated at less than 50. The third control patient (W. H.) was a five year old boy with mongolism of the 21 trisomy type. The control patients weighed 17.5, 37.2 and 17.9 kg., respectively. All had normal motor function. Concentrations of uric acid in their serum were 4.0, 2.7 and 4.0 mg. per 100 ml. and in their cerebrospinal fluid 0, 0 and 0.4 mg. per 100 ml., respectively. The concentrations of electrolytes, glucose, cholesterol, lipid and protein were within normal limits in the plasma of all control patients. Concentrations of glycine in the plasma ranged from 0.6 to 1.7 mg. per 100 ml.

All patients were given a "purine free" diet containing 110 calories per kg. per day and 3.5 gm. protein per kg. per day three to four days prior to the initiation of study. The diet contained no meats or leguminous vegetables. The excretion of uric acid was constant throughout the period of study. In both patients with hyperuricemia (M. W. and E. W.) the sizes of the uric acid pools and their rates of turnover were determined after the intravenous injection of uric acid-2-C<sup>14</sup>. In these patients and in the control patients the formation of uric acid was studied by determination of the rate of incorporation of isotope into the urinary uric acid following the intravenous injection of glycine-U-C<sup>14</sup>. Following the injection of each isotope, serial twelve hour urine collections were initiated, and the uric acid from an aliquot of each collection period was isolated, purified and its specific activity determined as counts per minute per milligram uric acid.

In experiments with uric acid-2-C<sup>14</sup>, urine was collected until isotope could no longer be found in the

TABLE I  
MISCIBLE POOL OF URIC ACID AND TURNOVER RATE

Patient	Body Weight (kg.)	Dose Injected (mg.)	Antilog Intercept (c.p.m./mg.)	Miscible Pool (mg.)	Slope (day <sup>-1</sup> )	Turnover (mg./day)	Turnover/Kilogram (mg./kg./day)
M. W.	14.3	0.250	$1.82 \times 10^4$	530	2.06	1,090	76.2
E. W.	16.3	0.288	$1.26 \times 10^4$	787	1.61	1,270	77.9

NOTE: Pool sizes were calculated from the equation  $A = a \left( \frac{I_i}{I_0} - 1 \right)$  in which A is pool size; a, milligrams of uric acid injected;  $I_0$ , antilog of the intercept; and  $I_i$ , specific activity of the isotope administered ( $3.44 \times 10^7$  c.p.m. per mg.) [3,4].

urinary uric acid. The natural logarithm of the specific activities of the urinary uric acid were plotted against time. In view of the virtual linearity obtained, the best straight line was drawn to describe the points and extrapolated to the intercept to give the specific activity of a miscible uric acid pool. The size of the pool was calculated by a standard isotope dilution formula [2,3]. (Table I.) Turnover rates were calculated from the slopes of the lines and multiplied by pool size to obtain total daily turnover in milligrams of uric acid. These lines were also calculated by the method of least squares, but since the slopes and intercepts found did not differ from those obtained graphically, the graphic method has been illustrated.

In experiments on the formation of uric acid from glycine-U-C<sup>14</sup>, the specific activity of the uric acid isolated from the urine in each collection period was determined and plotted as a function of time. From these data, the total volumes of urine and their uric acid concentrations and the total isotope (c.p.m.) excreted per day in uric acid were calculated. The per cent conversion was calculated as

$$\frac{\text{total c.p.m. excreted in twenty-four hours as uric acid}}{\text{total c.p.m. injected in glycine}} \times 100,$$

and this was plotted cumulatively for seven days [4,5].

Uric acid-2-C<sup>14</sup>\* had a specific activity of 0.65  $\mu$ c. per mg. It was dissolved in 0.73 per cent lithium carbonate, sterilized by filtration through a sterile sintered glass funnel and diluted with isotonic saline solution. The concentration of isotope and uric acid were determined in an aliquot prior to injection. It was injected intravenously in a dose of 1  $\mu$ c. per kg. in a volume of 5 ml. Glycine uniformly labeled with C<sup>14</sup> (glycine-U-C<sup>14</sup>†) was obtained in 0.01 N hydrochloric acid in a specific activity of 82 mc. per mM. It was neutralized with sodium hydroxide, diluted and assayed for isotope content. It was assayed for radiochemical purity on Moore-Stein columns [6].

\* Nuclear Chicago Corp., Des Plaines, Illinois.

† New England Nuclear Corp., Boston, Massachusetts.

Aliquots for injection were made isotonic with saline solution and sterilized by autoclaving. They were injected intravenously in a dose of 2  $\mu$ c. per kg. in a volume of 5 ml.

Assay for uric acid concentration was carried out by the enzymatic spectrophotometric method as described by Liddle et al. [7] on each twelve hour specimen of urine and on lithium carbonate solutions of the purified uric acid isolated from these urine samples. Serum concentrations of uric acid were routinely determined by the method of Archibald [8] with which the values for normal persons vary from 2 to 6 mg. per 100 ml. in this laboratory, but similar values were obtained on the serum using the enzymatic method. Plasma glycine concentrations were determined chromatographically [6]. Two methods were employed for the isolation of uric acid from the urine. The high concentrations of uric acid (>1.0 mg. per ml.) present in the urine specimens of the patients with hyperuricemia permitted isolation directly by acidification and cooling. Glacial acetic acid was added in the amount of 2 ml. to 50 ml. of urine. The amount of urine used varied from 100 to 400 ml. depending on the quantity available. The acidified urine was allowed to stand at 4°C. for twelve to eighteen hours. The precipitate was collected by centrifugation and washed with cold distilled water. The precipitate was then dissolved in 30 ml. of 0.73 per cent lithium carbonate. Small amounts of charcoal (Norit A\*\*) were added in sufficient quantity to produce a colorless supernatant fluid after centrifugation. The solution was filtered by gravity, and 1.0 ml. glacial acetic acid was added to the filtrate and the solution stirred vigorously. The precipitate obtained immediately or after one to two hours at 4°C. was collected by centrifugation. After the precipitate was washed with 40 ml. cold distilled water and collected by centrifugation it was dissolved in 6 to 10 ml. of 0.73 per cent lithium carbonate and filtered through a sintered glass funnel. The purified uric acid was precipitated by dropwise acidification with 2.0 M

\* The Pfanstiel Laboratories, Inc., Waukegan, Illinois.

acetic acid to pH 5.5 and cooled. The precipitate was collected by centrifugation. Recrystallization from lithium carbonate by this procedure was repeated three times.

This procedure was not applicable to the isolation of uric acid from the urine of control patients in whom the concentration was less than 1.0 mg. per ml. For this purpose an isolation method was developed which represents a modification of the analytic method of Carr and Pressman [9]. A 300 to 400 ml. aliquot of urine was adjusted to pH 7.5 and passed through a Dowex-2-X10<sup>®</sup>\* acetate form column (7 cm. by 2 cm.) with suction. The neutral effluent and that obtained on washing with 50 to 100 ml. distilled water contained no uric acid and were discarded. The column was eluted with 350 ml. of a solution made by mixing equal volumes of 0.04 M hydrochloric acid and 1.0 M sodium chloride. This effluent which contained the uric acid was evaporated *in vacuo* in a flash evaporator to approximately 5 ml. The moist uric acid-sodium chloride mixture was transferred with a minimum of cold 2.0 M acetic acid to a small Erlenmeyer flask and placed in the cold for thirty-six hours. The uric acid was collected by centrifugation, extracted with cold dilute acetic acid to remove any remaining salt and dissolved in 15 to 25 ml. lithium carbonate solution. The solution was decolorized, centrifuged, filtered and precipitated as described previously. Recrystallization from lithium carbonate was repeated once. When aliquots of the same urine were subjected to both methods of isolation the specific activity of the uric acid obtained was identical.

To determine specific activity the isolated uric acid was dissolved in 4 to 8 ml. of lithium carbonate solution. An aliquot was diluted 1:500 and its uric acid concentration determined. Undiluted aliquots (0.2 ml.) were plated directly on stainless steel planchets, dried and assayed for radioactivity. The apparatus used for the determination of radioactivity (D-47†) records 1  $\mu$ c. as  $5.71 \times 10^6$  c.p.m.

#### RESULTS

*Urinary Excretion of Uric Acid.* The ranges of twenty-four hour urinary excretion of uric acid in these patients and the three control patients are shown in Table II. It is clear that there was no overlap between the two groups. In the patients the mean rate of excretion was 690 mg. per day, which is in the range of adult patients with gout who have been classified as "hyper-excretors" on the basis of excreting more than 600 to 628 mg. per day [10,11]. In contrast, control children excreted a mean of 233 mg. per day. When the data were adjusted for differ-

TABLE II  
TWENTY-FOUR HOUR URINARY EXCRETION  
OF URIC ACID\*

Patient	No. of Samples	Mean (mg.)	Range (mg.)	Corrected for Body Weight (mg./kg.)
M. W.	7	669	487-792	46.8
E. W.	7	712	518-918	43.7
B. S.	7	176	56-265	10.1
E. S.	7	289	198-364	7.8
W. II.	7	233	201-268	13.0

\* Urinary excretions of uric acid in patients (M. W. and E. W.) and control patients (B. S., E. S. and W. II.) on a low purine diet.

ences in body weight, the patients were found to excrete 45 mg. per kg. per day, a value that was four and a half times that of the control patients.

The pH of the urine in these patients varied from 5.5 to 6.5. In one patient (M. W.) the urinary excretion of uric acid was 487 mg. per twenty-four hours when the urinary pH was between 5.5 and 6.5 and 461 mg. per twenty-four hours after a period of alkali therapy which raised the urinary pH to 7.5.

*Miscible Pool of Uric Acid and Its Rate of Turnover.* Following injection of uric acid-2-C<sup>14</sup> the specific activity of the uric acid isolated from the urine of these patients fell relatively rapidly over a period of three days. (Fig. 3.) Isotope was not detectable after five days. The decline in the natural logarithm of the specific activity was linear over the three day period in both patients. These data indicate that the slopes of the lines are functions of endogenous production of uric acid and are consistent with clinical observations that there were no tophi. In the presence of tophi, slow equilibration of solid urate with miscible urate has been demonstrated [12], and the semilogarithmic plot of the isotope concentration against time does not yield a straight line [13]. Calculation of the sizes of the miscible pools after extrapolation of the lines to the intercept is given in Table I.

In the first patient (M. W.) the miscible pool of uric acid was 530 mg. In his brother it was 787 mg. When these data were corrected for body weight, a mean pool size of 43 mg. per kg. was obtained, a value similar to that observed in adults with nontophaceous gout [3].

The theoretic concentration that would result if the uric acid of the total pool were uniformly distributed throughout the total body water,

\* Dow Chemical Co., Midland, Michigan.

† Nuclear Chicago Corp., Des Plaines, Illinois.

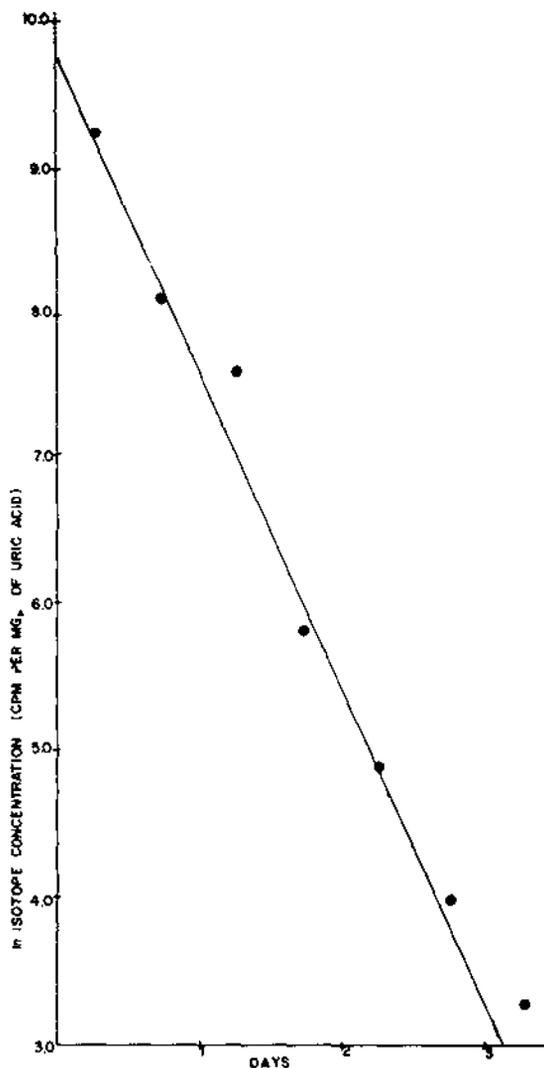


FIG. 3A. Semilogarithmic plot of the isotope concentration in urinary uric acid following intravenous injection of uric acid-2-C<sup>14</sup> in Patient M. W., age five years, weight 14.3 kg., slope—0.086 hours<sup>-1</sup>, miscible pool 530 mg., daily turnover 1.090 gm. and turnover time 0.49 days.

estimated at 70 per cent of the body weight, was calculated [2]. Uric acid concentrations of 5.3 and 6.7 mg. per 100 ml. were obtained, which approximated half the plasma concentrations. This was the relation observed in normal adult subjects [12] and in adult subjects with non-tophaceous gout [3]. These data are confirmatory of the absence of tophi and indicate that all the uric acid in the measured pool was present in soluble form. In this situation values obtained for the size of the pool and its rate of turnover would be expected to have considerably greater validity than when these criteria are not met.

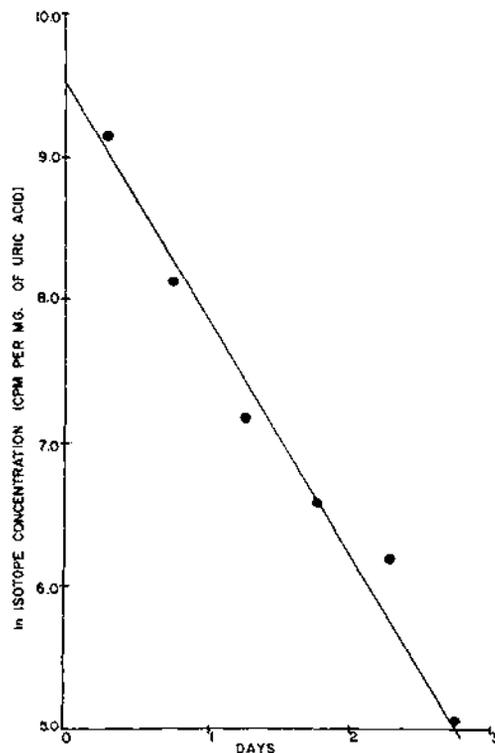


FIG. 3B. Semilogarithmic plot of the isotope concentration in urinary uric acid following intravenous injection of uric acid-2-C<sup>14</sup> in Patient E. W., age eight, weight 16.3 kg., slope—0.0673 hours<sup>-1</sup>, miscible pool 787 mg., daily turnover 1.272 gm. and turnover time 0.62 days.

The turnover rates obtained in both patients described (M. W. and E. W.) were 2.06 and 1.61 pools per day, respectively. These are extremely high rates of turnover for uric acid. Multiplication of these data by the number of milligrams of uric acid in the pool gave values of 1.09 and 1.27 gm. of uric acid per day. Adjustment for the body weight gave values of 76.2 and 77.9 mg. per kg. per day. The amounts of uric acid excreted in the urine represented 58 per cent of the total amount formed each day as indicated by the turnover rate. This relationship is consistent with the observation of others on adult subjects [3].

*Incorporation of Isotopically Labeled Glycine into Uric Acid.* The concentration of isotope in urinary uric acid during the seven days following the injection of glycine-U-C<sup>14</sup> is indicated in Figure 4. In the patients, maximal specific activity was observed in the first twenty-four hours. After thirty-six hours there was a gradual decline in specific activity. In the control patients, peaks in the curves were not prominent,

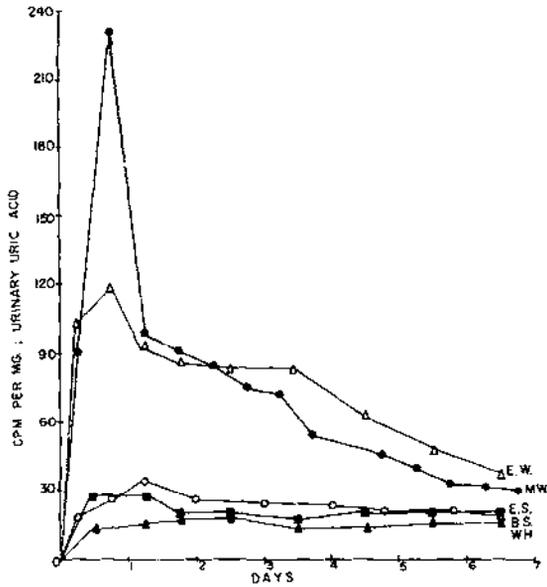


FIG. 4. Specific activities of urinary uric acid following intravenous administration of glycine-U- $C^{14}$ .

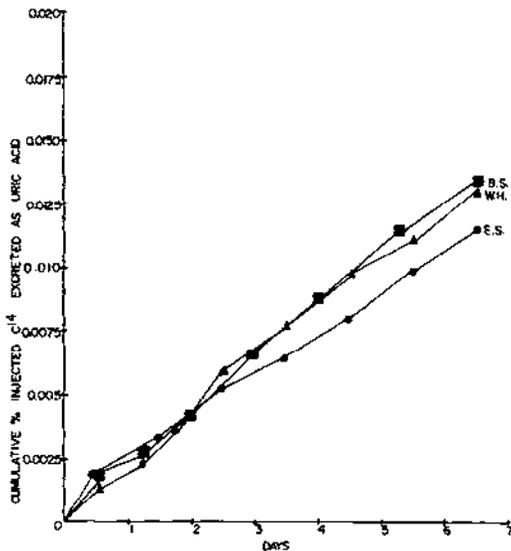


FIG. 5. The cumulative excretion of  $C^{14}$  in urinary uric acid in three control patients following the intravenous administration of glycine-U- $C^{14}$ .

but the highest specific activities were found in the first thirty-six hours; a low level of activity was observed throughout the period of study. The patients described differed clearly from the control patients, and there was no overlap between the two groups. At their peaks, the specific activities of the patients described were four to eight times those observed in the control patients.

When experiments of this sort have been

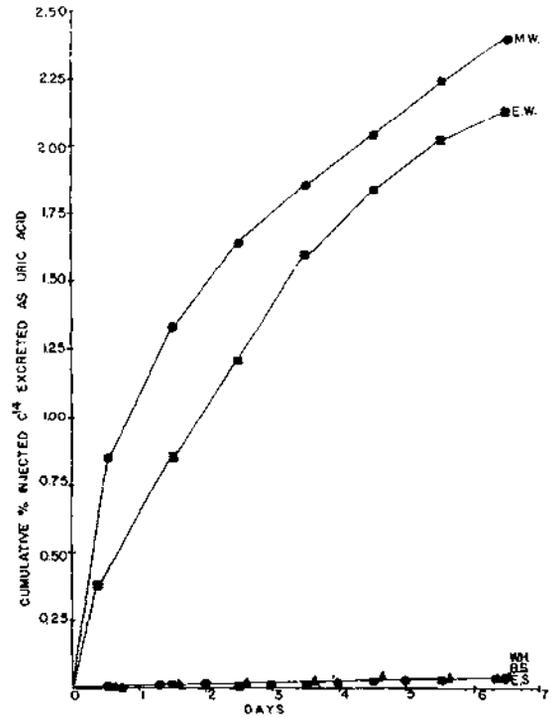


FIG. 6. The cumulative excretion of  $C^{14}$  in urinary uric acid in three control patients (B. S., E. S. and W. H.) and patients with cerebral palsy and hyperuricemia (M. W. and E. W.) following the administration of glycine-U- $C^{14}$ .

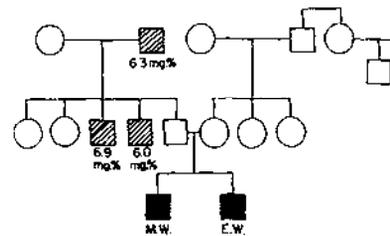


FIG. 7. Survey of the family for serum concentrations of uric acid. The open figures represent normal serum uric acid levels; the cross-hatched figures represent asymptomatic hyperuricemia found in two paternal uncles and the paternal grandfather. The patients are indicated in black.

carried out in adult subjects with gout and in adult control subjects, it has not been possible to distinguish the two populations regularly on the basis of the specific activity of the urinary uric acid [5,17]. Thus the cumulative recovery of isotope in urinary uric acid over a seven day period after the administration of glycine has been employed to characterize those in whom gout is associated with overproduction of uric acid from glycine. The similarity observed when this analysis was performed in the three control children is documented in Figure 5. These

TABLE III  
HYPERURICEMIA IN CHILDREN LESS THAN TEN YEARS OF AGE

Investigator	Sex and Age of Onset	Mental Condition	Remarks
Scudamore [14]	F, 8 yr.	...	...
Garrod [15]	M, 9 yr. F, 7 yr. M, 8 yr.	Probably intact Probably intact	Psoriasis, anemia, general poor health
Still [16]	F, 3½ yr.	...	Gout in father and grandfather
von Schopf [17]	M, 5 wk.	Neurologic intact	Severe tophi on fingers, white blood cell count 34,000 per cu. mm., with shift to left, died 5 days later with bronchopneumonia
Rauch [18]	F, 3½ yr.	Intact	Insidious onset, hands affected first
Recht [19]	F, 5 yr.	Intact	Severely deformed by age 27
Talbott [20]	M, 6 yr.	Intact	At 6 yr. diagnosis of tuberculous arthritis of hip, at 12 yr. diagnosis of rheumatic fever, gout diagnosis at age 15, severe tophaceous gout
Catel, Schmidt [21]	M, 2½ yr.	Choreoathetosis, mental retardation	Family history of mental retardation, gout, and renal disease; elevated uric acid level, no nitrogen retention
Riley [22]	M, 3 yr.	Choreoathetosis, mental retardation, lip biting	Severe tophi by 8 yr.
Trousseau [23]	..., 6 yr.	...	...
Decker [24]	M, 6 yr.	Intact	Renal calculi preceding gouty arthritis, obstructive renal disease 6 yr., first arthritis at 13 yr., diagnosis of gout and hyperuricemia at 16 yr.
Smythe, Cutchin [25]	M, 6 mo. or 16 yr.	Neurologic intact, somewhat slow mentally	Failure to thrive and abdominal enlargement at 6 mo., obvious dwarfism 6 yr., tophi 16 yr., arthritis 17 yr., died in renal failure 23 yr.
Rosenthal et al. [26]	M, 3 mo.	Intact	History of gout in both maternal and paternal families

patients converted only 0.012 per cent of the injected isotope to urinary uric acid in seven days. The data obtained in the patients described is compared with those of the control patients in Figure 6. On this scale the curve representing the control patients is adjacent to the abscissa. In the patients described a mean of 2.25 per cent of the isotope of glycine injected was recovered in urinary uric acid in seven days. This represents 200 times greater utilization of glycine for production of uric acid than in the control patients.

*Genetic Studies.* A survey of the family for the levels of uric acid in the blood was carried out. (Fig. 7.) Both parents were found to have normal levels of uric acid. Asymptomatic hyperuricemia was found in two paternal uncles and the paternal grandfather.

#### COMMENTS

The striking clinical manifestations observed in the two patients described in this report, as well as its familial nature, suggest a distinct

syndrome. The cardinal features of the disorder are mental retardation, cerebral palsy, choreoathetosis, self-destructive biting and hyperuricemia. A review of the literature on cases of gout occurring in patients less than ten years of age has revealed fifteen cases reported since 1823 [14-26]. (Table III.) In two of these [21,22] choreoathetosis and mental retardation were also present, and in one [22] a photograph clearly illustrates a severely bitten lip. Metabolic studies have not previously been carried out. With a total of four patients with similar manifestations, it appears that 24 per cent of patients reported to have essential hyperuricemia before the age of ten years have had this disorder. It seems likely that the total incidence of this condition may be considerably higher, for in populations of children with mental retardation or cerebral palsy serum concentrations of uric acid are rarely determined.

Studies of uric acid metabolism have further indicated that these patients have an unusual disorder. The uric acid pool size and its rate of

turnover has been determined by Sorenson [3] using uric acid-2-C<sup>14</sup> in adult control subjects and adult patients with gout, with results similar to those of earlier studies with uric acid-N<sup>15</sup> [2]. Correction for body weight of the pool sizes reported by Sorenson yielded a figure of 36 mg. per kg. in two adults with nontophaceous gout, which approximated three times the mean obtained in nongouty control subjects. Pool sizes of 37 and 49 mg. per kg. obtained in the patients described in this report appear to be similar to those of the adults with nontophaceous gout. On the other hand, the turnover rates observed in these patients were considerably greater than those of adults with or without gout [2,3,12,13,27]. Turnover rates of 1.61 and 2.06 pools per day constitute turnover rates higher than any previously reported. Adults, even in the presence of gouty tophi, have usually been found to turn over about half of the uric acid pool each day. The highest turnover rate previously reported in a patient with gout was 0.96 pools per day [27], a figure which can be considered too high for the person studied, since he was overtly tophaceous. The net turnover of over 1 gm. of uric acid a day in these children, weighing 14 and 16 kg., is in the same range observed in adults weighing approximately 70 kg. Expressed in terms of body weight, the amounts of uric acid turned over by these patients per kilogram of body weight was approximately six times that of gouty adult subjects. Consideration of the excretion of uric acid in the urine leads to similar conclusions as to the magnitude of the metabolic defect in these patients. The total amounts of uric acid found in the urine each day were in the range observed in the relatively small proportion of gouty adults who have been classified as "hyperexcretors." Adjustment of the excretion data for patient weight markedly accentuates the hyperexcretion of uric acid that characterizes these patients.

Studies of the formation of uric acid from glycine in these patients have differed from those previously reported in that the intravenous route was employed. In addition, with the idea that it might permit more versatility in the ultimate search for other metabolic products of glycine, the tracer was uniformly labeled with C<sup>14</sup>. In the studies of Gutman and colleagues [10], the ranges obtained for the cumulative excretion of isotope of glycine-1-C<sup>14</sup> in the urinary uric acid of control subjects were

similar to those obtained with glycine-2-C<sup>14</sup> when the isotope was given in trace amounts. In studies utilizing orally administered glycine-1-C<sup>14</sup> control adult subjects have been reported to convert a mean of 0.17 per cent in seven days [5,10,28]. The value in many gouty adult subjects does not differ significantly from this mean [5,10,28]. In gouty adults in whom overproduction has been designated and in whom increased quantities of uric acid are usually found in the urine, a greater conversion, averaging 0.5 per cent, has been reported [5,10,28]. The low rates of conversion of glycine to uric acid observed in the pediatric control patients could reflect differences in methodology or the diversion of glycine which enters the pathways of uric acid biosynthesis preferentially into the nucleic acids of growing subjects. However, Balis and Samarth [29] found that the incorporation of glycine into the ribonucleic acid adenine of young hamsters was significantly lower than in adult hamsters. The normal levels of glycine in the plasma of the patients described and the control patients suggest that significant differences in glycine pool size were not present. The children with hyperuricemia and cerebral palsy converted over 2 per cent of the glycine administered to urinary uric acid. Thus, whereas the gouty adult in whom overproduction can be demonstrated converts two to three times as much isotope-labeled glycine to urinary uric acid as do adult control subjects, these patients converted 200 times the amount found in control children.

The occurrence of such a marked metabolic defect in patients with unusual neurologic and behavioral characteristics suggests the possibility that the two may be related. A relationship between uric acid and central nervous system function has been considered for many years, because of the high incidence of gout among those who have been important in the intellectual development of western civilization. In view of the mental retardation of the patients described in this report, it seems possible that an excess of uric acid, or one of its products or precursors, could produce marked toxicity under the conditions of permeability and of development of neural structures that obtain in early infancy.

#### SUMMARY

A syndrome consisting of hyperuricemia, mental retardation, choreoathetosis and self-destructive

tive biting has been described in two brothers aged five and eight years. The uric acid pools in these patients were found to be similar in size to those reported for gouty adult subjects; their rates of turnover were greater than any previously reported. The daily excretion of uric acid in the urine was considerably higher than those of control patients and approximated total values found in gouty adult "hyperexcretors." The formation of uric acid from glycine in these patients exceeded that of control patients by 200 times. These data suggest that the patients described represent a distinct clinical and metabolic syndrome.

*Acknowledgment:* We gratefully acknowledge the assistance of Dr. Floyd M. Kregenow, physician of Patient M. W., and of the staff of the Rosewood State Training School for permission to study Patient E. W.

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