URIC ACID: ITS ROLE IN BIOLOGICAL PROCESSES AND THE INFLUENCE UPON IT OF PHYSIOLOGICAL, PATHOLOGICAL AND PHARMACOLOGICAL AGENTS[1]

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Uric acid has been of interest to clinicians and clinical biochemists for many years because, next to urea, it is perhaps the most significant fraction of non-protein nitrogen in humans. Furthermore, for the last thirty years, there have been colorimetric tests available for its determinations. By the use of these tests, the uric acid content of various body fluids has been studied extensively in health and disease.

It has been assumed generally that uric acid is related to tissue breakdown. Urea excretion most certainly is linked to protein intake and urea most nearly approaches the well-established concept of an exogenous substance. Uric acid, on the other hand, is excreted in relatively constant amounts in normal subjects, is influenced only casually by variations in dietary intake (except for close uric acid precursors such as purines or nucleic acids), and is poured out in great quantities in diseases in which there is rapid tissue breakdown such as resolving pneumonia and leukemia.

There is one anomaly of uric acid metabolism which, from the point of view of human biochemistry, has probably contributed more to the complexity and, at the same time, the fascination of the problem; this is the unique ability of humans to excrete uric acid. Most mammals convert uric acid to allantoin. The excretion of large, or at least significant, amounts of uric acid is reserved primarily for birds, reptiles and insects who enjoy what might be termed a uricotelic mechanism. When presented with the problem of disposing of nitrogen wastes, these creatures convert them to uric acid. Probably the low solubility of uric acid aids in the retention of water and the preservation of osmotic relationships. Other animals synthesize urea, which is a non-toxic, freely diffusible substance, but which requires a considerable quantity of water for its removal.

In the human, the feeding of purine rich material increases the excretion of uric acid and there seems to be no question that uric acid is a catabolic product of purine metabolism, whether this purine is of exogenous or endogenous origin. However, with a definite uricotelic mechanism rather widespread in the animal kingdom, it may be well to consider that at least a vestige of such a process might contribute toward reconciling the differences that are so commonplace in the literature in regard to the role of uric acid in the human organism. The

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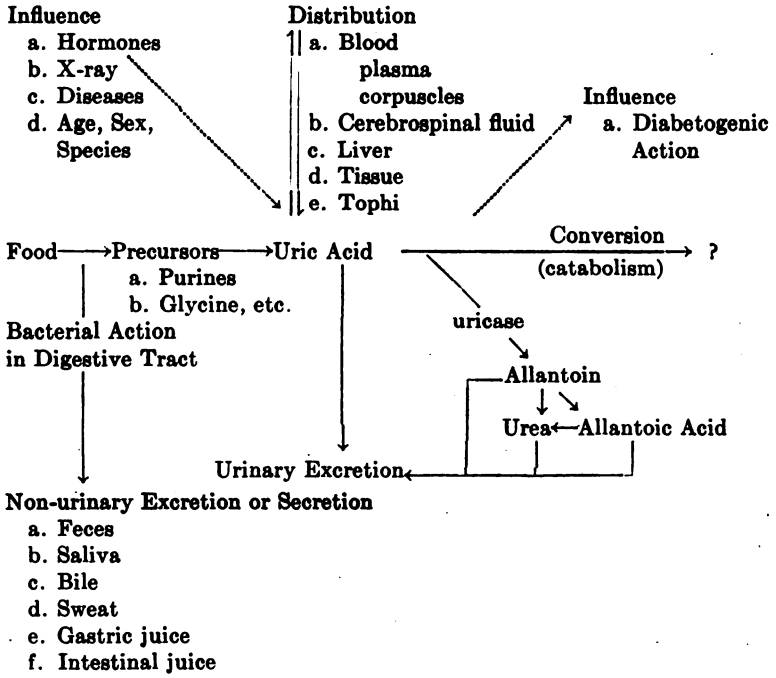
question of uricotelism versus ureotelism has been discussed by Baldwin (7) and the role of environmental adaptation carefully evaluated. The nitrogen excretion of invertebrates had been reviewed by Delaunay (78).

Figure 1 outlines the origin, distribution and disposal of uric acid in the animal body. Figure 2 indicates the chemical structures of pertinent compounds. No mention is made of the role of uric acid in plant metabolism, not because uric acid may not have significance in that regard, but because the present reviewers feel inadequate to undertake such a task. The first part of the review that follows will concern itself with the origin of uric acid and various phases of its metabolism as set forth in Figure 1. The second part will consider the

FIG. 1. Role of uric acid in the animal body



distribution and excretion of uric acid while the third part will review the catabolism of uric acid. The concluding part will review in greater detail the effects of various pathological and pharmacological agents upon uric acid in the body.

It should be noted that there have been several excellent reviews of uric acid metabolism. Haig's monograph of 1885 was perhaps the first (137). McCrudden's monograph (215) reviews the chemistry, physiology and pathology of uric acid and purine bodies prior to 1905. In the Harvey Lectures for 1915–1916, Benedict (16) brought the subject up to date. Rose (277) in 1923 reviewed purine metabolism for Physiological Reviews and, in 1924, Folin, Berglund and Derick (100) made a critical survey of the uric acid literature as a preamble to their important

studies. In 1940 Brøchner-Mortensen (38) presented in monographic form a mass of data of clinical significance in regard to uric acid. The monograph by Peters and Van Slyke on *Quantitative Clinical Chemistry* (253) contained perhaps the most recent general review on purines and pyrimidines including uric acid, until the appearance of Christman's review (67). The new book by Umbreit called *Metabolic Maps* (348) is a novel and highly successful attempt to depict metabolic processes by "maps" and schemes. Chapter XI of this book outlines the origin and breakdown of nucleic acids, purines, and pyrimidines and contains reference to much of the recent, especially the isotopic, literature. Concurrently the Annual Review of Biochemistry forms a running record of progress in the field.

There are many specialties, such as oncology, which have some, though perhaps no direct, interest in the uric acid problem. The literature here is too voluminous to be carefully screened. Furthermore, many papers have been deliberately omitted because the reviewers felt they were of lesser importance to the main topic discussed here or because the results were more critically presented by another investigator. No attempt has been made to assess priority.

Because of the wide variations in results obtained by various methods for determining uric acid, each student of this problem should consult the critical evaluation of methods prepared by Van Slyke in 1932 (252). Since that time many of the older methods have been revised and some new ones added. The use of the specific enzyme, uricase, has formed the basis for the more specific determinations of uric acid (23, 24, 48, 50), but the problem of interference in the colorimetric determination has not been completely obviated. Kalckar (167, 168) proposed the determination of the optical absorption of uric acid solutions at 290 mμ before and after uricase action, and this method or some modification of it would appear to offer the greatest specificity for the determination of small amounts of uric acid. In its present form, however, it is too tedious for routine clinical use.

PART I. ORIGIN OF URIC ACID AND VARIOUS PHASES OF ITS METABOLISM

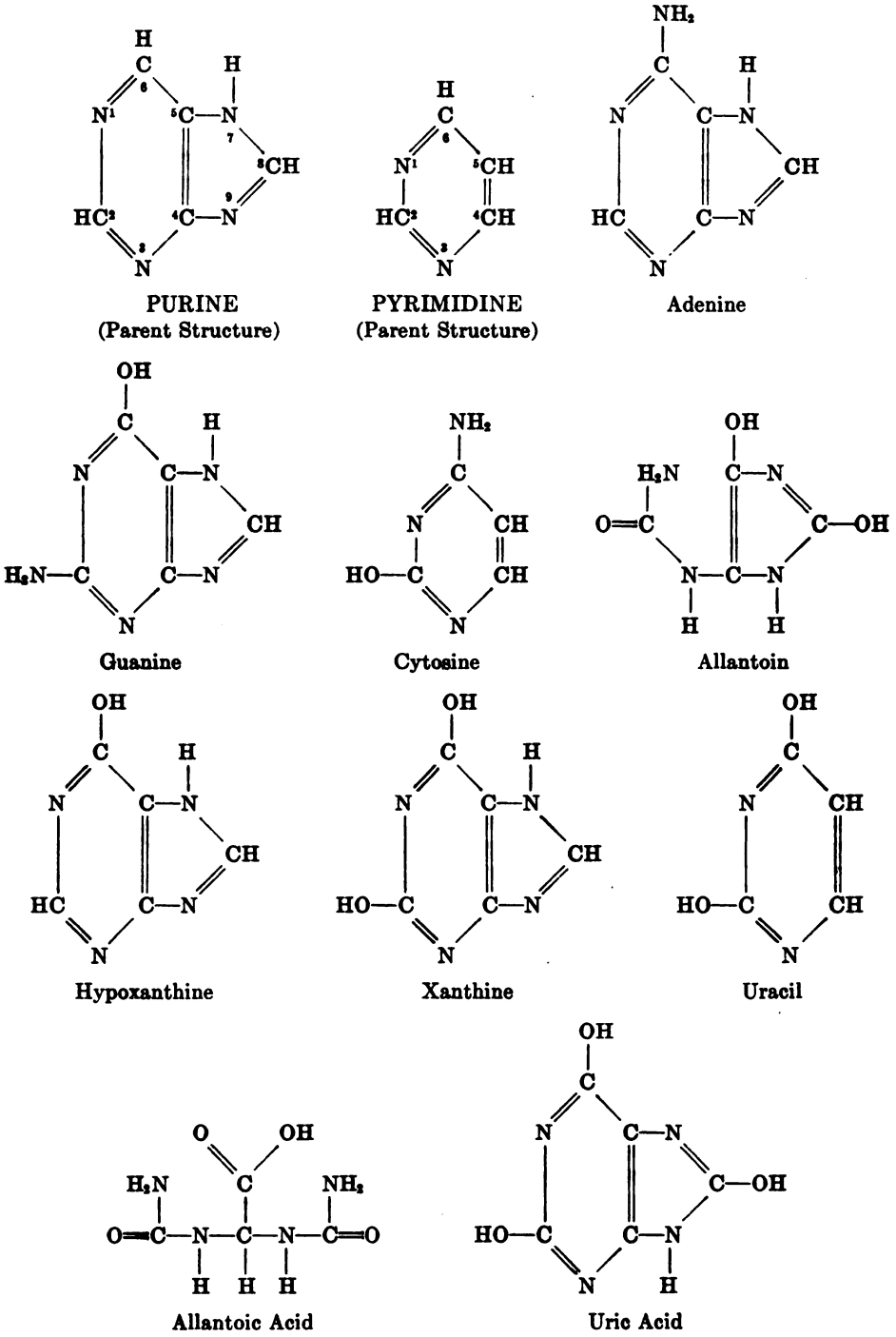
It has been generally recognized that the animal body is capable of synthesizing purine bodies. Animals, including humans, can be sustained on diets containing no preformed purines, the sole source of nitrogen being amino acids. It is also generally assumed that the animal body converts purines to uric acid or allantoin since the ingestion of purine-rich diets is followed by an increased excretion of uric acid or allantoin.

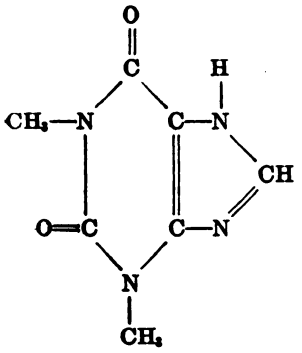
Use of isotopic compounds

The isotope approach has been applied in an attempt to gain insight into the intermediary mechanism of uric acid metabolism and, insofar as the technics have been applied and the data evaluated, the results should be the most conclusive of any available.

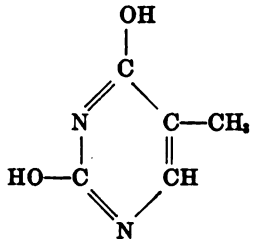
It has been demonstrated by various workers and in various species that the following substances may be incorporated into uric acid following administration: carbon dioxide, formate, lactate, glycine, serine, and threonine. Figure 3 sum-

FIG. 2. Chemical structures of compounds related to uric acid

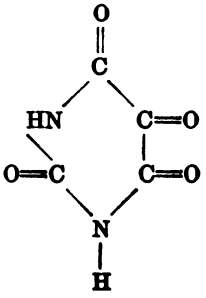




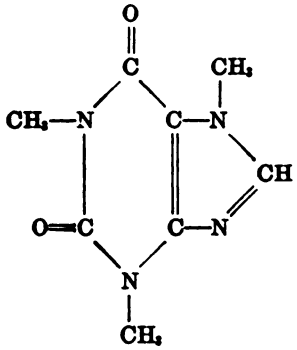
Theophylline



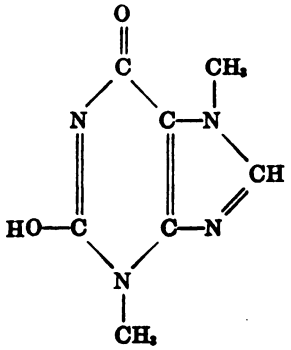
Thymine



Alloxan



Caffeine



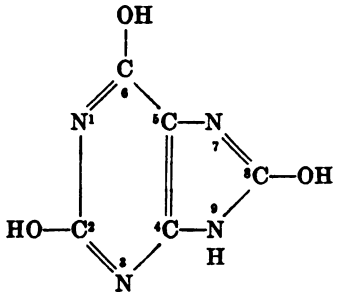
Theobromine

marizes the point of incorporation of the various compounds and indicates the species studied in that regard.

Barnes and Schoenheimer (8) showed that dietary ammonia (N^{15}) was readily incorporated into purines and pyrimidines of tissue nucleic acid in pigeons and rats. Furthermore, when isotopic guanine and pyrimidines, uracil and thymine, were fed to either of these animals, Plentl and Schoenheimer (256) found that there was no incorporation into nucleic acids although the guanine did appear as uric acid or allantoin. Bendich *et al.* (12) demonstrated no incorporation of N^{15} cytosine into tissue nucleic acid of rats. Brown *et al.* (42) fed labeled adenine to rats and found that both the adenine and the guanine of the tissue nucleic acids contained the N^{15}. This established the utilization of adenine for the synthesis of tissue nucleic acids. This latter work and its implications has been discussed by Brown (40). From these investigations it would appear that nucleic acid synthesis in the pigeon, rat and human is generally achieved from simple one-, two- and three-carbon chains. The only purine that is incorporated to any measurable extent is adenine. Pyrimidines, which are structurally related to purines, are probably not intermediates in nucleic acid or uric acid formation. The old concept that arginine and histidine, because of some similarity of their structure to that of the purines, might be involved in purine and hence uric

acid synthesis has been pretty thoroughly discarded (cf. Crandall (72)). Barnes and Schoenheimer (8) with the aid of isotopic nitrogen found no incorporation of arginine or histidine into purines, pyrimidines, uric acid or allantoin. The same conclusions had been arrived at a quarter of a century earlier by Lewis and Doisy (195) who found that high protein diets rich in arginine and histidine did not cause more marked rises in uric acid elimination than similar diets poor in these amino acids.

FIG. 3. Point of incorporation of isotopically labeled compounds into uric acid



Ref.	*Compound administered*	*Species*	*Incorporated at:*	*Remarks*
305	N^{15} glycine	human	N 7	Some to N 1, N 3, N 9
318*	formate, lactate	pigeon	C 2, C 9	
317*	CO_2	pigeon	C 6	
	lactate, glycine } carboxyl	pigeon	C 4	
	lactate (α or β C)	pigeon	C 5	
47	glycine (carboxyl)	pigeon	C 4	Lactate incorporated to lesser
	lactate (carboxyl)	pigeon	C 4	extent than glycine. Suggested
	lactate (α C)	pigeon	C 5	that lactate → (serine) → gly-
	CO_2	pigeon	C 6	cine.
46	formate	pigeon	C 2, C 8	Slight amount to C 4, C 5
169	formate	pigeon	C 2, C 8	
	glycine (carboxyl)	pigeon	C 4	
	CO_2	pigeon	C 6	
	glycine (methylene)	pigeon	C 5	also C 2, C 4, C 6, C 8
179	threonine (C 2)	rat	C 4	probably through glycine

* It was stated in (317) and (318) that acetate contributed to C 2 and C 8. Later it was reported (299) that the acetate was contaminated with formate. Uncontaminated acetate was shown not to be a precursor.

The effect of dietary intake on uric acid excretion (synthesis)

It was early recognized that foods differed in their purine content, and tables of such information have been compiled by Burian *et al.* (51, 52) and by Pratt (260). The ingestion of foods high in purine is followed by an increase in uric acid excretion. Galinowski (110) demonstrated that, after the ingestion of 20 gm. of nucleic acid or its sodium salt, the blood uric acid concentration increased for one hour, was at a maximum during the period of 4–8 hours, and gradually subsided. Increased uric acid elimination began within 2 hours and continued for from 2 to 4 days. The "extra" uric acid corresponded to

3–18% of the ingested purine. It should be noted, however, that the determination of "extra" uric acid depends upon the establishment of a normal level of excretion and, since this varies somewhat under the most rigorous of conditions, it sometimes becomes academic to discuss the quantity of "extra" uric acid excreted. Dirr (82) noted that humans fed yeast protein, which contains relatively large amounts of nucleic acid, excreted more uric acid and that their blood uric acid concentration increased. This has been disputed by Smith (311) who found no increase in urinary uric acid after the ingestion by humans of from 12.5 to 62.5 gm. of yeast cake solids (equivalent to 0.06–0.30 gm. purine N). Taylor *et al.* (337) maintained healthy young males on a diet first with milk and eggs as the source of nitrogen; later sweetbreads were substituted as the nitrogen source. It was noted that the greater part of the purine nitrogen was either destroyed or converted to non-purine nitrogen, such as urea. They concluded that the ingestion of moderate amounts of purine does not increase purine bases in urine but does increase the uric acid elimination. Salomon (284) reported the same increase in uric acid excretion with 10 gm. of yeast as with 100 gm. of meat. Herring roe and Liebig's meat extract increased uric acid excretion appreciably according to Plimmer *et al.* (257).

Because of the wide variation in daily uric acid output, Wilson, Bishop and Talbott (363) set up a factorial experiment in which basic diets were altered by the substitution of liver and sweetbreads for the usual protein sources. In a five-week study, three of the four subjects excreted significantly more uric acid on high purine diets than on equivalent basic diets. This appears to confirm the general consensus on this matter.

Since tea and coffee contain methyl derivatives of the purines (theobromine, theophylline, caffeine), it early became of interest to know whether the ingestion of them would cause an increase in uric acid excretion since in this case they might be contraindicated in the dietary of the gouty or hyperuricemic individual. At first it appeared that demethylation and oxidation did convert some of these products to uric acid (218, 236, 237). Buchanan, Christman, and Block (49) reinvestigated the problem in 1945 and found that the ingestion by humans of caffeine or theophylline but not theobromine was followed by the excretion of phosphotungstic acid-reducing substances. However, uric acid excretion, as determined by their uricase method, was not elevated, hence the compounds were probably methyl uric acids. It has been known for some time that several compounds related to uric acid may give some degree of color with the usual colorimetric reagents for uric acid.

The influence of protein, fat, carbohydrate, and total caloric intake on uric acid excretion (synthesis)

Folin (99) in 1905 observed that the addition of protein to a purine-free diet resulted in an increase of uric acid excretion. This has been confirmed by others (217, 264, 310). In 1919 Höst (152) reported that on a fixed purine-free diet the uric acid excretion varied from day to day up to eighty per cent. In a few individuals the excretion was constant but could be influenced by variation in the caloric intake and variations in the food protein. With a fixed caloric intake,

reduction of the protein and increase in the fat and carbohydrate reduced the uric acid output. Increase in the protein and reduction in the carbohydrate increased the output. With protein intake constant, reduction in the caloric intake decreased the uric acid excretion and an increase in the caloric intake increased it. This confirmed the earlier observation by Taylor *et al.* (337) that, with a considerable increase in the nitrogen intake, there was in consequence a sharp increase in the uric acid output without any appreciable effect on the creatinine output. Lewis *et al.* (196) reported that after the ingestion of egg white or cottage cheese there was a slight rise in uric acid excretion beginning in the second hour and reaching a maximum at the fourth hour. Equivalent amounts of amino acid such as glycine or alanine caused a sharp rise in the second hour followed by a prompt return to normal. The ingestion of a second portion was followed by the same response. Aspartic and glutamic acids caused a greater effect. However, other nitrogen sources such as NH_4Cl or urea had no such effect and it was suggested that the stimulation of cellular metabolism was responsible for the phenomenon. It was pointed out that the dicarboxylic amino acids caused a greater excretion of uric acid than glycine and alanine. It was re-emphasized that the amino acids stimulated uric acid production since successive single doses of glycine resulted in increased elimination of uric acid in each case. If the action were primarily on the renal excretory mechanism, it would be unlikely that successive doses would be as effective but this was not an unequivocal point. Sarcosine (N-methyl glycine) did not influence uric acid excretion. Christman *et al.* (68) confirmed the fact that the ingestion of glycine by a fasting man was followed by an increased hourly excretion of uric acid.

In contrast to the studies just cited, Rose (276) and Leopold *et al.* (192) fed a high protein diet for longer periods and demonstrated that the effect of the high protein diet wears off in a few days and that uric acid excretion again returns to normal. Borsook and Keighley (33) observed the same stimulating effect of amino acid ingestion on uric acid output but reported that, in addition, ammonium carbonate also increased uric acid excretion. In the previously cited factorial study of Wilson, Bishop and Talbott (363), it was demonstrated that on a high protein diet significantly more uric acid was excreted than on a high fat diet. A high carbohydrate diet yielded results intermediate between the other two diets and could not be significantly differentiated from either of them.

Folin, Berglund and Derick (100) studying adults, and Leopold, Bernhard and Jacobi (192) studying children, added large quantities of protein to a purine-free diet and observed that the blood uric acid concentration decreased while the urinary output of uric acid increased. Since the effect subsided shortly they concluded that the effect was one of expediting excretion.

The influence of fat upon uric acid excretion was studied by Lewis *et al.* (194) Fasting individuals who had previously been on a purine-free diet low in protein were fed up to 135 gm. of cream. The hourly rate of uric acid excretion was not influenced. The ingestion of 50 gm. of glycerol caused a marked increase in the excretion during the second and third hours but glycerol in amounts equal to the fat ingested had no such effect. (Polyhydric alcohols appear to have a uricosuric effect.) The ingestion of fat previous to glycine did not alter the stimulating

effect of the amino acid and thus one might infer that fat *per se* does not have a depressing effect upon either uric acid production or excretion. It should be remembered, however, that these were short term experiments. In the same study 100 gm. of lactose, sucrose or glucose did not influence uric acid excretion but amounts of honey or commercial glucose syrup greater than 200 gm. caused an increase that was neither constant nor so marked as with the glycerol or amino acid. Adlersberg *et al.* (3) reported that uric acid excretion was diminished on a high fat diet and that this was probably due specifically to the fat since an equivalent high carbohydrate diet did not cause this. Acidosis or ketosis was thought not to be of importance. However, Harding *et al.* (139, 140) felt that the increase in uric acid retention observed both during starvation and on high fat diets was related to ketosis. Dogs fed fat bacon exclusively developed fatty livers and uric acid stones in the kidney and bladder according to Groen (130).

It seems that many of these confusing and discordant observations might be brought together on the basis of the following hypothesis. In humans on a purine-free diet, uric acid is derived both from the breakdown of purines and nucleoproteins (endogenous, wear and tear source), and by more or less direct synthesis from the nitrogen pool as is common in birds and other animals. When the nitrogen pool is well stocked as after protein or amino acid feeding, more uric acid is synthesized by the second route and the overall uric acid output is increased. After the feeding of fat there is a greater preponderance of acidic fragments to be disposed of an these require more ammonia for neutralization at the kidney level. Thus nitrogen is lost from the metabolic pool and the direct synthesis of uric acid is curtailed. There is no need for marked acidosis or ketosis at this point since the changes might well be so slight as to go unnoticed. The fact that ammonium carbonate increased uric acid excretion (33) fits in well with this hypothesis since ammonium carbonate could supply base for neutralization of acid in the kidney. This would spare body ammonia and perhaps even contribute to the body nitrogen pool. A high calorie diet has a nitrogen-sparing action which allows more uric acid formation per gram of nitrogen ingested. On a low calorie diet the amino acids are expended more prudently because they must supply both protein synthesis and energy requirements and are not so readily available to the general metabolic pool. The tendency of the uric acid stimulating effect of protein or amino acid to decrease after a few days may be a homeostatic adjustment.

The role of the digestive tract in uric acid synthesis and destruction

In the human, synthesis and destruction of uric acid or uric acid precursors in the alimentary tract must not be discounted. Bishop and Talbott (unpublished results) found that a portion of the isotopic ammonia ingested was excreted as labeled uric acid. It appeared from the elimination curve, however, that uric acid *per se* was not the primary compound formed. Furthermore, synthesis would not of necessity have had to take place before the absorption of the ammonia. Steudel (323) suggested a relationship between fermentation in the feces and uric acid excretion. The excretion was low when fermentation activity was unusual. Hirchstein (148) affirmed that, following digestion of purine-free

proteins *in vivo*, measurable quantities of purine could be identified in the digestive mixture. He postulated that these purines arose from the digestive glands which furnished a secretion containing purines.

Uric acid is apparently added to the contents of the digestive tract at various sites. Lewis *et al.* (198) reported that saliva contained about thirty per cent as much uric acid as blood samples drawn concomitantly. Updegraff and Lewis (349) later redetermined the average value to be forty per cent (range, 15.6–93.1 %). Lowenstein and Gies (205) gave the figures 2.1 mgm. % for men and 1.1 mgm. % for women. Maupetit (214) gave values of 1.5–4.5 mgm. % but warned that clinical samples of saliva must be protected against bacterial action. In subjects with nitrogen retention, the concentration was as great as 12.0 mgm. %.

The gastric juice of children removed by an Einhorn tube one hour after a test meal of rice mucilage was found to contain 1.0–4.9 mgm. % (81). Ferrannini and Conese (90) stated that the uric acid levels of gastric juice and that of blood appeared to be unrelated except that blood was always higher. Histamine increased the amount of uric acid in gastric juice. Robecchi *et al.* (272) reported levels of 0.5–1.2 mgm. % and noted that uricemia as well as damage due to disease of the mucosa caused an increase in the amount of uric acid.

Uric acid is presumed to be secreted in the bile. Lucke (206) noted that its passage into the bile could be demonstrated by the intravenous injection of uric acid. Garot (111) also found that bile was a normal channel of uric acid elimination in dogs. Bergami (17) was unable to detect uric acid in the bile of dogs normally; but when more than 100 mgm./kg. was injected, 30–50 mgm. of uric acid per 1000 parts of bile was found. Bile obtained post-mortem in humans contained from a trace to 50 mgm. % of uric acid with an average figure of about 19 mgm. % (44). Minibeck (225) reported the duodenal secretion of uric acid. Schroeder *et al.* (292) observed that the degree of intestinal excretion of uric acid by cats after intravenous injections paralleled the blood uric acid level and was increased by substances that stimulated intestinal secretion.

Geren, Bendich, Bodansky and Brown (113) injected intravenously N^{15}-labeled uric acid in one subject and recovered more than ninety-five per cent of the dose as urinary uric acid. When a comparable dose was ingested, this recovery was only about forty-five per cent. This might be due to intestinal destruction of ingested uric acid or it might be related to the fact that the ingested uric acid passed through the liver before it entered the general circulation.

Lucke (207, 208) reported that uric acid given orally could be followed until it reached the region of the alimentary tract high in content of E. coli. Thereafter the amount diminished. The daily fecal excretion was estimated to be 30–50 mgm. This was considerably higher in subjects with hyperuricemia. Morris *et al.* (228) added infusions of feces to a medium containing uric acid and observed destruction of uric acid. Several micro-organisms are known to utilize uric acid.

In some birds the liver is capable of converting either ammonia or amino acids to uric acid. In other birds, especially the pigeon, the liver forms a precursor which is converted to uric acid by the kidney, (98, 108, 187, 280, 293–298).

The liver in dogs is apparently not the site or at least not the only site of

uric acid formation. Following total removal of the liver, the formation of uric acid is unimpaired (27). Moreover, dogs with Eck fistula (and liver atrophy) excreted more uric acid after the ingestion of pancreas than did normal dogs (26). This was probably due to the fact that purines could be converted to uric acid elsewhere than in the liver and the liver was not able to convert the uric acid to allantoin. Nephrectomy and hepatectomy studies in rats showed that the conversion of uric acid to allantoin occurred chiefly in the liver (57). Paroulek (251) injected uric acid into the vena porta and found that almost none of it entered the general circulation. When a similar quantity was injected directly into the general circulation, however, the blood uric acid concentration was increased for a period of from 2 to 4 hours. Chauffard *et al.* (63) sampled blood from both the portal and hepatic veins of anesthetized dogs. In dogs fed sweetbreads, liver and spleen, and in some fed a varied diet, there was an arrest of uric acid by the liver as great as 50 per cent. According to Borsook *et al.* (32), isolated rat tissues incubated in Ringer's solution formed uric acid but no allantoin in every tissue except liver. Allantoin was formed only in the liver where added uric acid was also converted to allantoin. Furth *et al.* (109) showed that rat liver contained 8–12 mgm. % of uric acid, but this diminished during fasting or after feeding a pure protein diet. Normal human livers contained 7–10 mgm. % whereas cirrhotic or fatty livers contained only 2–5 mgm. %.

In hepatectomized dogs, uric acid is not destroyed and accumulates in the blood and tissues or is excreted if the kidneys continue to function (210). In hepatectomized dogs there is a large increase in uric acid excretion with a corresponding decrease in allantoin. Destruction of uric acid in normal dogs depends upon liver function (28).

In the dog spleen perfused with defibrinated dog blood, there was a marked increase in uric acid as well as free and bound purines. It was concluded that uric acid originates not only from adenylic acid but also from nucleins in the spleen (315).

PART II. DISTRIBUTION AND EXCRETION OF URIC ACID

Concentration in whole blood and plasma in the non-gouty subject

Urates are present in body fluid in a concentration considerably less than the maximum solubility of sodium urate in distilled water. Sodium urate is a relatively soluble substance and in distilled water it is soluble to the extent of approximately 100 mgm. % (131). The lower solubility in body fluids is presumed to be due to the concentration of other ions normally present (253). Gudzent (131) obtained a final solubility in serum equivalent to 8.3 mgm. % whereas Bechold and Ziegler (11) obtained solubilities more than two-fold this value under conditions which permitted equilibrium to be established over a period of several days. When uric acid is added *in vitro* to serum of gouty patients, concentrations as high as 25 mgm. % may be obtained within a few hours (335). Naturally occurring urate may be present in the serum of patients with gout in concentrations as high as 20 mgm. % (140).

When urate is added to whole blood, it distributes itself between serum and cells in the same proportion as the naturally occurring urate (335). The

distribution of uric acid is affected by pH and CO_2 tension according to Gibbs-Donnan law of equilibrium as applied to blood by Van Slyke and associates. There is a migration of urate ions from the serum to the cells as the serum becomes more acid. A reverse migration takes place as the serum becomes more alkaline. At pH = 7.40 the urate distribution ratio as defined by the relation $\frac{\text{cell urate}}{\text{cell water}} / \frac{\text{serum urate}}{\text{serum water}}$ is approximately 0.60. If blood, to which urate is added, is oxygenated or reduced, the urate ratio changes in a manner similar to the chloride and bicarbonate ratios.

The concentrations of uric acid in serum have been reported by most observers to be greater than in red cells (146, 177, 355). Theis and associates (340) determined the urate concentration in plasma and blood cells in one hundred and four subjects. An equal distribution was reported in fifty-one instances while the concentration was greater in the corpuscles in eight and greater in the plasma in forty-five. In fourteen of twenty bloods investigated, added uric acid did not enter the red cells while in six instances the added uric acid was distributed equally between corpuscles and the plasma.

The concentration of uric acid in whole blood in normal subjects is said to be not greater than 4 mgm. % (101, 165, 273). The concentrations in serum or plasma are approximately 1 mgm. % higher. Wu (369) reported that in human blood the uric acid concentration in plasma was 3.9 mgm. % and in corpuscles, 1.9 mgm. %. That is, corpuscles contained only forty-eight per cent as much urate as plasma. Folin and associates (103) reported a considerably lower value, *i.e.*, twenty-two per cent as much uric acid in corpuscles as in plasma. Schmidt (290), using the Morris-MacLeod method, obtained an average value of 4.3 mgm. % in 4268 samples. In 2000 cases selected because of freedom from kidney disturbance, the average was 3.53 mgm. %. Block (24) reported a range 2.35–4.42 mgm. %.

A difference between males and females in concentration of urate in body fluids has been reported from time to time. Males exhibit a slightly higher concentration both in whole blood and in plasma. In a study of 157 individuals between the ages of five and sixty Greisheimer and Arny (127) noted the blood levels to be 3.07 ± 0.029 mgm. % for females and 3.417 ± 0.034 mgm. % for males. Tastaldi (336) reported the following:

SEX	WHOLE BLOOD	PLASMA
	mgm./%	*mgm./%*
Male	1.9–3.9	2.9–5.7
Female	1.5–3.4	2.0–4.7

Bulger (50) reported an average value for whole blood of 3.5 mgm. % in females and 4.4 mgm. % in males. Smyth, Stecher and Wolfson (314) suggested that, because of the difference between sexes, the standards should be revised so that the accepted range for males would be approximately 0.5 mgm. % higher than for females. Brøchner-Mortensen (36) in 1937 noted that such factors as weight

and stature might influence the concentration of serum urate in non-gouty subjects. Blood from the umbilical cord of 120 infants was reported by Berger (18) to have an average of 4.97 mgm. % (range, 2.68–8.48). The concentration of uric acid in fetal and maternal blood was studied by Plass and Matthew (255).

The concentration of serum urate may be elevated above the normal range in several states not associated with clinical evidence of gouty arthritis. Renal insufficiency is one of the commonest. In the early part of this century clinicians gave hopeful consideration to the prognostic significance of increased blood uric acid in patients with renal impairment (88). The optimistic predictions made by many workers of that time have been largely disproved. It is now believed that with renal incompetence the increase in concentration of uric acid in body fluids is merely a reflection of the inability of the kidney to excrete nitrogenous end-products. Lennox (191) reported that during fasting there was a retention of uric acid. As the plasma level rose, there was a shift of uric acid into the red cells and other tissues. About sixty per cent of this retained uric acid was excreted later, after the fast was over. Feeding of fat did not relieve the retention but feeding of carbohydrate, thyroid extract, amino acids or protein did. Previously Lennox (190) reported data on twenty-two starvation periods of eight days or longer in seventeen epileptic and two normal subjects. From a prestarvation level of 4 mgm. % the blood uric acid rose to over 10 mgm. % but without any retention of non-protein nitrogen or urea.

Patients with leukemia, polycythemia vera or multiple myeloma (85, 160, 199, 344) frequently show an increased concentration of serum urate. Pernicious anemia (115), lead poisoning (275), starvation (190), asthma (19), carcinoma of the stomach (92), eczema and allied dermatoses (286), cardiac decompensation (362), myocardial infarction (285), angina pectoris (35) and certain acute infections such as pneumonia may cause an increase in the concentration of uric acid that is not reflected by a similar percentage increase in urea nitrogen. Ficarra (92) associated the hyperuricemia in patients with carcinoma of the stomach with hypoproteinemia.

In a comprehensive study of 25 normal female college students, Okey (243, 244) noted that the concentration of uric acid in the blood rises just before or at the onset of menstruation and is followed by a decrease from one to three days later. During labor an increase in plasma uric acid as well as urea occurs (73). Normal values are observed by the third day following delivery. In eclampsia the blood uric acid content increases and this is a delicate indicator for the degree of kidney injury (147).

Williams (361) studied uric acid levels in toxemias of pregnancy and reported the following averages:

5 patients with eclampsia	7.84 mgm. %
13 patients with pre-eclampsia toxemia	3.98 mgm. %
7 patients with hyperemesis gravidarum	4.91 mgm. %
6 normal pregnant patients	1.94 mgm. %

Hellmuth (147) reported that during attacks of eclampsia the blood uric acid concentration was about three times normal. Cadden *et al.* (58) found that the

blood uric acid concentration in five women with eclampsia was high but that there was no decrease in the uric acid output. They concluded that this was due to impaired hepatic destruction of uric acid. Shaffer *et al.* (303) postulated that the hyperuricemia in eclampsia might be due to a decrease in uric acid clearance. Simultaneous reduction in inulin and urea clearance indicated that the decreased uric acid clearances were due to reduction in the glomerular filtration rate.

Uric acid appears as an excretory product in the newborn, and uric acid infarcts in the urinary tract are not uncommon. Trautner (345) believed that after the mother's blood had been swept out, there was no uric acid in the newborn until E. coli appeared in the feces. Schloss *et al.* (289) found the uric acid output of children to be high, both on a relative and absolute basis. This was attributed to their rapid anabolism and catabolism. The uric acid blood level in infants a few days after birth, however, is generally reported to be lower than in adults. Liefmann (200) found a level of 1.3–1.7 mgm. % in infants on a purine diet. In growing children it slowly increased up to 2–4 mgm. %, the level for adults. The excretion of uric acid in the urine of a male and female child was followed by Starkenstein (320) over a period of sixteen years from the age of three. The excretion increased gradually from an average of 120 mgm. per day to 440 mgm. per day at the age of eighteen. Hoeffel and Moriarity (150) reported the following blood data:

	BLOOD URIC ACID MGM. %		
	Minimum	Average	Maximum
20 infants up to 22 months.....	1.28	3.1	6.76
30 children, 2–15 yrs.....	2.56	3.8	5.88
Adults.....	3.28	4.05	4.75

In normal persons older than seventy years Currado (74) observed a decrease in uricemia.

No difference was noted in the concentration of uric acid between normal persons inhabiting the tropics and those inhabiting the temperate zone (338). Borchardt (29) noted that the blood uric acid content of healthy individuals at high altitudes is approximately fifty per cent of the level of lowland inhabitants. Males bathing in water at 11–14°C. for several hours showed an increased urinary output of uric acid with a mild diuresis (306).

Non-affected relatives of gouty patients may have an increased concentration of uric acid in the serum. The increased concentration is thought to be determined genetically and to be associated with the inborn error of metabolism (312–314, 322, 328).

Concentration of uric acid in gouty subjects

The concentration of uric acid in the serum is of considerable aid in the diagnosis of gout. The concentration usually is elevated irrespective of the presence of acute or chronic joint symptoms. Because of the difference in concentration between serum and red cells and because there are compounds

in the red cell which interfere in the normal colorimetric determination of uric acid, the determination is almost always made on serum. The concentration of uric acid in the serum in patients with gout is usually greater than 6 mgm. %. Particular attention should be given, however, to the possibility of uricosuric drugs having been administered immediately prior to the collection of blood. It will be recalled that the concentration of uric acid in the serum for normals is less than 5 mgm. %. Since the concentration for most gouty patients is greater than 6 mgm. %. this leaves an intervening range of 1.0 mgm. % which separates gouty individuals from non-gouty subjects (329). In one study by the authors the concentration of uric acid in the serum was determined two or more times in each of one hundred patients with clinical gout. A total of more than nine hundred determinations was performed. Approximately ninety-eight per cent of the total number of determinations were greater than 6 mgm. %. The values ranged from 5.7 to 16.2 mgm. %. The average was 8.8 mgm. %. Jacobsen (162) and Brøchner-Mortensen (36) reported similar data.

The concentration of urate in other body fluids, with the exception of spinal fluid, is similar to that of a protein-free filtrate of plasma (112, 234, 268). Brogsitter and Krauss (39) reported a similar concentration in serum and pleural fluid, ascitic fluid and edema fluid. Bauer (9) analyzed the synovial fluid from five gouty patients and found a 1:1 ratio between serum and fluid. We have confirmed this observation in a large number of unpublished studies. Most observers have reported a low concentration of uric acid in spinal fluid. Fine and associates (97) reported the uric acid concentration of cerebrospinal fluid to be only five per cent of that in blood. However, of the other non-electrolytes only urea appeared to be readily diffusible. Its level was eighty-eight per cent, of the level in blood. Myers and Fine (235) examined fifteen patients with nitrogen retention and noted a similar ratio for serum and spinal fluid in regard to urea as well as urate. Reiche (268) analyzed the spinal fluid in more than one hundred non-gouty subjects and reported that the average concentration of spinal fluid urate was approximately one-third of serum. Talbott (329) reported a similar percentage in twelve patients with gout. The concentration of non-protein nitrogen in the spinal fluid in contrast to the low content of urate was only slightly below that of serum.

Byers and Friedman (56) studied the concentration of urate in the cerebrospinal fluid of normal dogs and observed it to be similar to that in serum. In the Dalmatian dog, however, the urate level in the spinal fluid was similar to that of the normal dog while the serum level was approximately double this amount. Furthermore, when a solution of urate and creatinine was infused into either a normal or Dalmatian dog, the uptake of creatinine in the cerebrospinal fluid was greater than the uptake of urate. This phenomenon was attributed to some peculiarity of the blood-brain barrier.

The physico-chemical state of uric acid in body fluids has commanded the attention of investigators for several decades. It has been presumed by some that uric acid exists in forms other than as simple molecules in true solution. Speculations, which are mostly *post hoc*, presume that uric acid exists variously in a dimeric, polymeric or colloidal form or as a protein-bound moiety. Gudzent

(132) in 1909 concluded that uric acid exists in the blood only in the form of the mono-sodium salt. Bornstein *et al.* (31) stated that approximately fifty per cent of the blood uric acid was in a combined form. Benedict (15) presented evidence for a combined form of uric acid in ox blood. Davis and Benedict (77) isolated from beef blood a compound composed of one molecule of uric acid and one molecule of pentose. Morris and MacLeod (231) in applying their procedure for uric acid determination (230) observed that some values were identical with those obtained by the Folin-Wu method but that other blood samples gave considerably higher results. However, if the Folin-Wu filtrates were first treated with potassium oxalate before proceeeding with the determination of uric acid, the methods gave similar results. They suggested that uric acid existed in two forms, only one of which was determined by the Folin-Wu method. The addition of potassium oxalate "liberated" the other form so that it could be determined.

Several studies have been carried out in which serum uric acid is ultra-filtered through a membrane, usually cellophane. Theoretically, simple molecular aggregates of uric acid would be ultra-filtered while polymeric and colloidal forms would not. The precise conditions of each experiment, however, should be carefully considered before general conclusions are accepted. Adlersberg and associates (4) studied twenty-two normal patients and noted that from four to twenty per cent of the total serum uric acid was not filtrable. In ten gouty subjects the values ranged from one to sixty-five per cent. Jones (163) had concluded some time earlier that only about seventy per cent of the plasma uric acid was ultra-filtrable. Khouri (171) reported that trichloracetic acid filtrates of serum contained substances that were hydrolyzed by sulfuric acid to give from zero to seventy per cent of the free serum uric acid concentration. These substances were not present in tungstate filtrate and it was suspected that they were polypeptides containing purine nuclei. Levine *et al.* (193) postulated that polymeric and protein-bound forms of uric acid existed.

Recently this problem has been reopened by Wolfson *et al.* (366, 368). An enzymatic determination for plasma and cerebrospinal fluid was utilized in nine subjects. The following results were observed:

	TOTAL URATE	CHROMOGEN	TRUE URATE
	(values are expressed in mgm./100cc.)		
Average CSF concentration.....	0.61	0.37	0.24
Average plasma concentration...	4.76	0.74	4.02
Average CSF concentration/ Average plasma concentration	0.13	0.50	0.06

By the use of cellophane, the ultra-filterability of plasma urate in two subjects was measured, with results as follows:

	SUBJECT A	SUBJECT B
Per cent total plasma urate ultra-filterable.....	74.3	83.6
Per cent chromogen ultra-filterable....	79.2	92.4
Per cent true urate ultra-filterable.....	72.9	81.4

Thus, although seventy to eighty per cent of the true plasma urate was ultrafilterable, the concentration of true urate in the cerebrospinal fluid was only six per cent of that in plasma. By combining these studies with those obtained from renal clearance observations, Wolfson and Levine (364, 367) concluded that most of the plasma urate circulated as a polymeric complex.

Chabanier (62) dialyzed serum against isotonic solutions containing various amounts of uric acid in order to determine if this substance exists in an absorption compound with the serum colloids. When the concentration of uric acid was equivalent to that obtained by analytic methods, no dialysis took place. It was concluded that uric acid exists entirely in the free state.

Sweat contains uric acid. Lobitz studied the intermittent type of palmar sweat in thirty-four individuals and observed a mean uric acid concentration of 0.8 mgm. %. Thermally-induced sweat did not contain detectable quantities of the substance (203). Saiki reported that the uric acid concentration of sweat varied from 0.72 to 2.52 mgm. per liter (282), while Adler observed it to be from 0.03 to 0.3 mgm. per cc. (2). Rzentkowski (281) considered this secondary excretory pathway in the elimination of uric acid as of no clinical significance for patients on a purine-free diet who perspired on exposure to dry heat.

Human tissue obtained at biopsy or at post-mortem examination has been reported to contain uric acid (94). Analysis of human muscle by Valenti (350) showed the average content of uric acid to be 0.0379% and that of purine nitrogen to be 0.0158%. Following the injection of uric acid in the dog, Folin (100) observed no marked uptake of uric acid by muscle tissue removed at a time when the kidney was saturated with this substance. Von Przylecki and associates (351) presented evidence for "bound" uric acid in tissue since less uric acid was obtained with simple water extraction or extraction with lithium carbonate than after hydrolysis of the tissue. Caution in regard to interpretation of results from hydrolysis procedures is necessary since conversion of precursors of uric acid or decomposition of uric acid is possible. Deposition of uric acid in tissues of patients with gout is a frequent observation in afflicted patients. Brandenberger has identified the tophaceous crystals as those of monosodium urate monohydrate (34).

Excretion of uric acid by the kidney

The mechanism of uric acid transport through the human kidney is presumed to be similar to that of sodium and other selected electrolytes which are filtered through the glomerulus and partially reabsorbed by the tubules. Many of the functions of the human kidney are consistent with this hypothesis. The action of several of the uricosuric drugs can best be explained by this mechanism (329).

The classical experiments by Richards and associates suggest that in some of the lower animals, specifically snakes and frogs, uric acid is filtered through the glomerulus (30). In the frog kidney, Lueken (209) stated that uric acid was extracted by combined glomerular filtration and tubular excretion. In the rabbit, Gersh (114) affirmed that intravenously injected uric acid was eliminated only by glomerular filtration and there was no evidence of tubular participation. In chickens there is some evidence for tubular excretion of uric acid (213, 304).

O'Connor, on the other hand, presumed that in this animal uric acid was excreted by the second convoluted tubule (242). Shannon (304) observed that, at normal plasma levels of uric acid, the uric acid-inulin clearance ranged from 7.5 to 15.8 cc. per min. As the concentration of uric acid in the plasma was increased, however, the ratio fell. He concluded that this evidence suggested tubular excretion and estimated that at normal levels this accounted for approximately ninety per cent of the total uric acid excreted by the chicken.

Brøchner-Mortensen (37) postulated that uric acid was actively reabsorbed by the kidney tubules with a renal threshold of 4–5 mgm. %. When the serum uric acid level was increased, uric acid clearances amounted to at least fifty per cent. An interesting observation has been made by Praetorius and Kirk (259) on a twenty-eight year old male. The plasma uric acid varied between 0.2 and 0.6 mgm. % while the concentration of purines was several times the normal (0.2–2.1) and was as high as 5.2 mgm. %. Uric acid clearance was 175 cc. per minute (10 cc. is the average normal) while the inulin clearance was normal, *i.e.*, 120 cc. per minute. It was concluded that either tubular excretion of uric acid occurred or there was formation of uric acid in the kidneys. It is believed that this observation on a single individual must be interpreted with caution.

The determination of uric acid clearance by modern technics has been reported from several laboratories. Brøchner-Mortensen (38) reported a mean value of 7.0 cc. per minute in normals while Coombs and associates (71) reported slightly higher values. When comparison was made with inulin clearance in the latter study, it was calculated that approximately ninety per cent of the uric acid which appeared in glomerular filtrate was reabsorbed and ten per cent was excreted in bladder urine. In patients with gout but without demonstrable evidence of renal impairment, there may be little or no change in the urate clearance (71).

In pre-eclampsia and eclampsia, a decrease in uric acid clearance was associated with a reduction in glomerular filtration according to Shaffer and associates (303). Chesley and Williams (65) observed that in addition to a decrease in glomerular filtration rate there was an increase in tubular reabsorption of uric acid to account for the decreased urate clearance. Following a meal rich in purine, urate clearance may be increased appreciably and thus is associated with an increased concentration of uric acid in the serum.

The uricosuric action of a number of substances can best be explained by the filtration reabsorption theory. To interpret the increase in uric acid output following salicylate ingestion, it was presumed that the drug interfered with tubular resorption (104). In dogs Grabfield *et al.* (125) noted that the intravenous injection of hypertonic solution of polyhydric alcohols, sucrose, fructose, glycerol and especially sorbitol increased the excretion of uric acid and allantoin. This work extended the observations by Talbott (329) who studied the intravenous injection of hypertonic glucose only in humans. The several solutions are associated with a diuresis but it seems probable that a tubular mechanism is primarily involved either by specific blockade or because of transport of glomerular filtrate through the tubules so rapidly that uric acid cannot be adequately reabsorbed.

The solubility of naturally occurring urate in urine is affected by several factors. These include concentration of hydrogen ions and the concentration of sodium ions. Within the physiological range the more alkaline the urine the greater the solubility of urate. At a constant pH the presence of sodium ions depresses urate solubility. Peters and Van Slyke (253) have calculated that approximately 100 mgm. of uric acid would be kept in solution if there were sufficient sodium ions present to form a saturated solution of sodium urate at pH 6.9. Greater amounts exist only in supersaturated or colloidal forms but it should be remembered that urea and probably other compounds act as peptizing agents to stabilize such solutions. The experimental observations on gouty subjects agreed with the theoretical calculations. The maximum solubility of slightly more than 100 mgm. per 100 cc. of urine has been observed in several gouty subjects (333).

Urates present in bladder urine are presumed to come from endogenous as well as exogenous sources. Urate concentration data best serve their purpose if endogenous urates only are measured. The patient meanwhile is on a low-purine diet. Talbott (329) reported a series of twelve non-gouty patients under such circumstances and the maximum concentration of urate was less than 50 mgm. per 100 cc. of urine in all except one subject. These observations agreed with those of Folin *et al.* (100), Grafe (126) and Loewenhardt (204). The observations of Talbott on non-gouty patients were extended to include forty-two patients with the malady. Thirty-one of this series showed some evidence of renal impairment and were unable to concentrate urate above 50 mgm. per 100 cc. of urine. On the other hand, eleven patients showed a concentrating ability greater than 50 mgm. It ranged from 67 to 224 mgm. per 100 cc. of urine. The concentration of serum urate in this group of patients ranged from 6.7 mgm. to 14.2 mgm. %. Folin and associates (100) reported two gouty patients with a similarly high concentrating ability.

The total uric acid excreted in twenty-four hours by normal controls on a low purine diet varies from 300 to 600 mgm. Hanzlik *et al.* (138) reported an average daily output of 600 mgm. in a study of ten males, nineteen to twenty-nine years of age, on a normal mixed diet which contained 1.33 gm. of protein per kgm. of body weight. Many patients with gout show a similar twenty-four hour excretion. A few patients, notably those with a high concentrating ability, may excrete more than one gram of uric acid in twenty-four hours. A few subjects in our experience have excreted more than 2 gm. in twenty-four hours (333). Friedman and Byers have re-emphasized the increased excretion of uric acid by young gouty persons (107). Chauffard *et al.* (64) studied the urinary excretion of ten patients with gout. The twenty-four hour uric acid excretion varied from 550 mgm. to 1260 mgm. The concentration of uric acid in the serum ranged from 7.5 to 12.5 mgm. %.

The diurnal variation of uric acid was studied by Leathes (188) who noted that on a purine-free diet the excretion of uric acid was maximal in the early waking hours and minimal at night. There was a similar but less marked variation in creatinine excretion. Lindberg (201) identified the maximum excretion as between the hours of three and six in the afternoon at which time the urine

volume was largest. The minimal excretion was during the night. Siven (309) concurred with Leathes and suggested that the period of increased urinary excretion coincided with maximum physical activity. Simpson (307) and Galinowski (110) observed a decreased excretion during sleep. Rougihiteh (279) found no comparable diurnal variation in five healthy male infants studied between the ages of six and twelve weeks of age. Ambard (6) noted no correlation between uric acid excretion and water diuresis. During salt diuresis in sheep Morris *et al.* (229) observed that the excretions of uric acid and urea were similar while in the rabbit a greater efficiency in concentrating uric acid in comparison with urea was noted. Morris *et al.* (232) found that uric acid excretion was increased to a similar degree by chloride and sulfate diuresis. There was little evidence that the increased uric acid output was directly related to increased renal activity.

Faustka (86) commented on the constancy of uric acid excretion in individuals. In one subject studied first in 1886, 231 mgm. of uric acid were excreted in twelve hours. In 1911, 235 mgm. of uric acid were excreted by this individual in a similar length of time. This observation is probably a coincidence.

Variations in uric acid excretion following the injection of isotonic and hypertonic solutions indicated that it behaves as a non-threshold substance. Holden *et al.* (151) demonstrated the analogous effects of reduced rates of urine flow on plasma clearance for several substances including uric acid. The volume-clearance effect for each substance could be represented by an expotential equation of the type that Dole (83) proposed for urea.

Swanson (327) reported that the ingestion of sodium benzoate by normal men was followed by an increased blood uric acid level and a decreased urinary uric acid output. Denis (80) had reported the exact reverse of this after the ingestion of 8 gm. per day. Quick (261) confirmed Swanson's observation but noted in addition that when 2 gm. of glycine were taken one hour before 3 gm. of benzoic acid the decrease in uric acid excretion was prevented. When 5 gm. of glycine were taken one to two hours after 6 gm. of benzoic acid, the uric acid that had accumulated was rapidly excreted.

The variable results obtained after feeding benzoate or glycine or both can probably be attributed to the paradoxical position of benzoate in the metabolic schema. Benzoate reacts with glycine to form hippurate and thus the concentration of one of the good precursors of uric acid is reduced. At the same time, however, benzoate appears to have uricosuric properties. Therefore, benzoate reduces uric acid formation but promotes its excretion. Since we know little of the time relationships of these reactions, it is virtually impossible to predict what will happen under a particular set of conditions. Michael *et al.* (221) have considered the relation between uric acid excretion and hippuric acid synthesis in man.

Goudberg (120) observed that faradic stimulation of the muscles of rabbits on a constant purine intake caused an increase in uric acid excretion. Rakestraw (265, 266) noted that after short periods of strenuous exercise the blood uric acid increased during a recovery period of one and one-half hours. Norris and

Weiser (240) also observed a decreased excretion of uric acid following muscular exercise. Quick (263) reported that strenuous exercise reduced the uric acid excretion while mild exercise did not. He suggested that over-production of lactic acid might be responsible since the ingestion of this compound led to a decrease in uric acid excretion. A decrease in uric acid output following administration of lactate had already been pointed out by Gibson *et al.* (116) and by Michael (220). In 1951 Nichols, Miller and Hiatt (238) published a detailed study in which they showed that strenuous exercise caused a decrease in urate clearance and that this depression persisted for at least an hour. Moreover, during exercise the decrease in urate clearance was proportional to the decrease in glomerular filtration rate but returned to normal more slowly. Oral administration of buffered sodium lactate solution caused a similar depression of the urate clearance. It thus appears that the decrease in uric acid excretion during and after strenuous exercise depends upon several factors which include 1) reduction in the glomerular filtration rate during the exercise, and 2) overproduction of lactic acid which depresses urate clearance. The latter effect is not dependent upon the production of acidosis.

Fever is associated with an increased urinary output of uric acid as well as of creatinine (189). These observations were extended by Cathcart, Kennaway and Leathes (60) to include exposure to cold and severe exertion. The increased uric acid output coincides with the rise in fever, coincides with and outlasts by many hours exposure to cold, and follows and outlasts by several hours physical exertion.

The Dalmatian coach hound

Benedict (16) noted that the Dalmatian hound excreted large amounts of uric acid in contrast to the normal dog which excreted almost none. On a purine-free diet a 10 kgm. Dalmatian excreted as much uric acid as a normal human. Furthermore, uric acid injected subcutaneously was excreted almost quantitatively whereas the normal dog oxidized ninety-eight to one hundred per cent of it. It was emphasized (16) that the Dalmatian, in spite of his large uric acid output, excreted allantoin also. Klemperer (175) found the liver of the Dalmatian rich in uricase, hence this was not the explanation for its failure to oxidize uric acid more thoroughly. Friedman *et al.* (105) found that sodium salicylate did not effect a change in the uric acid clearance of the Dalmatian. In a subsequent study (106) they showed that in the Dalmatian the clearances of allantoin, uric acid and creatinine were quantitatively similar. In the non-Dalmatian, allantoin and creatinine clearances were the same but the uric acid clearance was much lower. Hence the Dalmatian simply lost a significant portion of uric acid from the body before it became converted to allantoin, the normal pathway for other dogs. It was also shown by ureteral ligation that the Dalmatian was capable of converting uric acid to allantoin although the process was not one hundred per cent efficient. Since the Dalmatian was resorbing no uric acid, tubular blocking agents like salicylic acid were ineffective. This explanation would also seem to hold for the results of Miller *et al.* (223). Wolfson *et al.* (365),

however, claimed that in the Dalmatian the true urate clearances (as determined by the uricase method) considerably exceeded the glomerular filtration rate. This, of course, suggests tubular secretion of urate.

The characteristic of the Dalmatian to excrete uric acid is apparently under genetic control (247).

PART III. CATABOLISM OF URIC ACID

In the animal body, uric acid may be converted to allantoin. This conversion is ordinarily associated with the enzyme, uricase. There has been evidence advanced by several investigators that this oxidation takes place by way of a symmetrical intermediate. Cavalieri and Brown (61), after citing many of the pertinent references, oxidized isotopically labeled uric acid with alkaline permanganate. The uric acid was labeled with N^{15} in the one and three positions, but the resulting allantoin was uniformly labeled. A mechanism was suggested which included a symmetrical intermediate and the results appeared to confirm those of the earlier non-isotopic experiments. Brown, Roll and Cavalieri (41) reached a similar conclusion from experiments in rats fed uric acid labeled in the one and three positions.

The enzyme, uricase, or at least uricolytic activity, has been demonstrated in the livers of many species not including man. The kidneys of some species also show activity but other tissue does not. A number of studies have been made on the sources of the enzyme and the mechanism for its action (5, 27, 28, 84, 89, 118, 173, 174, 210, 248, 249, 346).

The question whether uric acid is catabolized in the human has been warmly debated for many years. The evidence is mainly of three sorts: 1) attempts to demonstrate uricase or uricolytic activity in human tissue; 2) recovery of injected uric acid; and 3) evaluation of the role of allantoin in human metabolism. The evidence in each of these categories will be considered.

Enzo (84) was able to demonstrate no uricolytic activity in the livers of three humans who died of other than liver ailments. Freeze-dried human placentas had no activity (211). Wells *et al.* (358) found no evidence for uricolytic activity in either fetal or adult tissue. Jones (164) discovered no uricolytic enzymes. However, Schittelhelm *et al.* (288) and Wells (357) had the opportunity to examine the tissues of patients who died after six and nine days, respectively, of anuria. Considerably less uric acid was recovered than should have accumulated from the normal rate of production. They concluded that some must have been destroyed. In general, the direct evidence for or against uricolytic activity in the human is not convincing. Negative evidence may mean that the proper conditions have not been satisfied.

Uric acid recovery studies have been performed by several investigators. Burian and Schur (53) injected uric acid subcutaneously into human males and recovered approximately fifty per cent in the urine. Soetbeer and Ibrahim (316) claimed complete recovery, but Folin, Berglund and Derick (100) in an extensive and critical study were able to recover variable amounts, the approximate value being fifty per cent. Koehler (176) was able to recover not more than

half of the uric acid injected intravenously as the monolithium salt. Some investigators "recovered" two or three times the amount given. There are valid objections to these experiments. The quantities of uric acid injected were often great enough to cause discomfort, if not acute illness. Because of the insolubility of uric acid, various solvents such as piperazine and lithium carbonate were used and these contributed to the unreliability of the results as well as to the discomfort of the subject. Furthermore, the recovery of injected extra uric acid is based upon the daily normal rate of uric acid excretion. This is a variable function.

With the advent of isotopic technics it became possible to determine quantitatively the amount of uric acid that could be recovered following intravenous injection. Geren, Bendich, Bodansky and Brown (113) conducted two experiments with isotopic uric acid. Following the ingestion of N^{15} uric acid, there was extensive conversion of it to urea. Following injection, however, almost complete recovery in the urine in less than a week was observed. Benedict, Forsham and Stetten (13) calculated the pool size and turnover rate of body uric acid. When the theoretical amount of uric acid turned over by the body was compared with the amount excreted in the urine, it appeared that the latter was from twenty to twenty-five per cent less. Buzard, Bishop, and Talbott (54) injected N^{15} uric acid into normal human subjects and recovered only sixty-five to seventy-five per cent of the dose as urinary uric acid. When the mean urinary excretion was compared with the calculated turnover, the values in each case were quite similar to the actual recovery figures. This suggested the possibility of catabolism.

The role of allantoin in human metabolism is poorly understood. Paget *et al.* (250) determined the allantoin excretion of ninety human subjects (fifteen in good health) to be from 10–70 mgm. per day with the majority of values in the range of 15–25 mgm. Wiechowski (359) determined the allantoin excretion on a purine-free diet to be not more than 11 mgm. per day. He assumed this resulted from the oxidation of uric acid as in other animals. Later Wiechowski (360) noted that subcutaneously injected allantoin was excreted unchanged and concluded that allantoin was not an intermediate in uric acid catabolism in humans. This is consistent with the impressions of some investigators that urinary allantoin arises directly from the diet. If it could be shown that allantoin is turned over fairly rapidly, then the failure of the human to excrete large quantities of it would not necessarily mean that it might not be a pathway for uric acid catabolism. The paucity of data on urinary allantoin in humans seems to be related to the paucity of allantoin in human urine.

In addition to the oxidation of uric acid to allantoin, there are scattered reports of uric acid being converted to other compounds. Beard and Pizzolato (10) found that, when young rats were injected with uric acid as well as with other purines, an increase in the muscle creatinine and urinary creatinine followed. Dirr (82) fed yeast protein to humans and observed an increase in serum creatinine but not urinary creatinine. Zwarenstein (372) reported an increased creatinine excretion after uric acid ingestion. Plasma fibrinogen levels in rabbits were

increased following the administration of uric acid and other purine compounds (93).

PART IV. PHARMACOLOGIC AND THERAPEUTIC AGENTS

Pharmacologic agents have been studied in regard to the effect upon uric acid metabolism, which effect may or may not be of clinical significance in correcting the clinical manifestation of gouty arthritis. Furthermore, the active material may be studied largely in relation to clinical benefit with concern given to uric acid metabolism. Thus this phase of the review may be considered in relation to: 1) action upon intermediary metabolism of endogenous uric acid; 2) action upon the renal transport of uric acid; and 3) action upon the articular symptoms of gouty arthritis. Illustrations of the first action lack definitive proof. Cinchophen and salicylates are good examples of the second action. Colchicine is a good example of the third. Since there may be overlapping actions, this arbitrary division must be interpreted liberally.

Intermediary metabolism of endogenous uric acid

Several accessory food factors have been studied in relation to the action upon uric acid metabolism. Kühnau *et al.* (182) noted an increase in nucleotides in the blood of gouty subjects. *In-vitro* experiments on samples of blood from gouty persons revealed the presence of a factor which interfered with the decomposition of nucleotides. Vitamin B_1 prevented this interference. Intravenous therapy with thiamine was then instituted in gouty subjects (352) and the symptoms of gouty arthritis were reported to have disappeared in a short time. Further clinical experience with thiamine reveals no consistent therapeutic merit either with oral or intravenous administration (329). Experiments by Capellini (59) with ingestion of large quantities of nucleo-proteins resulted in anticipated increase of uric acid in the blood and an increase in urinary excretion. The injection of ascorbic acid reduced the blood level but did not influence the excretion. As will be noted below, unrelated substances also are reported to have reduced the concentration of uric acid in body fluids without a concomitant augmentation of urinary uric acid output. Nicotinamid in normal persons appeared to have no effect upon uric acid metabolism, but in patients with liver disease the injection of this substance following the injection of lithium urate resulted in a marked decrease in the concentration of uric acid in the blood (219).

Secretions of the endocrine glands have been noted to influence either uric acid metabolism or urinary excretion. The injection of insulin or epinephrine into rabbits increased uric acid excretion according to Miller *et al.* (224). No effect in humans was noted with similar therapeutic amounts. Rosenberg (278) observed a decrease in the concentration of uric acid in the blood of man following injection of insulin. This effect appeared to be unrelated to a decrease in concentration of blood sugar. Ricci (269) noted that patients with diabetes mellitus fed a high purine diet had an elevated blood uric acid which persisted above normal for more than six hours. Normal subjects exhibited a maximum peak at three hours which had returned to normal at six hours. Insulin converted the

diabetic to a normal response. In 1927 Kurti and Gyorgyi (184) observed an increased excretion of uric acid in the urine following administration of insulin as well as an increased concentration of uric acid in the blood. This second observation is not easy to interpret. Lindberg (201) reported no effect upon uric acid metabolism following the injection of epinephrine.

The action of insulin may be associated with the mobilization of epinephrine. It has been appreciated recently that epinephrine acting by way of the hypothalamus and pituitary-adrenal axis is responsible for an increased elaboration of adrenal-corticosteroids and an increased excretion of uric acid in the body. Since neither ACTH nor cortisone has been shown to possess a direct effect upon the intermediary metabolism of uric acid, it is presumed that the action resides in the kidney. Cortisone and to a greater extent ACTH is followed by a decrease in the concentration of uric acid in the serum and an increase in the urine output. This will be referred to later.

In 1948 Griffiths (128) reported that, when injected into glutathione-deficient rabbits, uric acid had a diabetogenic action somewhat like that of alloxan. He later elaborated on this finding (129) and reiterated that uric acid was diabetogenic in rabbits whose blood glutathione had been lowered to about half the initial value by feeding a methionine- and cystine-deficient diet. In general, this work has not been confirmed and is accepted with reservations because of its implications in the pathogenesis of diabetes.

Subcutaneous injection of thyroxin in rabbits resulted in an increased oxidation of uric acid with a rise in allantoin formation, according to Mori (227). A decrease in concentration of blood uric acid followed perfusion of this substance through the liver (227). In gouty patients, Harpuder and Spitz (141) noted that desiccated thyroid augmented the uricosuric action of cinchophen and resulted in an increased excretion from 0.8 gm. to 1.3 gm. per day following administration of 0.6 gm. of this preparation. Hypothyroid patients treated with desiccated thyroid exhibited an increase in uric acid excretion. This was not observed in normal or hyperthyroid subjects (324). The clinical significance of the action of thyroxin upon uric acid metabolism is not fully understood. It is a clinical observation, however, that some patients with gout may be mildly hypothyroid and that administration of desiccated thyroid is associated with clinical improvement (334).

Goldner and Gomori (117) observed an increase in the concentration of blood uric acid as well as the deposition of sodium urate crystals in serous membrane of pigeons following the intravenous injection of alloxan or dialuric acid. This substance was observed by Kionka (172) to cause an increased concentration of uric acid in the blood. The increase in blood sugar from a normal of 150 mgm. % to 400 mgm. % was noted in the former investigations. This is surprising in view of the fact that glycosuria in humans is associated with an increased urinary excretion of uric acid and a decrease in serum uric acid (329). The Claude Bernard piqûre produced a transient but significant increase in allantoin elimination in rabbits (222).

In hypertension the serum contains larger amounts of uric acid with diminished

excretion as a result of the injection of epinephrine, according to Krauss (180). Ferrannini noted that 1 mgm. of histamine decreased the concentration of uric acid in the blood sixteen to forty-eight per cent (91). Iberti (154) fed bromide to rats for several months and observed a depression of purine metabolism. In zinc-deficient rats the concentration of uric acid in the blood decreased. Following the addition of zinc to the diet, the levels were restored after a period of five weeks. The zinc-deficient rats, however, had normal concentrations of uricase in the liver (353).

Injection of ovarin and pituitrin was followed by an increase in the excretion of exogenous uric acid (241).

X-ray emanation has been related to uric acid metabolism. In 1913 Gudzent (133) observed the disappearance of uric acid in the blood after exposure to radium emanation. Linser (202) reported an increased output of uric acid in the urine in individuals with a normal hématopoietic system following administration of X-ray. Hauenstein (144) confirmed the increased urinary output. Thannhauser and Curtius (339) compared the response of patients with acromegaly to that of normal individuals. They observed an increased minimum nitrogen output from 0.03 to 0.05 gm. per kgm. to 0.05 to 0.08 gm. per kgm. in acromegaly. Following deep X-ray to the pituitary the endogenous uric acid value observed in acromegaly reverted to normal. No change in the concentration of uric acid in the serum was noted.

The effect of lethal doses of total body X-ray on uric acid excretion in dogs has been observed by Krizek *et al.* (181). The significant augmentation of uric acid output occurred only a few days prior to death. No change was noted immediately following irradiation. In rabbits given 600 roentgen units, uric acid excretion was diminished.

An effect upon urinary output of uric acid has been attributed to a great number of drugs. One of the first to receive attention was salicylic acid. Byasson (55), Marrot (212) and See (301) observed an increased output following administration of this drug. In the early part of this century Denis (79) and Fine and Chase (96) reported on the increased elimination of uric acid from the body following ingestion of salicylates. Brugsch and Wolffenstein (45) noted that ortho-oxyquinoline salicylate reduced the amount of uric acid excreted but it did not cause the accumulation of uric acid in the blood. Yamaguchi (370) noted that alkali increased the diuretic action of salicylates while acids caused a decrease. Quick (262) observed an increased uricosuric effect if 15 gm. of glycine were added to 3 gm. of salicylic acid.

Fauvel (87) concluded that the action of salicylate was one on transport in the kidney and was not the result of increased production of uric acid by the blood.

Grabfield and Gray (122) affirmed that the action of salicylates upon uric acid metabolism depended upon renal innervation. These conclusions were based upon denervated kidney experiments in dogs. It has already been noted that Friedman and Byers (105) observed no action of salicylates on uric acid clearance of Dalmatians while a significant action upon uric acid clearance of

non-Dalmatian dogs was observed. In rats Friedman observed that glycine enhanced the excretion of uric acid and allantoin following sodium salicylate intake (104). The increased excretion of uric acid by salicylates was considered by Bohland to be a result of increased uric acid synthesis associated with leukocytosis (25). Shortly after, Schreiber and Zaudy (291) confirmed the increased excretion of uric acid following salicylates but noted that it appeared to be independent of leukocytosis.

Cinchophen (atophan) is a quinoline derivative whose uricosuric action is quite similar to that of the salicylates. Nicolaier and Dohrn (239) attributed the effect upon uric acid exchange to a toxic action in the body. Brugsch (43) postulated that cinchophen mobilized a portion of the uric acid that was deposited in osseous and soft tissue tophi. Theoretically such an action is possible. When 2-phenyl-quinoline-4 carboxylic acid (cinchophen) was fed to male subjects in doses of 0.25–1.0 gm. per day, there was an increase in the uric acid output followed by a decrease. The increase usually was from fifty to one hundred per cent of the control value but at times was greater than three hundred per cent and was observed during a purine-free regimen as well as when purines were allowed in the diet. Other quinoline-carboxylic acids which produced such an action contained the phenyl group, *viz.*, 2-phenylquinoline-3,4-dicarboxylic acid; 2-phenylquinoline-4,8-dicarboxylic acid; 2-phenyl-3-oxyquinoline-4-carboxylic acid; 2-phenyl-6-methylquinoline-4-carboxylic acid; 2-oxyphenylquinoline-4-carboxylic acid; 2,3-diphenylquinoline-4-carboxylic acid.

Folin and Lyman (102) studied urinary excretion in one healthy control subject and six patients with gout following the administration of cinchophen and concluded that cinchophen as well as salicylates lowered the threshold of the kidney for the uric acid. Cinchophen augmented the excretion of non-protein nitrogen and urea nitrogen as well. Abl (1) compared the urinary excretion following the administration of cinchophen, colchicine and croton oil. A twenty-five per cent increase in the urinary output of uric acid was observed following colchicine; a ninety per cent increase, following 2.0 gm. of cinchophen; and a fourteen per cent increase, following 60 mgm. of croton oil. Selected salts also were studied which resulted in a diminution in excretion of uric acid. Included were calcium salt, barium sulfate, bismuth nitrate and uzara. An increased uric acid excretion was produced by mustard, arsenic, thorium X, santonin, glycerol, choline hydrate, piperazine and strontium. Kaku (166) compared several cinchophen preparations in regard to uric acid elimination. It was noted that the uric acid-eliminating action of the derivatives, methoxylated in the phenyl radical, had a greater uricosuric action than those which were non-methoxylated. By the introduction of the methyl group in position six, this action was weakened but not when it was introduced in position seven. Methylation in the position eight increased the uric acid-elimination capacity. The following cinchophen preparations influenced uric acid elimination: 8-methyl-2-p-methoxyphenylquinoline-4-carboxylic acid; 8-methyl-2-phenylquinoline-4-carboxylic acid (isocinchophen); 7-methyl-2-p-methoxyphenylquinolinecarboxylic acid; 2-p-methoxyphenylquinoline-4-carboxylic acid; 6-methyl-2-p-methoxyphen-

ylquinoline-4-carboxylic acid; 2-phenyl-quinoline-4-carboxylic acid (cinchophen); 7-methyl-2-phenylquinoline-4-carboxylic acid; 6,8-dimethyl-2-p-methoxyphenyl-quinoline-4-carboxylic acid; 6,8-dimethyl-2-phenylquinoline-4-carboxylic acid.

Following the observation of Grabfield and Gray (121), Sugihara (325) noted that splanchnic nerve section reduced the capacity of all tissues to retain uric acid with a resultant increase of uric acid in the blood and with a decreased urinary excretion. This author also noted (326) that the subcutaneous injection of 0.2 gm. of cinchophen per kgm. of rabbit produced an increase in the uric acid excretion in the bile without increasing the amount of bile. Bilateral splanchnic section produced a slight increase in the amount of bile and a decrease in the urate excretion. If followed by cinchophen, the urate excretion was increased above the normal. Haida (136) noted in dogs that subcutaneous injection of cinchophen in doses of 100 mgm./kgm. increased the uric acid content of the lymph and that injection of 200 mgm. of cinchophen per kgm. into rabbits after stimulation of salivary secretion by pilocarpine increased the uric acid concentration of the saliva. In pursuing the matter further Grabfield and associates (123, 124), using dogs whose kidneys had been denervated, concluded that administration of cinchophen caused a decrease in urinary excretion of uric acid under such experimental circumstances and that the effects of cinchophen upon uric acid in the dogs were mediated by the adrenergic fibers to the kidney. The observations of Grabfield were confirmed by In (158). Starkenstein (319) maintained that cinchophen inhibited the formation of uric acid by virtue of its action upon purine-forming enzymes in the liver, particularly xanthine oxidase. Weintrad (356) attributed the action of cinchophen to metabolic changes in the kidney.

The increased excretion of uric acid in the urine following cinchophen administration in normal or gouty patients is transient. The maximum effect is reached within two or three days and a rebound occurs after discontinuance, with a significant fall in the amount of urine uric acid and an increase in concentration of uric acid in the blood (95). Daniels and McCrudden (76) noted that attacks of gout would appear although blood uric acid concentration had been reduced by cinchophen. This observation has also been noted following other drugs which depress the concentration of uric acid in the serum.

Ulrici (347) observed a slight decrease in uric acid output following administration of benzoic acid. This was confirmed by Lewis and Karr (197). Swanson (327) reported an increased blood uric acid following a decrease in urine uric acid after sodium benzoate intake. It was suggested that this was associated with a synthesis of glycine from a substance normally converted into urea. Michael *et al.* (221) observed that 80 mgm. of sodium benzoate per kgm. of body weight in man caused a decrease in urinary excretion of uric acid from 29 to 7.7 mgm. per hour.

Recently a new anti-rheumatic agent, H.P.C. (3-hydroxy-2-phenylcinchoninic acid), has been investigated. Chemically it is closely related to cinchophen and its pharmacologic action is believed to be similar to that of cinchophen. Rather optimistic reports of clinical improvement have followed its use in the treatment of acute gouty arthritis (308).

Ranke (267) observed a decreased excretion of uric acid in man following quinine. Similar findings in dogs were reported by Kumagawa (183) and in cats by Mendel and Brown (216).

According to Ries (271) and Pfeiffer (254), alcohol decreases the excretion of uric acid. Opposite results were observed in man by Schultz (300) and in dogs by Chittenden (66). Landau (186) attributed a decreased excretion of exogenous uric acid, following administration of alcohol, to a decreased permeability of the kidneys to uric acid.

Alkalies and especially lithium salts have been used in the treatment of gout for more than half a century. Alkalies generally enhance the solubility of urates while lithium urate specifically is more soluble than other salts of urate. Gonsky (119) noted a slight increase in the excretion of uric acid following administration of lithium carbonate, and Zagari and Pace (371) noted the same following ingestion of other alkaline salts. Salkowski (283) noted a uricosuric effect of sodium acetate in dogs. Daniels (75) administered 1 gm. of lithium citrate daily to a gouty patient but observed no increased excretion in the urine. Following the injection of 1 gm. of monolithium urate, Koehler (176) recovered approximately fifty per cent in the urine, associated with slight elevation of blood uric acid. Rockwood (274) observed no increase in excretion of uric acid following ingestion of lithium carbonate.

The salts of rare earths, which included cesium, didymium and thorium, had no uricosuric action. Salts of samarium and yttrium had a uricosuric action (258). Kuznitzky reported negative effects when studying the action of thorium X upon uric acid deposition in the cornea (185). Haskins (143) investigated the uric acid solvent power following piperazine, lysidine, lithium carbonate, and other alkalies. Lysidine was active but large doses were required to produce the effect. Lithium carbonate was effective but appeared to be endowed with no additional advantage over sodium carbonate or sodium citrate. Minibeck (226) reported no effect upon uric acid excretion following piperazine.

Caffeine and theophylline ingestion (49) was not associated with an increase in true uric acid chromogens in the urine. Wardell and Myers (354) observed an increased urinary excretion of uric acid following caffeine in two subjects. Theophylline also caused an increase but theobromine did not. Piperazine increased the uricosuric effect by enhancing the solvent power of the urine, particularly if alkalies were given and a diuresis avoided. Hexamethylenetetramine was found to have a uricosuric action by Haskins (142), in large therapeutic amounts. Humpert (153) observed an increased urinary excretion of uric acid with a corresponding fall in blood uric acid following administration of sarsaparilla preparation (renotrat).

In patients with pernicious anemia the endogenous uric acid metabolism was altered significantly by administration of crude liver extract. An increase in serum uric acid from 4.0 to 9.0 mgm. % and in urinary uric acid from 424 to 2000 mgm. per day, was observed by Riddle (270). No comparable change in uric acid metabolism was noted in normal control subjects. Several years later Scheinberg (287) observed that concentrated liver extract did not affect the uric acid concentration in blood of patients with nephrosclerosis or chronic

nephritis. Following hemolysis in the Dalmatian coach hound produced by phenylhydrazine (178), the urinary excretion of uric acid increased from 265 to 436 mgm. per day associated with a significant reticulocytosis. The injection of uricase (5) into chickens which had been on a high meat diet resulted in a decrease of seventeen to eighty per cent in the concentration of serum uric acid. The effect of santonin upon the excretion of uric acid and its sodium salt was noted by Seel (302). In rabbits an increased excretion of uric acid was noted. In humans a thirty per cent increase in urine uric acid followed the administration of 50 mgm. of santonin. Subsequently a decrease in excretion occurred. The increased excretion in patients with gout persisted for two or three days. Some benefit upon chronic gouty arthritis was noted by the author.

The effect of an injection of an extract from the stinging nettle (*Urtica dioica*) was investigated by Keeser (170) in ducks and geese. A reduction in the uric acid content of the blood by as much as 3 mgm. % followed administration of the extract. This observation was instigated by the current belief that the stinging nettle was endowed with therapeutic value in the treatment of gouty arthritis.

There are several references in the Japanese literature to the use of the glucoside, fraxinin, obtained from the cortex of *Fraxinus borealis* Nakai. The glucoside causes paralysis of the central nervous system in frogs and mice, when injected in large quantities. It has an antipyretic, a diuretic and a uricosuric action in rabbits. It is presumed that the diuresis results from an increased blood flow through the kidney associated with a concomitant urinary excretion of uric acid (155–157, 245, 246). Mun (233) noted that vomiting in dogs was associated with an increased urinary excretion of uric acid.

Hedon *et al.* (145) observed an increase in serum uric acid of approximately one hundred per cent following injection of peptones in dogs. Serial bone marrow studies in patients with pernicious anemia were correlated with the level of the uric acid in the blood by Stasney and Pizzolato (321). With an increase of reticulocytes and disappearance of nucleated red cells in the marrow, there was an increase of uric acid in the urine of 450 mgm. to 750 mgm. per day.

In normal subjects a decrease in circulating eosinophils and a significant increase in the urinary uric acid:creatinine ratio follow the injection of ACTH (341–343). A fifty-eight per cent increase in urine uric acid followed the daily administration of 40 mgm. of ACTH intramuscularly. Conn and associates (70) produced temporary diabetes mellitus by the daily injection of ACTH. The majority of the subjects exhibited spontaneous glycosuria a few days after cessation of ACTH administration, which was associated with a marked increase in the urine uric acid output. It was suggested that this was caused by the elaboration of endogenous ACTH after prolonged depression of its production. Conn further stated that in the diabetes-like state following ACTH administration there is a correlation between the loss of tolerance of carbohydrate, the increased endogenous purine metabolism, and the depressed blood glutathione (69).

Ingbar and associates (159) noted an increase in the clearance of uric acid

following ACTH and cortisone. An increase in the urate clearance of from nine to twenty-nine per cent followed the administration of 575 mgm. of ACTH during a three and one-half day experimental period. An increase of from ten to eighteen per cent followed administration of 1 gm. of cortisone given over a two-day period. In another cortisone experiment, no change in uric acid clearance was noted. The site of action of ACTH and cortisone is believed to be similar to that of salicylate and cinchophen. In clinical studies, ACTH has been of benefit in the treatment of acute gouty arthritis (135). Cortisone has been less effective. Neither preparation is believed to have outstanding therapeutic value in chronic gouty arthritis. On the basis of a few isotope studies in humans, Bishop, Garner and Talbott (20) have suggested that, whereas both cortisone and ACTH appear to have a uricosuric action, ACTH may also increase uric acid anabolism.

Since 1947, carinamide has received considerable attention as a uricosuric agent. Wolfson and associates (364) noted that a significant uricosuric action followed the ingestion of from 10 to 14 gm. of carinamide daily. During the past two years an improved carinamide, Benemid (probenecid) (p-(di-n-propyl-sulfamyl)-benzoic acid), has been investigated (21, 331). This is a powerful uricosuric agent which exerts its action soon after ingestion (332). The site of action is believed to be the tubular cells, the drug causing partial inhibition of reabsorption of urate from glomerular filtrate. This results in an increase in urate clearance which, measured by twenty-four hour specimens, may be as great as fifteen per cent. The increase in the amount of uric acid excreted may be from thirty to fifty per cent, with not more than 2 gm. of Benemid ingested in divided doses each twenty-four hours.

The action of Benemid may be apparent within a few hours after ingestion and is associated with a significant decrease in the concentration of uric acid in the serum as well as an increase of uric acid in the urine. The maximum effect upon the concentration of uric acid in the serum with maintenance doses of 2 gm. per day may be observed within the first week after beginning administration. Thereafter the effect in the serum diminishes slightly but is not abolished and in most patients a clinically significant uricosuric action may be demonstrated so long as the drug is administered daily, *i.e.*, more than two and one-half years in our series (22). In one experiment the concentration of serum uric acid was determined over a three-year control period prior to the beginning of Benemid in a patient with gouty arthritis. The concentration in the serum varied from 7.6 to 10.5 mgm. %. At the beginning of Benemid ingestion a decrease in serum concentration of uric acid to 3.0 mgm. % was noted. At the end of one month the serum level was 5.2 mgm. %. During the following twenty-four months the level fluctuated between 3.8 and 5.4 mgm. % but at no time did it rise to 6 mgm. %, the lower limit for most patients with gout not receiving uricosuric agents. In another experimental subject suffering from gout the daily excretion of uric acid was determined in a pre-Benemid control period and was found to be 650 mgm. A maximum of 1700 mgm. of uric acid was excreted on the first day of Benemid therapy. After the first week the

quantities of uric acid in the urine fluctuated between 900 and 1500 mgm. per day.

The influence of salicylates and Benemid upon the metabolic pool and turnover rate of uric acid has been determined. Benedict, Forsham and Stetten (14) have observed a decrease in the metabolic pool of uric acid in one experimental subject from 31 gm. to 2 gm., five months after beginning ingestion of salicylates. The mean serum level of uric acid showed little change, *i.e.*, 9.5 and 10.2 mgm. %, respectively. The authors have carried out isotope studies on two patients on Benemid (21). The uric acid pool in the control subject was 964 mgm. and the turnover rate was 0.666 pool per day. A compilation of total uric acid excreted during a seven-day period on Benemid revealed approximately 2705 mgm. in excess of the quantity calculated from the decrease in the size of the pool. One explanation for this excess uric acid is mobilization from a pool larger than the immediate miscible pool. In a gouty patient this might be from the urate deposits or demonstrable tophi. In the gouty subject the control values were 2205 mgm. and 0.484 pool per day. A few days after beginning Benemid therapy the pool had decreased to 1622 mgm. and the turnover rate had increased to 1.006 pools per day. The "extra" uric acid excreted during a six day period was 4889 mgm. Twenty-two months after beginning Benemid the functions were redetermined and the values were essentially the same. Thus the significant metabolic function affected by Benemid appeared to persist with little change in magnitude so long as Benemid is ingested daily. The prolonged ingestion of Benemid is associated with clinical benefit even though acute attacks of gout may develop soon after initiation of a Benemid regimen, at which time the concentration of uric acid in the serum is within normal limits.

The third category of therapeutic agents for gouty arthritis concerns those substances endowed with an effect upon acute articular gout with little or no demonstrable effect upon uric acid metabolism. Colchicine is the best example of this type. His (149) was able to detect no uricosuric effect. This was confirmed by Denis (80). Jackson and Blackfan (161) reported an increased excretion of urinary uric acid following colchicine while Gudzent and associates (134) noted an increase in blood uric acid as well as an increased daily excretion of urinary uric acid. In cats, Schroeder and Raginsky (292) reported an increased excretion of uric acid in the ileum following colchicine. Talbott (329) observed no effect upon uric acid clearance by the kidneys following colchicine. Rockwood and Van Epps (274) reported a decreased urinary uric acid from 340 to 314 mgm. daily, following colchicine.

The effect of colchicine upon the metabolic pool was studied in two gouty patients by the authors (20). A slight decrease in the metabolic pool and an increase in the turnover rate were observed. It was not believed that these changes were of statistical significance although further experiments seem indicated. Thus no one has conclusively proved that therapeutic amounts of colchicine either in the treatment of the acute attack of gouty arthritis or in smaller amounts in the prevention of acute attacks has any demonstrable effect upon uric acid metabolism.

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