1967

# Serum uric acid and disease

Robert C. Nelson
*University of Nebraska Medical Center*

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By

Robert C. Nelson

Submitted in partial fulfillment for the degree of Doctor of Medicine

University of Nebraska College of Medicine

February 1, 1967

Omaha, Nebraska

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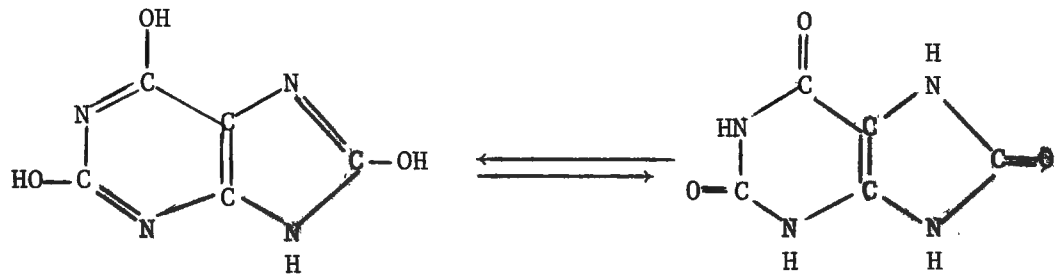
## Introduction

The association between serum uric acid levels and gout is well established. However, various other conditions are coming to light in which hyperuricemia manifests itself with or without gout or gouty diathesis. The purpose of this thesis then is to investigate recent literature on this subject.

I. Metabolism of Purines (1)

Uric acid is the naturally occuring end-product of purine metabolism. The purines and pyrimidines found in nucleic acid are not required in the animal diet, but are synthesized de novo. The basic purine nucleus from which the nucleotides of adenine and guanine are produced is known as inosinic acid.

Uric acid exists in equilibrium between the lactim and the lactam forms.



Lactim Form Lactam Form

a) Digestion of Nucleic Acids

The digestion of nucleic acids in the body occurs mainly in the duodenum since they are unaffected by gastric juices. The nucleases for digestion of the nucleic acids are secreted in the pancreatic juice. Pancreatic ribonuclease hydrolyzes only ribonucleic acid. Pancreatic deoxyribonuclease acts in the presence of $Mg^{++}$ or $Mn^{++}$ to hydrolyze deoxyribonucleic acid to small oligonucleotides. The intestine is also thought to form nucleases and diesterases which aid in the digestion of low molecular weight nucleic acids and oligonucleotides. Then, the liberated nucleotides are hydrolyzed by intestinal phosphatases or nucleotidases to yield nucleosides and orthophosphate. There is, in

addition, a specific intestinal phosphatase which cleaves adenosine 5'-phosphate but does not attack the isomeric adenosine 3'-phosphate or adenosine 2'-phosphate. Hydrolysis of the nucleosides probably occurs in various tissues, such as: spleen, liver, kidney, bone marrow, etc. There are two types of specific purine and pyrimidine nucleosidases:

a. Hydrolytic: Uridine + $H_2O$ $\xrightarrow[\text{nucleosidase}]{\text{pyrimidine}}$ uracil + ribose

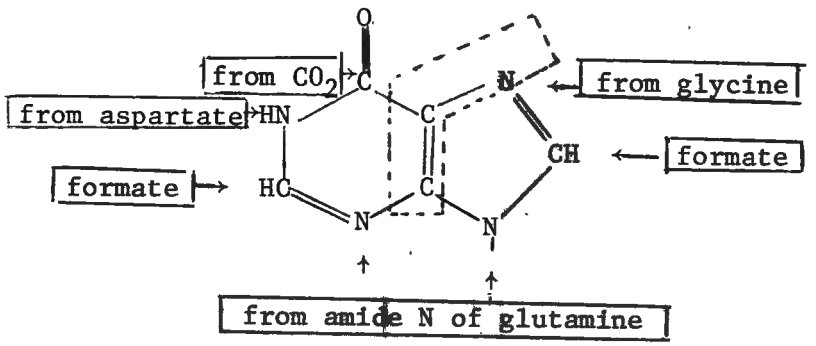
b. Phosphosolytic: guanosine + phosphate $\xrightarrow[\text{phosophorylase}]{\text{nucleoside}}$ guanine + ribose 1-phosphate.

Apparently, most of the purine or pyrimidine bases taken into the body are not incorporated into tissue nucleic acids, but are excreted as urea. Isotopic trace studies indicate that when an animal is fed $N^{15}$ labeled ammonium citrate that the $N^{15}$ shows up on the animal tissue purines and pyrimidines, but that when fed $N^{15}$ labeled uricil, thymine, or guanine, the nitrogen was not found in the nucleic acids, but found in the excreted urea. However, when animals were fed $N^{15}$ labeled adenine in positions 1 and 3 of the molecule, the $N^{15}$ was found both in adenine and in guanine of the animal's tissue nucleic acids. Thus, adenine can not only be incorporated directly into tissue nucleic acids, but can be converted to guanine as well. The incorporation of adenine by the tissues seems to be largely into RNA unless the animal has an organ undergoing a rapid regeneration process. In this instance, there is extensive incorporation of adenine into the DNA.

b) Main Pathway to Purine Synthesis

In the main pathway to purine synthesis neither free purines nor nucleo-

sides appear as intermediates. This process is essentially a stepwise synthesis of the purine ring beginning with the conversion of ribose-5-phosphate to 5-phosphoribosyl-1-pyrophosphate. In the next step, utilizing glutamine and Mg++, the 5-phosphoribosyl-1-pyrophosphate is converted to 5-phosphoribosyl-1-amine. This latter step is referred to as the "committed" metabolic step of purine biosynthesis since it is here that the feedback mechanism for control of purine synthesis is thought to act. Indeed, it is at this step that azoserine, an antibiotic, acts to inhibit utilization of the glutamine. Azoserine has been shown to inhibit growth of certain neoplasms. Thus, the stepwise synthesis of the basic purine nucleus, inosinic acid, continues with the various carbon and nitrogen atoms being donated from various compounds, as shown in the following diagram.




In addition, the reactions require enzymes, Mg+, and at least two reactions require K+. In the reaction where $CO_2$ is placed on the imidazole ribonucleotide ring, high concentrations of bicarbonate are required. The pathway to purine synthesis can be summed up in the following manner:

a. $2NH_4^+ + 2HCOO^- + HCO_3^- +$ Glycine + Aspartate + R-5-phosphate-inosinic acid + fumarate + 9 $H_2O$

b. 9 ATP + 9 $H_2O \longrightarrow$ 8 ADP + 8 $P_i$ + AMP + $PP_i$ + 9 H+

Further metabolism of the purine nucleotide interconversions. Thus, inosinic acid plus GTP and aspartic acid are converted to adenylosuccinic acid which undergoes nonhydrolytic cleavage to adenylic acid, and inosinic acid is oxidized to xanthylic acid which further reacts with ATP and glutamine to form guanylic acid.

c) Salvage Pathways

However, there are other pathways of purine nucleotide formation. These routes are regarded as salvage pathways in the tissues where purine nucleotides are formed from free purines and purine nucleosides. This permits the reutilization of purine or purine derivatives by the tissues. Thus, free purines can react directly with 5-phosphoribosyl-1-pyrophosphate to yield nucleotides. An example of such a reaction is: Adenine + phosphoribosylpyrophosphate adenylic acid + $PP_i$. The same general reaction seems to hold true for guanine and hypoxanthine. Also, there are salvage pathways which involve the conversion of free purines to nucleosides and the nucleosides to nucleotides. An example of these, catalyzed by phosphorylase, are the following:

a. Hypoxanthine + ribose 1-phosphate $\rightleftharpoons$ guanosine + $P_i$

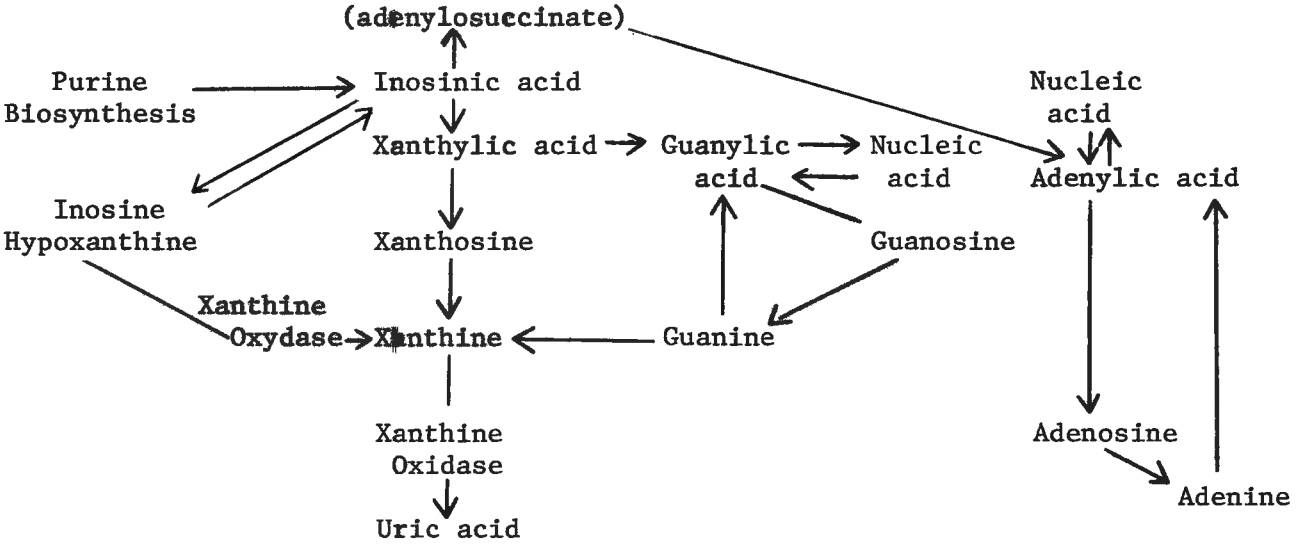
b. Guanine + ribose 1-phosphate $\rightleftharpoons$ guanosine + $P_i$

A known reaction for the conversion of a nucleoside to a nucleotide is the conversion of adenosine by adenosine kinase to adenylic acid.

c) Uric Acid Formation

Uric acid formation in mammals takes place in the liver. Pertinent

to this is the deamination of purines, such as: adenine and guanine to hypoxanthine and xanthine respectively. This can be done by adenase and guanase. However, since adenase is sparse in body tissues adenine can be deaminated through the nucleotide adenylic acid, by adenylic acid deaminase to form inosinic acid. An enzyme, xanthine oxidase, can convert hypoxanthine to xanthine and the latter to uric acid. Some species can further convert uric acid to allantoin, however, man and other primates cannot. Thus, uric acid is the end product of purine metabolism in man. Purine interconversions and uric acid formation are shown in the following diagram (2).




The concentration of uric acid in normal plasma is about 2 to 6 mg.%. The average for females is about 3.5 mg.%, while the average for males is about 4.5 mg.%. Hyperuricemia occurs not only in gout but in many other conditions. Gout will only be mentioned in connection with other manifestations of hyperuricemia since the disease gout has been extensively reviewed in the past. Hyperuricemia has been frequently observed in the asymto-

matic male relatives to gouty individuals. Many cases of hyperuricemia may be due to such diverse factors as impaired renal function, toxemia of pregnancy, essential hypertension, and leukemia. Uric acid in the urine is sparingly soluble and thus, a large fraction of all renal calculi consists of uric acid and its salts. In gout, large amounts of sparingly soluble monosodium urate are deposited in so called tophi in cartilage.

In normal individuals, about 50% to 75% of the body uric acid is replaced each day by newly formed uric acid. This means that the daily production of uric acid is about 0.5 to 0.86 gm./day. The production of uric acid appears to exceed the urinary output by 100 to 250 mg./day. However, studies with isotopic nitrogen labeled uric acid indicate that there may be partial catabolic breakdown of the purine nucleus as isotopic nitrogen is found in urinary urea and ammonia of people who have been given uric acid with labeled nitrogen. Further, $^{14}CO_2$ is formed when $^{14}C$ labeled uric acid is injected intravenously. The latter was reported in a personal communication with Dr. Denham Harman, The University of Nebraska College of Medicine.

It is interesting to note that there is a wide biological distribution of the end products of purine metabolism. Although man and other primates as well as birds and reptiles excrete mainly uric acid, many other mammals and other lower animals excrete allantoin, allantoic acid, urea, or ammonia. Those species which excrete nitrogen mainly as uric acid are called uricotelic. Those species which excrete nitrogen mainly as urea are called ureotelic.

II. Renal Handling of Uric Acid

The serum uric acid levels are probably increased in conditions associated with increased serum uric acid through 1 of 3 mechanisms. These are: primary endogenous overproduction, increased breakdown of nucleic acids within the body, and a defect in renal excretion.

Evidence for tubular elimination of uric acid is given by Praetorius (3) who studied a patient having an abnormally low serum uric acid. However, this patient's daily excretion of uric acid in the urine was normal. Considering inulin clearance as being equal to glomerular filtration rate, comparisons between this patient's inulin clearance and uric acid clearance showed his uric acid clearance to be much higher than his glomerular filtration rate. Therefore, it was concluded that, at least in this case, uric acid must be excreted by tubular secretion or be formed in the kidneys. At that time, all attempts to demonstrate the latter by locating xanthine oxidase in the renal tubules had failed.

Certain medical textbooks indicate that very little uric acid is reabsorbed by the renal tubules. However, Gutman and Yu (4) have indicated that about ninety-two percent of the filtered urate is reabsorbed. Also, as the filtered urate load is increased, the amount reabsorbed is also increased to a limited amount. Thus, the normal filtered urate load is usually far smaller than the tubular capacity for reabsorption.

We now have two mechanisms for renal handling of urate, which appear likely. The first suggests that the filtered urate load is reabsorbed and then urate is secreted by the kidney tubules. The

The second suggests that a certain amount of the urate load is reabsorbed and that the amount excreted is the difference between the filtered urate load and the amount reabsorbed.

III. Role of Kidneys in Primary Hyperuricemia and Gout

Is hyperuricemia, the Hallmark of gout, attributable to an error in metabolism which causes an overproduction of uric acid, or can it be attributed to an inherent defect in renal excretion of urate? Studies reported in 1907 (4) indicate that a significant number of gouty patients have normal or slightly depressed levels of uric acid excretion in the urine which is evidence for a defect in excretion.

On the contrary, later studies have been carried out in which significant numbers of gouty patients were shown to have a higher mean urate excretion in 24 hours, than seen in normal individuals. These investigators inferred that renal impairment, which is frequently found in older gouty patients, was the basis for previous reports of low or normal urate excretion in gouty patients. Gutman and Yu (4) report from their own studies in 1952, that a significant minority of patients with gout regularly excrete excessive quanities of urate in urine, while on a basal diet.

In their 1957 study, Gutman and Yu (4) showed that in general, the measurable parameters of renal function in gouty patients are comparable to those in non-gouty patients of a comparable age group. It is interesting that in the hyperuricemic relatives of gouty individuals that these people had increased filtered urate loads, normal glomerular filtration rates, and increased rate of urate excretion. The patients with low twenty-four hour urate excretions or significantly reduced effective renal plasma flow, had presumptive renal disease or evidence of vascular disease. Also, in gouty individuals there is a tendency for a decrease in twenty-four hour

urate excretion as time goes on and renal function deteriorates. There does seem to be an increased tendency for tophaceous gout as the renal urate excretion decreases. A predisposition to renal disease as a cause of death in gout has long been appreciated. Some of this may result from degenerative vascular disease, while other causes like pyleonephritis due to calculus formation and urate in the collecting system may be more directly related to the hyperuricemia. This suggests that there may be early tubular damage from urate deposits which is later complicated by vascular changes due to aging. This sets up a vicious cycle whereby early tubular damage and aging reduce the filtered urate load, potentiating hyperuricemia, which causes further renal damage. This secondary hyperuricemia then, is a consequence, not a primary cause of gout or hyperuricemia (4).

Why then, do all people with gout or hyperuricemia, and reasonably normal kidney function not excrete large amounts of urinary urate? This can probably be reasonably answered by remembering that as the filtered urate load increases, there is a limited increase in tubular reabsorption of urate. Therefore, the degree of hyperuricemia must be quite high before excess urate starts showing up in the urine.

Where would a defect in renal handling of urate causing hyperuricemia lie? Thannhauser (5) suggested that a slight increase in tubular reabsorption would markedly increase serum uric acid levels over a period of time. However, this was not borne out by Gutman and Yu (4) who have shown that the variable seems to be the filtered urate load and not the amount reabsorbed. Also, we have seen that one suggested mechanism of urate excretion is that after reabsorption the urate is then secreted by the tubules. Thus, an inherent defect in secretion

could bring about hyperuricemia. However, this does not explain the finding of hyperexcretion in some gouty and hyperuricemic patients, while those with decreased rates of urinary excretion can be explained as having already had severe renal impairment.

In order to help determine whether the metabolic disorder of gout could represent an increased endogenous production of uric acid or a decreased rate of elimination, a glycine containing $N^{15}$ was given to normal and gouty individuals (1). Then, the amount of $N^{15}$ in the urinary uric acid of these individuals was determined. It was found that almost three times as much of the $N^{15}$ appeared as uric acid as it did in normal subjects. This indicates that the metabolic defect in gout is an over production of uric acid, presumably an overproduction of purine nucleotides.

Two mechanisms for de novo overproduction of uric acid in hyperuricemia have been suggested in a later review by Gutman (6). First, in the production of uric acid in the body there is a so called "shunt pathway" whereby uric acid is made directly from inosinic, adenylic, and guanylic acids. This process presumably operates in normal man; however, in gout unexpected high incorporation of glycine $N^{15}$ into uric acid may represent enhancement of this shunt. The second has to do with the controlling step of purine synthesis. As seen earlier, this is the amination of 5-phophoribosyl-1-pyrophosphate from glutamine. Therefore, an increase in one of the precursors of this step could drive the reaction towards increased production of purines. Thus, a metabolic defect causing increased availability of glutamine to this reaction could conceivably give rise to an increased de novo purine

and hence uric acid synthesis. Glutamine is also the major amino acid participating in the sequence of enzymatic reactions which take place in the kidney to form ammonia, and certain data suggest a modest impairment of renal production of ammonia in patients with gout. Therefore, it has been suggested that a defect in the utilization of glutamine by the kidney to make ammonia in these people could explain primary gout and hyperuricemia. In other words, we may have a diversion from one metabolic pathway to another.

In addition, there is evidence to indicate that the defect in purine synthesis may occur as an alteration of the feedback system operating at the committed step of the purine biosynthesis. It will be recalled that this step is the addition of glutamine to 5-phosphoribosyl-1-pyrophosphate.

Therefore, it appears that there is fairly good evidence to indicate that the primary defect in gout and essential hyperuricemia is one of increased endogenous production of urate, rather than an inherent defect in renal excretion. However, one can see that subsequent renal damage in gout can be an important secondary factor in producing hyperuricemia.

## IV. Heredity in Gout and Hyperuricemia

As far back as ancient times hyperuricemia and gout have been accepted as inherited traits. However, recent investigations into this subject do not necessarily support such a notion. A significant problem encountered in studying the genetics of hyperuricemia and gout is that these are not homozygous conditions. In other words, there are several causes of hyperuricemia and some of these may be inherited while others are not. Therefore, if these are inherited traits, there is little agreement as to the mode.

Some writers report hyperuricemia as a single autosomal dominant trait (7). However, it has been shown not to fit well with prediction by Mendelian inheritance (8). Studies by Hauge and Harvald on uric acid levels of siblings and probands with gout suggested that the trait is polygenic (9). Likewise, a study of O'Brien et al (10) of the Blackfoot and Pima Indians found that analysis of hyperuricemia as a simple trait did not fit a hypothesis of random distribution, simple recessive inheritance, or simple dominant inheritance. They concluded that if it was a genetic trait at all that it would necessarily be a polygenic one. They then examined the degree of inheritance of the trait and found it to be quite low, suggesting that the trait is for the most part, not a genetic one, but largely determined by environmental factors. As a polygenic trait they also found evidence that some of the genes involved were sex-linked dominants.

Blumberg (8) has suggested the trait is one which when inherited does not show up unless certain environmental factors are present.

In association with this was a study by Decker (11) of a population living in the same environment, which contains a large number of different races. In his study the Filipinos were shown to be more strikingly hyperuricemic. The Filipinos have been previously shown to have a high incidence of hyperuricemia and gout, out of their environment, while this has not been seen in Filipinos living in the Philippines (8).

On the contrary, in a recent study of hyperuricemia and gout in the Mariana Islands, there was a high degree of these conditions in the Chamorros and Carolinians living in the Mariana Islands (12). It has been said that a bimodal distribution curve of uric acid levels would be suggestive of a monogenic trait (10), and this was the type of curve reported in studying the uric acid levels in 160 Chamorro males. Although this contradicts those who say that the trait is polygenic, the uric acid levels were not corrected for age, sex, and body surface in the Mariana study, which would make the findings more significant.

At this time, there are probably so many environmental factors obscuring the possible inheritance of hyperuricemia that the postulation of the presence or absence of a specific genetic mechanism is probably not warranted (10). In addition, although the statistics of many people interested in this subject show a high degree of familial tendency among probands with gout and their relatives, the familial nature of a disease does not make it a genetic trait (8).

V. The Epidemiology of Hyperuricemia

Hyperuricemia has long been associated with gout, but it is found that the incidence of hyperuricemia is much greater than the incidence of gout in the general population. In fact, it has been shown that there is no definite increase in the incidence of gout in the relatives of probands with symptomless hyperuricemia, unless the proband himself had gout (7).

However, since uric acid is not broken down further in significant amounts in the body, and as yet has no known use in the body, its presence in elevated amounts is considered pathogenic (13). The known general causes of hyperuricemia include increased endogenous synthesis, accelerated nucleic acid turnover, massive cell destruction, increased purine destruction, and a decrease in renal excretion. These mechanisms probably encompass such conditions as polycythemia rubra vera, chronic leukemias (especially with chemotherapy), myleoproliferative diseases, psoriasis, toxemia of pregnancy, renal failure, and primary hyperuricemia with or without gout, which are associated with raised serum uric acid levels. In addition, many drugs, such as pyrazinamide, chlorothiazid, acetozolamide, chlorthalidome, and salicylates (in low dosages) are known to increase serum uric acid levels. Therefore, the finding of an elevated serum uric acid must be evaluated quite carefully (13).

There are other conditions where associations with uric acid levels are suspected. These include diabetes mellitus, coronary artery diseases and atherosclerosis, hyperlipidemias, and a characteristic central nervous system disturbance; these subjects are discussed in this thesis.

In answer as to how hyperuricemia should be defined, the World Health Organization Committee has chosen 7 mgm.% for males and 6 mgm.% for females as the level of definitely high serum uric acid levels, at least for gout survey purposes. It has been shown that there is minimal chance of urate precipitation at concentrations below 7 mgm.% by the enzymatic spectrophotometric method (13). It is well known that the monosodium salts of uric acid are sparingly soluble and that when these solubility limits are exceeded by increased concentrations of uric acid, the resultant crystal formation causes the clinical manifestations depending on the site of crystal formation (renal tubules, synovial spaces, etc.). The proposed mechanism in gout seems to represent a vicious cycle where a precipitate of uric acid crystals occurs in the synovial space which produces inflamation, which in turn lowers the pH, which favors further precipitation of uric acid crystals (13). The risk of disease with hyperuricemia has been calculated for gout to be less than 2% for persons with serum uric acid levels below 6.9 mgm.%, 16.7% for persons with serum uric acid levels of 7-7.9 mgm.%, and 36% when the initial serum uric acid is 8 mgm.% or more (4) (13). As mentioned earlier, the increased risk between hyperuricemia and other diseases will be discussed in this thesis.

VI. Hyperuricemia and Hyperlipidemia

From a review of literature in 1962 (14), it is apparent that hyperuricemia has been reported to be frequently associated with persons having familial hypercholesterolemia. Evidence for such associations are seen in various early studies in patients with a trait for hypercholesterolemia which indicates that roughly 1/3 to 1/2 of these people also had increased serum uric acid levels. The review mentioned four cases where a high incidence of hyperlipidemia and hyperuricemia occured in immediate families. For instance, in one family the father and two out of three sons had hyperuricemia and hyperlipidemia. The third son had only hypercholesterolemia while a fourth child, a female, had no chemical abnormalities. Thus, suspicion was raised that the metabolic defect in families with hypercholesterol and hyperlipidemias may not be limited to the lipids but include anomalies of other metabolic pathways which, in part, manifest themselves in an elevation of the serum uric acid. Unfortunately, these studies did not include such factors as age and sex distribution, presence or absence of renal disease, or the presence or absence of hemopoietic disease. Further association between hypercholesterolemia and hyperuricemia have been seen in patients with myxedema, a condition noted for its association with an increased serum cholesterol level. In a group of 28 patients, slightly less than 2/3 had elevated serum uric acid levels, and in 21 of the 28 patients studied, the myxedema was of the secondary type. Low doses of thyroid hormone were effective in reducing the serum cholesterol, however, the serum uric acid was not reduced unless

high doses of the thyroid hormone were used. One might expect to find a high incidence of hyperuricemia in diabetic patients since hypercholesterolemia is well known to be associated with diabetes. However, as will be discussed later hyperuricemia may not necessarily be more frequent in diabetics, and if there is a common factor between hyperuricemia and diabetes it is probably not cholesterol per se.

Arteriosclerosis appears to be one of the frequent complications of gout (14). On the basis of the observation of uric acid crystals in coronary vessels in two patients suffering from gout, the suggestion was made that uric acid molecules might act as cationic agents attaching themselves to larger cholesterol particles, thereby enhancing contact with the intimal layer of arteries. It has been argued that this process may contribute to arteriosclerosis. However, in a study of patients with peripheral vascular disease, one of the complications of arteriosclerosis, the incidence of hyperuricemia in these persons was actually higher than that of hypercholesterolemia. In this series, 21.9% of the patients with peripheral vascular disease had high serum uric acids, while 18.6% had high serum cholesterols. This study was reported by Kramer and mentioned in the present review.

Studies were also reported where the incidence of hypercholesterolemia in patients with gout was studied. In summary of the data mentioned by Marinoff et al (14) on this subject, one can see that 25 out of 38 subjects with clinical evidence of gout had associated hypercholesterolemia.

Now, however, the later studies are beginning to discredit any association between hypercholesterolemia and hyperuricemia. It is thought that the previously reported correlations were probably due to overlooked hypertriglyceridemia in patients with high uric acids (15). A later more conclusive study of hyperuricemia in familial hypercholesterolemia has been reported by Jensen in the 1966 Lancet (16). In a study of 185 members of twelve Danish families with a known trait for hypercholesterolemia, where serum uric acid and cholesterol levels were performed on all members of each family, no differences were found between the serum uric acid levels in those with the trait and those without the trait. Jensen explains that the report of associated hyperuricemia and hypercholesterolemia in the review by Mandel in 1962, was probably the result of these families being branches of one larger, unusual kindred. On the contrary, the pedigrees of the 185 persons in Jensen's report make certain that none of the families were related. Thus, Jensen feels that the finding of hyperuricemia in familial hypercholesterolemia is unusual and that hyperuricemia cannot play an inherent part of familial hypercholesterolemia. In the Framingham study (17), no statistically significant correlation could be made between hyperuricemia or gouty patients and elevated blood cholesterol levels. However, there was a mild trend towards higher cholesterol levels in the markedly hyperuricemic group and in the gouty group.

Berkowitz (15) has shown that the uric acid level in patients with hypertriglyceridemia was significantly higher than the mean uric acid levels in patients with normal triglyceride values or

elevated cholesterol values. Likewise, 84% of the patients whom he studied with gout had abnormally high triglyceride levels, while only twenty per cent of these had abnormally high cholesterol levels. In addition, it has been shown that increased serum uric acid levels correlate better with peripheral vascular disease than do cholesterol levels (14). Also, significant correlation between the alpha/beta lipoprotein ratios and serum uric acid levels in atherosclerotic patients have been found (14). Likewise, it has been found in most studies that high uric acid levels are found more often than elevated cholesterol levels in coronary heart disease. It is also being shown that hypertriglyceridemia correlates better with coronary atherosclerosis than hypercholesterolemia does (15).

Berkowitz offered no definite mechanism by which hypertriglyceridemia and hyperuricemia are related, but his studies indicate they both reflect an inherited component, and acute fat loading and fat clearing studies show that neutral fat levels are a primary factor in concomitant uric acid levels. Alderberg (18) has been reported to have shown that uric acid excretion may be decreased by high fat feedings.

We see evidence for an association between hyperuricemia and hypercholesterolemia on one hand and an association of hyperuricemia and elevation of various other serum lipids on the other. We find that hyperuricemia and hypercholesterolemia have certain aspects in common: 1) Each is thought to arise from a genetic defect inherited as a Mendelian trait. 2) There is a similar pattern of distribution of both tophi and xanthomate. 3) There is an increased incidence of coronary heart disease in both essential hypercholesterolemia, and gout. Hyperuricemia is also frequently found in patients with

coronary heart disease and myocardial infarction. 4) As with cholesterol, the gap between serum uric acid in males and females seems to close after menopause. However, we find that agents which lower cholesterol or serum uric acid levels such as nicotinic acid and probenecid respectively do not alter the other component. In addition, it has been reported that serum uric acid may correlate significantly with cholesterol in normal individuals, however, in individuals with arteriosclerotic disease the uric acid levels correlate significantly with the lipoprotein fractions. It is well known that stress will increase the serum cholesterol but in studies performed on a group of medical students, no concomitant rise in serum uric acid could be shown (14). One can also see that studies by Jensen and Berkowitz indicate that there is a greater correlation between hypertriglyceridemia and hyperuricemia than there is between hypercholesterolemia and hyperuricemia. Thus, earlier reports which favor associations between serum uric acid and serum cholesterol may actually reflect the presence of undetermined concomitant high triglyceride values.

VII. Relationship of Hyperuricemia and Coronary Heart Disease

a) Common Factors

It appears that hyperuricemia and coronary heart disease have several common eiologic factors, namely; maleness, massive physique, and age. In a study of 92 males who had suffered myocardial infarction prior to the age of forty, as compared with a control group matched according to age, physique, and occupation, twenty-four per cent of the coronary group had serum uric acid concentrations in excess of 6 mg.%, while only 6% of the matched control group had uric acid levels this high (14). In relation to body habitus, Gertler (19) has found significant correlation between increased serum cholesterol with the mesomorphic habitus. He also found significant correlation between increased serum uric acid levels and the endomorphic group. Since the "coronar physique" seems to be a mesomorph with secondary endomorphy, we have a common factor which might relate these two conditions. However, when comparing the serum uric acid levels of a coronary heart disease group with the serum uric acid levels of a matched control group of the same body build, he found that there were significant elevations of serum uric acid in the coronary group as compared with the control group. Thus, there must be additional factors contributing to the difference in serum uric acid levels other than body build. As early as 1954, Gertler had emphasized that the concentration of cholesterol is not a reliable index to the venerability of an individual to ischemic heart disease. Instead, he felt that the ratio between cholesterol and lipid phosphorous was probably more important than either component alone and attempted to relate

coronary artery disease to a biochemical index called the "cup index";

$$\text{serum cholesterol mgm.\%} \times \frac{\text{serum uric acid mgm.\%}}{\text{serum lipid phosphorous mgm.\%}} \quad (19)$$

The mean cup index was found to be significantly higher in the coronary heart group than in the matched control group. This was felt to separate the normal group from the coronary heart group more effectively than any other index present at the time (19). In explanation, Gertler goes on to suggest that lecithin, which is about 80% of the serum phospholipids, acts as a cationic surface active agent while on the other hand, serum uric acid in its lactam state could act as an anionic surface active agent. In this way, serum uric acid could have some enhancing effect on a deposition of serum cholesterol in the intimal tissue by alteration of the permeability as do some other surface active agents. He quoted Huchard (1899) who said, "Gout is to the arteries what rheumatism is to the heart".

In the previous section possible associations between hypercholesterolemia and hyperuricemia have been discussed, but more important there is evidence that there may be an association between triglycerides and serum uric acid. In addition, it has been shown that the triglycerides may be important in coronary heart disease and other complications of atherosclerosis. As mentioned, Gertler, in 1954, suggested that cholesterol alone was not a reliable index on which to evaluate coronary disease. Since uric acid and triglycerides may well be a common factor in cornary heart disease, as well as another important disease, diabetes, it might be interesting at this time to summarize a paper by Albrink (20), which discusses the relation of serum triglyceride abnormalities to vascular disease.

b) Relationship of Triglyceride Abnormalities to Vascular Disease

As a result of various ultracentrifical and chemical techniques, the basic postulate that coronary heart disease is associated with abnormal high concentrations of very low density lipoproteins in the serum has been made.

There are four types of circulating serum lipids, the chylomicrons, free fatty acids, and high and low density lipoproteins. The latter are referred to as alpha and beta respectively. Of the alpha and beta lipoproteins the ones which have been best correlated with coronary artery disease are the lower density group of beta lipoproteins. The increased lipid concentrations of the serum seen in coronary artery disease can almost always be found to be an increase in one or both of either the low density lipoproteins or chylomicrons.

The various low density lipoproteins may be thought of as protein-cholesterol-phospholipid moieties, which differ only in the amount of triglycerides. As the amount of triglyceride increases, the molecule becomes less like a protein and more like a fat molecule. Thus, a decrease in serum lipoprotein density plus turbidity of the serum is associated with an overabundance of triglycerides.

The density of lipoprotein can be subdivided into various density (D = density) groups. Thus, D 1.063 divides the low from the high lipoproteins. In a nonprotein solvent D 1.063, the lipoproteins will float at different rates, the low densities having the highest flotation rates. The class of low density lipoproteins which predominate in the serum are the D 1.019 - 1.063 group with $S_f$ 0-12. These are 21% protein, 47% cholesterol and ester, 23% phospholipid,

and 9% triglyceride. The category which contributes most to turbidity during lipemic states is the class D 1.006, and chylomicrons. The latter category is ordinarily inconspicuous in normal serum. There are two classes of hyperlipidemias in the low density spectrum These are known as familial hypercholesterolemia and essential hyperlipemia. The lipoprotein changes in the former are reflected mainly in an increase in the cholesterol dominated proteins, while in the latter, the changes are due mainly to increased levels of triglyceride-laden, low density lipoproteins of class $S_f$ 100-400 of D 1.006. In determining the Atherogenic Index, the triglycerides with a very low density of the lipoproteins decrease, total triglycerides are a good indication of the concentration of the low density lipoproteins. Chylomicrons are of great significance in coronary heart disease, as will be discussed later.

As the triglyceride levels increase, an increasingly larger amount of low density cholesterol is seen in the very low density lipoprotein fractions. It would appear that the important factor then, is the absolute amount of low density cholesterol, which is in turn regulated by the serum triglyceride level. Thus, an individual can have a normal total cholesterol, but a large part of it may be in abnormal lipoproteins. This can only be detected in turn by knowing the serum triglycerides.

This author showed in one study that 80% of the coronary group had triglycerides in excess of 5.45 mEq./l. On the other hand, very few patients had increased cholesterols with normal triglycerides. Only one half of the patients with coronary heart disease and increased

triglycerides, also had increased cholesterol levels.

About one third of the apparently normal middle age men with high serum triglycerides had a positive family history of coronary artery disease and diabetes. Such men are most often of mesomorphic body build. Thus, it is thought that the very low density lipoproteins, reflected by the triglycerides, correlate well with coronary heart disease.

The lipid abnormality then can be better detected by the determination of cholesterol and triglycerides than by statistical manipulation of several lipoprotein classes. It is to be noted that lipid determinations are not valid in recent infarct cases for at least ten days post-infarct, because of a depressing effect by the infarct on blood lipids.

In addition to abnormal triglycerides in coronary heart disease, another common finding is an increase in chylomicrons. These are fatty particles absorbed from the gastrointestinal tract after a meal. They are responsible for the lactescence of the serum, usually lasting 6 to 8 hours following an ordinary meal. They are made up mainly of triglycerides, small amounts of protein, cholesterol, and phospholipid. They have a very low density with a high flotation rate. The chylomicrons appear to reach the general circulation through the lymphatic system after once originating from the process of alimentary fat absorbtion. They are said to be broken down in two phases: A rapid phase of triglyceride removal, and a slow phase concerned with disposing of very low density lipoproteins derived from the intracellular hydrolysis of lipids carried in the chylomicrons. An error in either phase can be associated with increased triglyceride levels

and the latter slow channel is the one implicated in coronary heart disease. Indeed, it is thought by many that abnormally prolonged responses to fatty meals might be a better indicator of a fat defect in coronary artery disease.

The question of lipoprotein lipase, an enzyme in the body activated by heparin, was reviewed as a possible mechanism for hypertriglyceridemia. This enzyme appears to be important in the clearing of the triglycerides from the serum. However, it appears to only apply to the rapid phase of the alimentary chylomicron removal and not to the removal of the very low density lipoproteins. The evidence in one study which showed no decrease in mortality in coronary patients given heparin over those which were untreated, bears out the suposition that accumulation of abnormal triglycerides in coronary disease patients is a defect in the slow phase. However, the case of lipoprotein lipase still remains unproven. On the other hand, increased triglycerides or the very low density lipoproteins could be a result of endogenous over production rather than the above discussion advocating impaired removal of these lipoproteins.

In relation to diet, the cholesterol and triglyceride portions of lipoproteins are quite different. While cholesterol varies with the amount of fat in the diet and type of fat, triglycerides increase in high carbohydrate diets. Also, triglycerides are apparently unaffected by the type of fat. Triglycerides are also very sensitive to total calories.

In relation to weight gain, it has been found that men who have gained over ten pounds since age twenty-five, have higher serum tri-

glycerides and coronary heart disease shows a similar correlation.

Diabetes is another condition which may be associated with high triglyceride levels. This has been seen in normal individuals with a positive family history for diabetes. This could have some bearing in the relation of triglycerides to coronary heart disease and suggests a possible common eitology between coronary heart disease and diabetes related to excessive weight gain.

Although the exact connection between abnormal serum triglycerides and coronary heart disease remains to be worked out, a number of studies of the role of serum lipids in the clotting mechanism suggests a possible link between the thrombotic aspects of coronary heart disease and the triglyceride abnormality. Among others, a reduction of anti-coagulant activity of heparin during clearing of lipids and an increased tendency to thrombus formation caused by the sodium salts of long chained fatty acids were mentioned. In addition, low density lipoproteins in atheromatous plaques have been shown to be identical to these same lipids in the serum.

As mentioned in the above paragraphs, fat tolerance studies might be an important parameter indicating the susceptibility of a patient to coronary heart disease. Berkowitz (21) uses an isotopic triolein tolerance test to perform fat tolerance studies. He found this test to be abnormal in 82% of one hundred patients with coronary heart disease.

c) The Framingham Findings

Getting back to the subject of hyperuricemia and coronary artery disease, one of the best studies of a prospective nature dealing with

this subject, is the Framingham study (17). In this study, 5,127 men and women ages 30 to 59, were studied for a period of 14 years, and the incidence of coronary heart disease assessed at the end of ten years. In addition to other studies, serum uric acid determinations were made on admission and over the next six years. The individuals were grouped according to their uric acid levels as less than 4, 4 to 5.9, 6 to 6.9, and 7 or above. These groups included the individuals who had gout. In addition, the gouty dividuals were shown as a group. The incidence of the development of heart disease in each group was then determined. For the total population it was 9.2 per 100. In the population of persons having a serum uric acid of less than 4, it was 7.1/100, in the 4 to 5.9 group, it was 9.5/100, in the 6 to 6.9 group, it was 9.1/100, in the 7 or above group it was 14.2/100, and in the gouty group it was 18/100. This was interpreted to mean that there was a significantly higher incidence of coronary heart disease in the subjects with gouty arthritis, and that there also appeared to be a trend towards more coronary heart disease in the groups with the higher uric acid levels. However, when the subjects with gouty arthritis were removed from the population at risk the association between uric acid and an increased incidence of heart disease was significantly lowered. In this case, the population having a uric acid of 7 or above had an incidence of coronary heart disease of 11.3/100 while the gouty populations incidence remained 18/100. This was interpreted to mean that there was something unique about people having gout which predisposed them to the development of coronary heart disease. However, both coronary heart disease and gout are diseases in which the incidence increases with age. It is,

therefore, reasonable to suspect that the age of the patients in the gouty group was greater than the asymptomatic hyperuricemic group, and that since there is also an increased incidence of coronary heart disease with age, this would seem to be a common factor relating the gouty patients and patients with coronary heart disease. Also, the patients with severe hyperuricemia who were asymptomatic would probably represent a significantly younger group by the fact that they had not yet developed gout. Somewhat in support of the Framingham findings, Friedberg (22) says that there is no significant correlation between the occurrence of coronary heart disease and uric acid levels in nongouty patients. However, he also quotes some other workers' materials , which indicates that uric acid crystals may be found in heart muscle, cardiac valves, or blood vessels (23). He also reports a cure of heart block in a patient with gout by the administration of Benemid, which was attributed to the elimination of a gouty tophus in the conduction system (24). There is also a case of acute myocardial infarction where there was found difuse deposits of urate in the myocardium and a gouty tophus in the left ventricle adjacent to the left circumflex artery which was supplying the infarcted muscle. This artery was not, however, occluded by the gouty tophus (25).

d) Serum Uric Acid in Patients with Myocardial Infarction

Two different studies of serum uric acids levels in patients immediately following myocardical infarction have been carried out with somewhat contridicting conclusions. In one, Lal et al (26), in the treatment of acute myocardial infarction came across two patients who developed gout following rreatment for their myocardial infarction. This led them to check the uric acids in all new myocardial infarctions and it was found

by them that the uric acid was elevated in all cases. Their follow-ups on the uric acid levels revealed that by the tenth day, post infarction, most had gone down to within normal range, however a high normal range. In their study they could find no evidence that this hyperuricemia was due to diet or poor renal function. In addition, they did not feel that incidence of myocardial infarction in gouty individuals was high enough to be directly related to the uric acid values exhibited by the sufferers from gout, and they did not feel that an initial rise in uric acid directly precipitated the infarct or produced changes in the coagability of the blood leading to coronary thrombosis or occlusion. Their conclusion then, was that the hyperuricemia was the direct result of the death of the myocardium with increased destruction of the muscle nuclei. They further found that in cases of myocardial infarction which could not definitely be diagnosed by EKG or SGOT estimation, neither could any rise of uric acid nor a progressive fall over the days of recovery be demonstrated. They proposed that the determinations of the serum uric acids might be highly valuable in making a diagnosis of myocardial infarction.

Kohosla, Caroli, Guta, and Bahl (27) were stimulated by the previously mentioned work and carried out their own study on 54 cases of proved myocardial infarction and 23 cases of "angina of effort". They did determinations in these individuals of the SGOT levels and serum uric acid levels during the first 24 hours, 48 hours, 96 hours, 6 days, and at 6 weeks post infarct in the patients who survived. In addition, if there was clinical evidence of an extension of infarction the estimation was repeated at that time also. Their results indicated that there were raised serum uric acids in 66.7% of the cases of myocardial infarction and raised serum uric acids in 60.8% of the patients with angina pectoris. As with

the above group, they could not correlate the serum uric acid levels with the extension of infarction nor the size or severity of the infarct. The Serum uric acids also did not correlate well with the SGOT levels, and the SGOT levels tended to go down as the patient recovered while the serum uric acid levels did not fall with the passage of time. This is in direct contrast to the above study in which the serum uric acid levels were reported to be down to almost normal by the tenth day post infarct. In fact, in the latter group, three-fourths of the patients who survived, still had elevated serum uric acids at the end of six weeks. Thus, in contrast to Lal, they did not feel that the rise in serum uric acid levels was necessarily the result of myocardial necrosis but thought that it was more probably a metabolic defect which could be considered as a background factor, such as diabetes or hypertension in the predisposition to coronary artery disease. Also in contrast, they did not feel that serum uric acid estimations could be of much value in the diagnosis of acute myocardial infarction.

e) Potentiating Effects of Hyperuricemia

Another factor noted in observing the literature on this subject is that there seems to be a tendency for the potentiation of certain cardiovascular conditions in the presence of hyperuricemia. Breckinridge (28) correlated hyperuricemia with the incidence of severe hypertension, gout, cerebral vascular disease, ischemic heart disease, serum cholesterol, and pregnancy. In comparing the severity of hypertension in patients with raised serum uric acid and normal serum uric acid he could find no significant increase in the severity of hypertension in patients with hyperuricemia. However, 15% of the patients with hyperuricemia and hypertension had presented

with cerebral vascular accidents as compared with only 6% of the hypertensives without hyperuricemia. This was considered a significant difference. Likewise, in ischemic heart disease, 17% of the patients with both hypertension and hyperuricemia had evidence of ischemic heart disease while only 3% of the hypertensives with normal uric acids had evidence of ischemic heart disease. This difference is again highly significant. He also showed a significantly greater number of hypertensives with hyperuricemia who also had elevated cholesterol levels as compared to the serum cholesterol levels in the hypertensive group with normal serum uric acid. His findings in relation to hyperuricemic patients with hypertension who become pregnant will be discussed later. In support of this, the study by Khosla and his associates (27), showed that one-fourth of the myocardial infarct cases with elevated serum uric acids expired while about one-sixth of the cases with normal serum uric acids expired. In relation to hyperuricemia and hypertension, the Framingham study again showed only a mild trend towards increased systolic blood pressuresin patients with hyperuricemia and gout.

It would appear from the material presented that there is no significant correlation between asymptomatic hyperuricemia and the development of coronary artery disease, although there is probably a mild to moderate trend for an increased incidence of coronary artery disease in asymptomatic patients with markedly elevated serum uric acids (7 mg.% or above). There seems to be significant correlation between coronary artery disease and gout, however, age may be a common factor which when considered might tend to make the correlation less significant.

Another interesting point covered is that there may be a tendency for

the serum uric acid to be elevated following a myocardial infarction due to the destruction of the cell nuclei, but it doesn't appear as yet that this would be a valuable guide to diagnosis. Possibly more important is the prognostic implications of the presence of hyperuricemia in patients with coronary artery disease and/or hypertension, since hyperuricemia, especially in combination with hypertension, seems to potentiate the incidence and severity of coronary heart disease and cerebral vascular disease.

VIII. Associations Between Hyperuricemia, Gout, and Diabetes

Since diabetes Mellitus is well known to be associated with certain lipid abnormalities, one might expect to see serum uric acid changes in patients with diabetes. The majority of the literature seems to indicate that there is a tendency for lower mean serum uric acids in patients who are primarily diabetic and conversely, an increased incidence of abnormal glucose tolerance tests in patients who have gout (29). Studies by Beckett and Lewis (30) indicate that although persons who have relatives with a history of gout tend to have an increased incidence of hyperuricemia, diabetics with relatives having a history of gout do not show this tendency for asymptomatic hyperuricemia. Also, in their diabetic patients who also had gout, the high levels of serum uric acid normally seen in gout were absent. In these patients the gout and the diabetes were both mild, although they did not escape the vascular complications of diabetes. On the other hand, there seems to be a family history of gout in patients with diabetes more frequently than in normal patients. Whitehouse and Kleary (31), over a nine year period, had 89 gouty patients, or 10%, with concomitant diabetes mellitus. In a later study, done over a five year period of 181 patients with gout tested for diabetes using a two hour post-prandial 100 gm. $CH_2O$ meal, 6% of these gouty patients had abnormal serum glucose levels after two hours. However, they tested another 45 patients two hours after administration of 100 gms. of glucose solution and 33% of these had abnormal levels of serum glucose after two hours. They felt that the latter method was more sensitive than the post-prandial method. Likewise, in a study of the Natal Indians, an abnormal glucose tolerance test was seen in 6.9% of a group of patients having gout or hyperuricemia (32),

and the authors of this study thought that abnormal uric acid metabolism was indeed a manifestation of pre-diabetes.

Kramer and others (33) found a lower incidence of hyperuricemia in diabetic patients than in nondiabetic patients, both groups showing evidence of atheromatous disease and elevation of cholesterol levels to a comparable degree (14). Bartels and co-workers found clinical improvement in 15 of 34 gouty patients after they had contracted diabetes (34). Beckett is also reported to have shown that the average level of uric acid was lower in a group of diabetics than in a control group (30). Therefore, one might conclude that diabetes has an ameliorating effect on hyperuricemia or gout. However, in direct contrast, Ishmael (35) noted that prior to 1944, none of the patients in their group had associated gout and diabetes. However, in a later study they found 10% of their gouty individuals to have diabetes. This apparent increase in the incidence of associated diabetes and gout could be attributed to an ameliorating effect of hyperuricemia on diabetes since in the latter investigation, 85 out of 100 patients studied had been receiving probenecid and colchicine which would tend to make their uric acid levels lower. It has been proposed by some that in patients who are predisposed to gout and diabetes that the lowering of the serum uric acid acid with uricosuric agents could be a pre-causative factor in the development of subsequent diabetes in the patient (36). Another observation which has made investigators feel that there is a possible ameliorating effect of hyperuricemia upon diabetes is that in diabetic patients who develop renal disease, with subsequent elevation of the serum uric acid due to renal failure, there is a decreased insulin requirement seen. However, it was explained in a

personal communication with Dr. Mary J. Henn of The University of Nebraska College of Medicine, that these people are generally very sick and anorexic. Thus, their $CH_2O$ intake is also decreased and could easily be the reason for a decrease in their insulin requirement.

Not all investigators agree that serum uric acid levels tend to be lower in diabetics and that diabetes is more frequent in patients with gout and hyperuricemia. De Candia (37) and Padova (38), found a very high percentage of diabetics with increased serum uric acid levels. In addition, there are at least three reports which indicate that diabetes is not more common in gouty individuals. Talbott suggests that gouty patients even have a lower prevalence of diabetes than in the general population. Hall found mean serum uric acids in diabetes to be the same as in the general population and also that the mean post-prandial blood sugar in gouty patients was the same as in the general populations. Mikkelsen reports lower serum uric acid levels in diabetes, but no association between diabetes and gout (26).

A variety of mechanisms for the association of uric acid and diabetes have been offered. Beckett and Lewis (30) suggest four possibilities for lower uric acid values in diabetes than in nondiabetic patients: a) the diabetes may increase urinary excretion of uric acid by competition for reabsorption of the uric acid by the glucose; b) uric acid production in diabetes may be less than normal; c) there may be further degradiation of uric acid in diabetic patients; d) a homeostatic mechanism may be set at a lower level. They also suggested that the higher levels of serum uric acid in mild diabetics as compared to severe diabetics, might be related to body build. As has been noted by Gertler, endomorphic persons tend to

have a greater tendency for increased serum uric acids and since the endomorphic body habitus is also associated with the mild form of diabetes, the body build could be a common factor. Another suggestion by the same group was that overweight diabetics have a tendency to be polycythemic, and that in polycythemia, there is also a tendency for increased serum uric acid.

In support of the premise that decreased serum uric acids in diabetics might be due to increased renal excretion of uric acid, urate clearances and creatinine clearances were done in a group of diabetic and control patients (39). It was found that the serum urate level was much lower in the diabetic group, and there was a significantly higher urate clearance in the diabetic group as compared with the control group. Also, their tables show that the patients with the lesser form of diabetes had the highest mean serum uric acids, while those with insulin treated diabetes had the lowest mean serum uric acids. In explanation, renal biopsies appear to show that patients with diabetes always have some degree of thickening of the basement membrane of the capillaries, glomeruli, and tubules in the kidneys. It was suggested that the thickening in the tubules could decrease urate reabsorption and account for an increased clearance of urate.

By what mechanism may an increased incidence of abnormal carbohydrate metabolism in gout and hyperuricemia occur? One explanation which has been offered is the similarity, chemically, between uric acid and alloxan (31). Alloxan is a drug which effects the Beta cells in the pancrease and is used to produce experimental diabetes. Since uric acid has a chemical structure quite similar to alloxan, it has been suggested that the former may be also be diabetogenic, However, it takes very large infusions of uric acid to be diabetongenic. In addition, patients with leukemia, a condition which tends

to raise the serum uric acid, do not appear to have an increased incidence of abnormal glucose tolerance tests (30).

Another common factor which was pointed out to be present in these two conditions is obesity and endomorphy (30). The incidence of insulin-independent diabetes in obese gouty patients is recorded to be higher than those in matched control groups. Therefore, it has been suggested that patients with concomitant obesity and hyperuricemia be watched carefully for the development of diabetes (31).

However, hyperuricemia is not limited to one type of body build. There is, however, another factor common to both diabetes and hyperuricemia, the serum triglycerides. Formerly, much attention has been paid to cholesterol-carbohydrate metabolism relationships, but Berkowitz (40) has shown a much greater association between abnormal glucose tolerance curves and abnormal triglyceride levels. He found that out of 25 patients with hypercholesterolemia there were 12% with abnormal glucose tolerance tests. In addition, he studied 25 gouty patients. Nineteen of these gouty patients had abnormal triglycerides, and 74% of the 19 also had impaired glucose tolerance tests. The Maoris of New Zealand have been shown to have a greater incidence of combined gout and diabetes than Maories in the Cook Islands, although they have hyperuricemia to a comparable degree (36). However, the Maori group from New Zealand also had a significantly higher mean triglyceride level than the other Maori groups. In correlation with Ishmael's observations (35), no one of the patients studied in the Cook Island group was under treatment for gout, so again the effect of depressing hyperuricemia on development of diabetes must be considered.

It has been noted that there can be an acute elevation of serum uric

acid in diabetics with ketosis (31). Padova (38) studied the serum uric acid levels, amount of ketosis and other variables in a group of eight patients through their course of diabetic-ketoacidosis. He found that 50% of this group had serum uric acid levels above normal initially, and that the mean for the whole group was higher than the mean for his control groups. In 7/8 of the group, the degree of hyperuricemia paralleled the degree of ketosis. However, when the ketosis had resolved, the mean for the entire group dropped to below the control mean, and likewise, the mean for the hyperuricemic group also dropped to below the control mean with resolution of the acidosis.

In explanation, Padova pointed out that these patients had essentially good renal function with a minimum of dehydration, no specific prevalence of other conditions associated with hyperuricemia (obesity, myxedema, eclampsia, pernicious anemia, starvation, hypoglycemia, myeloproliferative disease, rheumatoid arthritis, prolonged exercise, hypertension, or use of antihypertensive drugs), and none of the patients studied were on salicylates or diuretics. Latic acid, given to correct acidosis in diabetics, can raise the serum uric acid, but not this significantly. In addition, pyruvic acid, which goes up with insulin-glucose treatment, is shown to enhance uric acid excretion and would neutralize the lactate effect. The explanation offered by Padova as the most likely, is that with glycogen depletion in the liver leading to gluconeogenesis, there is a resultant increased production of purines from the breakdown of nucleoproteins causing and increased serum uric acid.

However, later studies of hyperuricemia with starvation and high fat feedings (41,42), indicated that the effect of ketosis on the kidneys may

be more important in causing hyperuricemia. In any case, Padova (38) feels that it is important to watch for the development of renal complications due to uric acid lithiasis in patients with diabetic-ketoacidosis.

Although this latter study demonstrates increased serum uric acids in diabetic-ketoacidosis, it does not rule out lower serum uric acid levels in controlled diabetic patients. One will notice that the mean value for uric acid in these patients was lower than the control mean once the keto-acidotic state was resolved. In addition, most of the studies showing either an increased incidence of diabetes in patients with gout and hyperuricemia, or a lower mean serum uric acid in patients with diabetes are dealing with the mild diabetic of late onset who can be controlled by diet or oral hypoglycemic agents. These patients again are not likely to develop keto-acidotic states.

IX. Hyperuricemia in Starvation and High Fat Diets

Elevated serum uric acid levels during fasting were first observed by Cathcart in 1907 (41). The 1920's were also a period of intense interest in the observation that serum uric acid increased and urinary urate excretion decreased during starvation (42). It was also noted during this time that feeding excessive amounts of fat or fatty diets in such a way that acetone was produced from fat metabolism, that similar changes took place in the serum and urinary urate.

More recently, observers showed a correlation between the infusion of a B-hydroxybutyric acid in humans and a simultaneous decrease in urinary urate excretion and an increase in serum uric acid (41).

Studies of patients on starvation diets have shown that there is a marked increase in serum uric acid which can be controlled with probenecid in most cases. If this serum uric acid increase is not controlled, a significant number of cases will develop gout while urinary insufficiency due to urate lithiasis was reported in one case. This hyperuricemia appears to correlate well with the degree of ketonemia present. In all cases, when high carbohydrate or protein diet are started, the serum uric acid promptly returns to previous levels.

Several theories to explain the above phenomena have been offered (41):

1) ketosis may compete with uric acid for excretion by the tubular cells.

2) a deranged enzymatic transport mechanism in the renal tubules causing a decrease in urate excretion.

3) a lower filtered glucose load, thus, less competition for reabsorption of uric acid and retention of urate.

In any event, the etiology of the hyperuricemia in these cases, as well as

those patients with diabetic-ketoacidosis, would appear to be the result of some unknown effect on the renal excretion of urate by plasma ketones in creased amounts. It might be well to add that patients who are placed on starvation or semi-starvation reducing diets should be given approximately 1 gm. of probenecid daily to control the resultant hyperuricemia.

X. Hyperuricemia in Myleoproliferative Disease

a) Hyperuricemia in Leukemia

Hyperuricemia is common in the myeloproliferative diseases and has been found consistantly in chronic granulocytic leukemia, but not in chronic lymphocytic (43). In patients with chronic granulocytic leukemia, hyperuricemia does not appear to be a complicating factor as long as the disease is under good control, and tends to be at its worse during the treatment of an exacerbation of the disease. Thus, this does not appear to represent an inherent biochemical defect, but an abnormality related to the activity of the hematopoietic disease.

Studies of the incorporation of Formate-$C_{14}$ into uric acid in patients with chronic granulocytic and lymphocytic leukemias reveal a diphasic curve for the former and a single phase curve in the latter. This was interpreted to mean that in chronic granulocytic, the leukocyte "turnover" contributes to the uric acid production producing the second peak of the curve, while in chronic lymphocytic, the leukocyte "turnover" does not contribute significantly to uric acid production.

Furthermore, studies with adenine-$C_{14}$ show that adenine seems to be incorporated promptly into the nucleic acids of both granulocytes and lymphocytes, but is evidently retained for a much longer time in the lymphocytes. This means that the abnormal lymphocytes either survive much longer, or that their nucleic acids are only partially degraded and then reused for nucleotide synthesis. This also helps explain why antimetabolities (6-MP and methotrexate) give much better results in chronic granulocytic leukemia. These are known purine inhibitors, and since the granulocytes seem to depend more upon "de novo" purine synthesis than do lymphocytes,

purine inhibitors have a much more satisfactory effect in the chronic granulocytic type of leukemia.

The incidence of secondary gout in chronic granulocytic leukemia is reported to be about 6% (43). It is believed that this figure would be higher if the survival time were as long in this disease as it is in other myleoproliferative diseases, such as polycythemia vera.

More important than gouty complications are the complications resulting from renal urate nephropathy, especially in patients with leukemia or lymphoma under radiotherapy or cytolytic chemicals. Probably 23% of leukemias will hav- severe hyperuricemia at some time during their course. In quite a few of these patients renal complications due to urate nephropathy are like threatening or directly related to the death of the patient. Therefore, in handling patients under cytolytic therapy, Krakoff (43) gives maximum fluids, $NaHCO_3$ to alkalinize the urine, and if severe life threatening hyperuricemia develops, extracorporeal hemodialysis can be used. However, since the xanthine oxidase inhibitor, allopurinol, is now available management of these cases should be much easier.

b) Hyperuricemia in Myleoloid Metaplasia

Hooey (44) and his associates report a case of myelofibrosis with myeloid metaplasia of the spleen who developed a marked hyperuricemia resulting in some impairment of renal function and later an attack of gout. They offered the explanation that such patients have a folic acid deficiency, which in necessarry for the manufacture of nucleic acids in the body and since the purines are not being used, they are being converted to uric acid. This case was controlled well, however, with allopurinol.

C) Hyperuricemia in Infectious Mononucleosis

Infectious mononucleosis is a disease markedly like leukemia in many ways such as: lymphademopathy, spleenomegaly, and abnormal leukocytes (45). There is also evidence that DNA and RNA synthesis increases in both of these situations in addition to myxovirus-like particles which resemble two types of animal leukemia viruses which have been isolated from bone marrow cultures in children with acute leukemia or infectious mononucleosis. Cowdrey undertook a study of uric acid levels in infectious monucleous to ascertain if the end product of increased DNA and RNA metabolism is elevated in infectious mononucleosis.

Thus, he took twenty-one patients with acute infectious mononucleosis and twenty-four controls which were all suffering from an acute viral febrile illness of one type or another. The mean serum uric acid levels of the controls were comparable with those of other reports in normal persons. He found that the mean serum uric acid level in the male patients with infectious mononucleosis was 8.2 mg.% while it was 6.0 mg.% in the female, both of these figures being a significant elevation over the controls. In addition, he found that the levels seemed to be highest during the first two weeks of the disease during which time the lymphocytosis is greater. Also, the elevations preceeded laboratory evidence of hepatic disfunction and often had reverted to normal prior to the height of liver function abnormalities. These findings tend to discount any effect on serum uric acid by a febrile illness, it also cast doubt on low dosage salicylate ingestion and self imposed dietary restriction as factors contributory to hyperuricemia. Previous reports of renal function from other studied of patients with infectious mononucleosis tend to discount impaired renal function also as a cause of hyperuricemia. The hyperuricemia tended to

parallel the length of abnormal lymphocytosis. Bertino has demonstrated increased levels of three enzyme systems involved in the folic acid metabolism in leukocytes in patients with infectious mononucleosis. Elevations in these enzymes have also previously been recorded to occur in leukocytes of patients with chronic and acute leukemia and are indicative of active DNA synthesis.

A proposed basis for the transit elevations of serum uric acid in infectious mononucleosis is that the increased in purine biosynthesis necessary to accommodate the stopped-up nucleic acid production would necessarily increase the uric acid production.

Although hyperuricemia is quite common in all of the myleoproliferative diseases, it is very rare that gout is the presenting symptom of one of these diseases. There is no reason to suspect that the onset of gout in a patient indicates later development of a myleoproliferative disorder. It is not uncommon to find a mild polycythemia in patients with primary gout, probably because many hyperuricemic individuals are somewhat obese.

It is apparent that when dealing with any of the myleoproliferative diseases (acute leukemias, lymphomas, chronic granulocytic leukemia, myeloid metaplasia, polycythemia vera, and other), especially during the treatment phase, that one must be aware of the complications which may occur due to hyperuricemia. Probably the most important of these complications is the development of urate nephropathy, which could be the cause of your patient's demise even though the treatment was bringing about a good remission. Forcing fluids, alkalinizing the urine, and now the use of allopurinol, can fairly successfully prevent these complications.

XI. Hyperuricemia in Eclampsia

It is generally accepted that one of the most outstanding biochemical changes observed in eclampsia and preeclampsia is an elevated serum uric acid (46). Attempts at demonstrating excessive endogenous production of uric acid in this case, have not been uniformly successful. Therefore, the most apparent etiology appears to rest again with the kidney. Chesley and Williams (46) have studied the urate and insulin clearances in normal and toxemic patients. Normal patients apparently do not show any changes in these values between their antipartum and postpartum states. However, this study, and later studies (47), show that in toxemia, there is a decrease in the inulin clearance and especially in the urate clearance. This means that the urate/inulin clearance ratio is reduced, meaning that the percentage of urate reabsorbed by the kidney is more in toxemia than in normal states. Thus, the hyperuricemia observed in eclampsia and preeclampsia could very well be the result of augmented reabsorption of renal urate plus a somewhat decreased glomerular filtration rate. It is interesting that the clearance of the uric acid in patients with toxemia returns to normal following delivery and has brought about speculation that there may be some dietary substance which is physiologically uricosuric that may not be available to the renal tubules of patients with toxemia of pregnancy (47).

In contrast to those patients with hyperuricemia, secondary to toxemia, Breckinridge (28) had two hypertensive-hyperuricemic patients who became pregnant. Both of these patients developed preeclampsia, and in one, the feus died at 28 weeks gestation. He also had three hypertensive pregnant patients with normal serum uric acids, and all three underwent pregnancy successfully and uneventfully.

Although hyperuricemia is to be expected as part of the course of toxemia of pregnancy, there is evidence that patients who have a tendency to be hypertensive-hyperuricemic before pregnancy are more prone to develop toxemia. No explanation was offered for the latter observation, however, one could speculate that pre-exisiting hyperuricemia could potentiate the renal abnormalities which occur in conjunction with toxemia.

XII. Uric acid and Cerebral Function

Nyhan, Lesch, Hoefnagel, Sass and others, have reported and studied several cases of childhood gout and/or hyperuricemia associated with a CNS disorder. These investigators feel that this represents a specific clinical syndrom, since all of the documented cases presented certain common manifestations. These are: 1) Hyperuricemia first perceived as an orange hematuria, to be followed by uric acid crystalluric, 2) SUA's in the range of 9-11 mg.%, 3) Severe mental retardation, 4) Severe cerebral palsy, 5) Extreme choreo-athetosis, 6) A striking tendency for the self-destruction through biting of the hands and lips (48,49).

Nyhan studied two brothers with this syndrome and found that they had a markedly high urinary excretion of uric acid, a very large miscible uric acid pool, and glycine-$C_{14}$ incorporation into uric acid in an amount of about 200 times what would be expected in the normal control child. Also, since the patients were brothers, a familial incidence is suggested (48,50). Although to say that this syndrome is inherited as a sex linked recessive trait would be premature at this time, Hoefnagel (51) studied one family which certainly suggests this mode of transmission.

The neurologic syndrome conforms with a syndrome called "double athetosis", which has formerly been ascribed to neonatal asphyxia, birth injury, or hyperbilirubinemia. However, it appears likely that an inborn error of metabolism leading to hyperuricemia can also cause "double athetosis" (51). Although CNS involvement in juvenile gout is quite rare, Sasspoints out that nervious system complications in adult gout are also quite rare, However, paraplegia, pheripheal neuritis or rediculitis, and mononeuritis due to local effect of tophaceous deposites have been reported in

adult gout. The concept of "gouty headaches" has never been documented (52). The close association between hyperuricemia and this syndrome would certainly lead one to postulate a toxic effect of uric acid on the CNS. Although this may seem reasonable, definite proof has not been shown. One of the most direct ways to demonstrate the pathogenesis of this syndrome would be pathologic study of specimens taken from a patient with this disorder. Such a study is reported by Sass (52). First of all, one must point out that these patients are also uremic with kidney findings compatible with gouty arthritis. Therefore, the microscopic changes in the brain of this patient could all be interpreted as changes known to occur in uremia. For instance, one of the lesions in this case was demylinization and demylinization does occur in uremia. However, it has been shown that demylinization does not occur in all cases of uremia and in those cases in which it has been demonstrated the SUA levels were not given. Furthermore, the central accumulation of granules staining for urates in the areas of demylinization in this case have not been previously described for uremia. This seems to suggest a role played by uric acid in the production of lesions which were previously ascribed to uremia. In contrast, another obvious mechanism is simply renal impairment due to hyperuricemia which in turn, produces the cerebral changes through the effects of uremia.

The clinical manifestations, the presence of hyperuricemia or gout, the demonstration of a large uric acid turnover, the possible familial tendency and finally, pathological changes which cannot be entirely ascribed to uremia point to a reasonable conclusion that this is a specific syndrome due to some error in urate metabolism, and resultant toxic effects on the

CNS. In addition, it is thought that early diagnosis through SUA determinations plus the use of uricosuric agents offers hope of some control over this syndrome (49).

## XIII. Conclusion

This thesis was written with the idea of investigating the part which serum uric acid changes play in various diseases, the most important being associations between hyperuricemia, coronary artery disease, and diabetes, disorders which seem to have a tendency to occur together.

From the material presented, it would appear that asymptomatic hyperuricemia does not correlate particularly well with either coronary artery disease or diabetes. However, gouty patients tend to have an increased incidence of abnormal glucose tolerance tests and an increased incidence of coronary artery disease. Of course, there are many factors common to these conditions, such as: age, obesity, diet, and heredity, but the one chemical abnormality shown to correlate best with these three conditions is that of abnormal serum triglycerides. Berkowitz showed that patients with hypertriglyceridemia have a significantly higher mean serum uric acid level. Likewise, the serum triglycerides are fairly consistantly elevated in patients with coronary artery disease and diabetes, and their relatives.

The reason that patients with gout seem to have more coronary artery disease and diabetes is not clear, but we have evidence that high fat feedings seem to elevate the uric acid levels.

In addition, Breackenridge has shown that in patients with vascular disease, concomittant with hyperuricemia, there is an increased morbidity due to complications like cerebral and myocardial infarctions. Thus, it appears reasonable to conclude that although the exact mechanism of the effect of hyperuricemia on ischemic heart disease, atherosclerosis, diabetes mellitus, hypertension, and other conditions

is not clear, it represents a type of background abnormality which the patient would be better off without. However, one must also consider that the presence of asymptomatic hyperuricemia in coronary artery disease and diabetes may actually, in many cases, represent a secondary elevation of serum uric acid as a result of abnormal elevations of serum triglycerides.

On the other hand, gout appears to be somewhat unique in predisposition to coronary artery diease and diabetes. Again, there is no good study of how significant this observation would be if factors such as age, alcohol, diet, and body build were removed from the picture.

We have seen a specific brain syndrome which appears to occur in children and is associated with hyperuricemia. Likewise, a syndrome in four leukemic children has been reported which consists of anorexia, nausea and vomitting, profound weakness, and markedly increased serum uric acids (53). Also somnolente and convulsions occurred in two or three of the patients. Formerly, when this syndrome occurred in patients with leukemia, it was attributed to uremia, but in these cases the symptoms did not correlate with renal insufficiency and none of the patients were in metabolic acidosis or had significantly elevated BUN's. Furthermore, infusions of uric acid into patients have produced similar symptoms at serum uric acid levels less than 20 mgm.%. Two of the above patients who became comatose also had marked elevations of cerebral spinal fluid uric acid. These two syndromes give us evidence that uric acid may be toxic to the body cells and it has even been suggested that the mental symptoms seen in uremia may actually be the result of increased serum uric acid levels.

The list of conditions with which hyperuricemia has been well

established include: myleoproliferative diseases, toxemia, renal failure, drug therapy, psoriasis, myxedema, starvation, rheumatoid arthritis, and prolonged exercise. Therefore, if we exclude the questionable role of uric acid in vascular disease and diabetes, we still have a rather long list of conditions which can precipitate secondary hyperuricemia with resultant gouty diathesis and serious renal damage. One should be aware of these complications with the above conditions since with proper care they can be prevented. Now that the xanthine oxidase inhibitor, allopurinol, is available, it would be rather careless to allow a patient with leukemia to go into renal failure due to uric acid nephrophathy during therapy.

Finally, it is shown in a recent work by Gutman that the primary defect in essential hyperuricemia and gout is probably a metabolic one. More, specifically, it may be a defect in the renal production of ammonia allowing an excess of glutamine to be available to work at the committed step in purine synthesis. This effect could very well be genetic in origin, but as we have seen, the familial nature of this disease may very much depend on environmental influences. Thus, given a person with this defect who is exposed to the right kind of diet with resultant tendency for endomorphy and relative polycythemia, we have a person who will develop hyperuricemia with possible gout and renal failure, who may also be predisposed to the development of coronary artery disease and diabetes.

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