CURRENT CONCEPTS OF THE ETIOLOGY OF UROLITHIASIS IN MAN AND ANIMALS

by

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INTRODUCTION

The term urolith refers to the stone formed abnormally in the urinary tract. Uroliths are also called urinary calculi, urinary stones, urinary concretions or urinary concrements. The anatomical location of the formed calculi is usually considered which thus give rise to terms such as renal calculi, cystic calculi, and urethral calculi. Cystic calculi, also known as vesical calculi, may be gravel-like as in cats, or larger stones as seen primarily in other animals. The small vesical calculi may pass through the urethra without apparent discomfort to the animal. Larger calculi are a particular problem in the male due to the anatomical position and structure of the urethra.

Urinary calculi may be due to dietary, climatic or other environmental factors. Silica calculi in cattle are common in the Western ranges of Canada as reported by Whiting et al. (1958). The occurrence of urinary calculi in the winter among cattle is commonly observed in this country. In India and China, as reported by Hawk et al. (1949), the percentage of urinary calculi was very high among children. Poor diet in children was thought to be a major factor. This was true to a certain extent in Europe and the United States until the middle of the 19th century. With improved diet this problem has almost vanished in this country.

In general, calculi may be classified as simple or compound. Simple calculi are composed of a single constituent, whereas compound calculi are composed of two or more constituents. Alexander (1928)

classified the stones as crystalloid and crystalloid-colloid types. Crystalloid stones are simple concretions such as uric acid stones. Crystalloid-colloid stones are formed by the crystalloids with a colloidal matrix. Stillman, as cited by Hawk (1949), reported the constituents of the crystalloid portion of the calculi. He analyzed 510 urinary stones from the human subject. Calcium carbonate, calcium phosphate or triple-phosphate stones constituted about 44% of the total; 49% were largely calcium oxalate with some admixture with phosphates and carbonates. Six percent were the uric acid calculi. Cystine calculi accounted for only 0.8 percent.

Cornelius and Bishop (1961) found a close relationship between the matrix portion and the crystalloid portion of the calculi from both man and dogs. Boyce and Sulkin (1956) analysed the matrix (colloidal) portion of 676 stones. They found that the organic matrix was evenly distributed throughout the stone, from the center to the surface and formed 2.5% of the total weight. Microscopically, the matrix appeared to be an amorphous and fibrillar substance. Histochemically the matrix was shown to be composed of mucoproteins and mucopolysaccharids. The protein and peptides of the matrix were composed of seven amino acids. Heijkerskjoeld and Mollerbury (1954) found ten amino acids in different combinations. King and Boyce (1954) showed seventeen amino acids, while Swingle (1959) showed the presence of sixteen amino acids in the matrix portion of the calculi. The major components of the carbohydrate (mucopolysaccharid) as shown by Boyce and Sulkin (1956), were formed by galactose, hexosamine and other sugars, which were not identified. Keeler and Swingle (1959) reported the presence of hexose, pentose and methyl pentose.

The size and shape of the urinary stones depend upon the composition of the stones and on the species in which they are formed. In cats stones are gravel-like. In other animals there may be a single large stone or multiple stones. In the equine species, as stated by Frank (1959), the stone is usually single and is in the bladder. The largest stone he reported was 25.4 cm. long and had a circumference of 58.42 cm. It weighed fifteen pounds.

Hawk et al. (1949) summarized the varieties of calculi as follows:

Uric acid and urate calculi furnish the nuclei of a large proportion of the urinary calculi. Yet the total stones which are composed primarily of uric acid and urates are relatively uncommon in man. Among the canine they appear most commonly in the Dalmation dogs. Such stones are always colored, the color varying from a pale yellow to a brownish red. The surface of such calculi is generally smooth but may be uneven and rough.

Phosphate calculi consist principally of triple-phosphate and other phosphates of the alkaline earths with an occasional admixture of urate or oxalate. The surfaces of such calculi are generally rough but may be occasionally smooth. The color is variable being either gray, white or yellow. Earthy phosphates calculi are characterized by their friability.

The calcium oxalate calculi are hard and rather difficult to crush. These calculi occur in two forms. The small smooth concretions are called hemp seed stones. The medium size or the large stones possess extremely uneven surfaces and are known as mulberry calculi. The roughened surfaces of the latter type of calculi are due to the protruding calcium oxalate crystals of the octahedral type.

Calcium carbonate calculi are fairly common in herbivorous animals and are very rare in man. These are small in size. The color may vary from gray to white. They may be smooth and spherical and are generally hard in consistency.

Silica calculi are commonly found in ruminants. These are small with rough irregular surfaces and usually gray in color. They are hard and brittle. The pure forms are uncommon as there is usually an admixture of calcium and magnesium in form of phosphates or carbonates (Gershoff and Andrus, 1961).

Xanthine calculi are rarely found. Of 510 urinary calculi analysed by Stillman, as cited by Hawk et al. (1949), xanthine calculi constituted only 0.8 percent.

Cholesterol calculi are extremely rare in occurrence. Hawk et al. (1949) listed cholesterol calculi in the classification of calculi but the other details seem to be rarely mentioned in the literature. Cholesterol is not a normal constituent of urine (White et al., 1959) but may appear in it in nephritis.

Cystine calculi are smooth, spherical and are more common in male dogs than other animals. A definite hereditary incidence of cystinuria and cystine calculi in man and dog has been reported by Pollock (1955).

MECHANISM OF FORMATION OF CALCULI

Considerable work has been done to study the exact mechanism of calculus formation. Shigematsu (1954), Tanaka (1958), and Engfeldt et al. (1962) as reported by Boyce and King (1963), incriminated the blockage of the mitochondrial system of the renal cells for the initial renal lesion.

In the absence of mitochondrial enzymes as succinic dehydrogenase and phosphatase, the cellular metabolism apparently alters and results in the intracellular accumulation of finely granular masses of mucoprotein. Eventually the cell ruptures and the mucoprotein accumulates in the tubular lumen. Here the material is believed to undergo reorganization to form fibrils which join together to form matrix spherules. The mucoprotein thus formed is apparently peculiar to the matrix of the calculus and has been designated "matrix substance A". This substance has been demonstrated in all calcigerous calculi. Boyce and King further reported that calcium accretion converted the spherule into spheroliths. The spheroliths develop microliths when they are retained in the urinary passage at a time when conditions favor the crystallization of urinary salts.

Future rate of growth and composition of the concretions forming about the microliths were shown to depend upon the changes within the urine. Adventitious absorption of insoluble or relatively insoluble substances seem to favor the rapid growth of calculi. Large calculi are shown to contain all possible combinations of matrix substance A, plasma proteins, epithelial cells, leucocytes, bacteria and admixture of various crystals. In the absence of any injury to the renal tissue or urinary system the calculus might retain the compositional characteristics of a large microlith, being formed of matrix substance A and calcium phosphate (apatite).

Boyce and Sulkin (1956) reported that the matrix concretions resulted from the retention of matrix spherules within the renal pelvis with little or no crystallization. Such spherules were occasionally large enough to fill the renal pelvis and calyces. They occurred commonly

in patients with advanced chronic payelonephritis having a twenty-four urinary calcium content of 30 to 50 mg. Analysis of these concretions revealed a high content of matrix substance A along with serum proteins and uromucoid.

Boyce and King (1963) postulated that the process of initiation of calculus formation might be essentially the same in all types of urinary calculi. The process of calculus growth might additionally involve the multiple factors common to urinary encrustation. Boyce and King concluded that the interrelation of several factors were highly speculative and the conclusions drawn were only as a working hypothesis for future investigations.

NUTRITIONAL FACTORS

Vitamins

Vitamins have an important role in all life processes. A deficiency of an individual vitamin may cause a disturbance in the physiological functions of a system where it has its specific action. Osborne and Mandel (1917) apparently were the first to show the effects of vitamin A deficiency in rats in relation to urinary calculi. They demonstrated phosphate stones in bladders of deficient rats. Hagan (1928) reported that vitamin A deficiency was a predisposing factor in man. This was associated with the infection of tonsils by Proteus ammoniae organism. The composition of the calculi was phosphate and carbonate of calcium and magnesium. Van Leersum (1928) supported these findings. In his experiments on rats, vitamin A deficiency produced phosphate calculi. Higgins in 1935 studied this problem more extensively. Rats were maintained on a vitamin A deficient diet. He found three constant factors.

These were keratinization of the urinary tract, urinary infection and alkalinuria. Keratinization occurred 8 to 10 days after the experimental diet was started. Infection of the bladder occurred within 30 days and infection of the kidney occurred in 60 days. The organisms isolated were streptococcus, staphylococcus or a mixture of organisms. Alkalinuria was a constant finding. The addition of ammonium chloride or vitamin A to the diet decreased the incidence. He also showed that addition of vitamin A to the diet or an acid-ash diet given to the patients aided in dissolving the calculi within 50 to 60 days. Higgins postulated that the keratinization of the epithelium of the urinary tract caused an irritation and that the irritation produced mucin-fibrin which formed a network in which the crystals were deposited. In his opinion desquamation and sedimentation were important factors. Basset et al. (1946) placed seventy-four pups and their dames on a vitamin A deficient ration and divided them into six groups. Each group was fed a different level of vitamin A, ranging from zero international units to 100 i.u. per kilogram of body weight. The incidence of calculosis seemed to be associated with the amount of vitamin A feed. No calculi were found in the group fed with 100 i.u. of vitamin A. The incidence was highest in the group getting the least amount of vitamin A. The dogs in this group, when necropsied, exhibited enteritis, pyelitis, general infection of urinary tract and urinary stones. Higgins (1951) studied the composition of stones formed in rats by vitamin A deficient ration. Rats were maintained on a vitamin A deficient diet for 30 to 250 days. In the first 30 days, the incidence was negligible. However, in 30 to 60 days, 14% of the rats developed stones in the bladder and in 150 to 180 days, 88%

of them died from vitamin A deficiency. The chemical composition of the stones was mainly phosphates with a trace of carbonates. When the phosphates were kept deficient, carbonates formed the bulk of calculi and phosphates were in traces. Fourteen percent of the rats developed renal stones in 60 to 90 days and 41% in 180 to 250 days. The chemical composition was the same for both, the renal and bladder stones. According to Higgins (1951) the reason for the preponderance of phosphate calculi was that the phosphates were precipitated in the alkaline urine. In rats calculi were formed in 9 to 10 months. He also demonstrated that dalmation dogs kept on vitamin A deficient ration which was high in purine developed uric acid calculi. In the cystinuric dogs kept on vitamin A deficient diet, he was able to demonstrate the formation of cystine stones. He was also able to produce oxalate stones by vitamin A deficient diets with high oxamide. Higgins concluded that vitamin A deficiency was a major factor in the formation of phosphate, carbonate, uric acid and oxalate calculi.

It seems from the literature that vitamin A deficiency is not an important factor in urinary calculi of cattle. Schmidt (1941) studied the effects of vitamin A deficiency in steers, cows and goats. In cattle he could demonstrate all the characteristic symptoms of vitamin A deficiency but none of urinary calculi. In castrated male yearling goats, eight developed urinary calculi and sixteen developed urethral occlusion, with seven dying from rupture of the bladders. In most of the fifty-two cases the occlusion was due to a mucous plug. The Schmidt report seems to be a solitary example in the literature of urinary calculi due to avitaminosis in ruminants. Beeson (1943) maintained

several sheep on vitamin A deficient ration for 150 to 160 days but failed to demonstrate a single case of urinary calculi. While studying effects of vitamin A deficiency in a ration with high $CaCO_3$, $MgCO_3$ and K_2HOP_4, Lindley et al. (1953) concluded vitamin A deficiency was not involved in urinary calculi in sheep. When vitamin A was added to the diet, the phosphorus excretion was decreased, that of calcium was increased, and there was no effect on magnesium. Swingle and Marsh (1956) analysed several blood samples of affected calves for vitamin A levels in plasma. In 46 calves with clinical urolithiasis the mean value of vitamin A was 15.3 m. mg per 100 ml. of plasma. The blood of 112 non-affected calves from herds where urolithiasis was common, had an average of 18.6 mg. of vitamin A per 100 ml. of plasma. The critical vitamin A plasma level was considered to be 16 mg. per 100 ml. of plasma. They concluded that vitamin A deficiency was not an important factor in the formation of calculi in calves. They also showed that the incidence was common in herds getting adequate amounts of vitamin A.

In recent literature other vitamins have been incriminated as causative agents of urinary calculi. Gershoff and Andrus (1961) reported primary renal deposits of oxalates occurring in rats maintained on diets deficient in vitamin B_6. This was accompanied by increased excretion of oxalic acid and xanthuric acid and a decreased excretion of citric acid. The addition of magnesium to this vitamin B_6 deficient diet prevented the deposition of oxalic acid although the rate of excretion of oxalic acid remained the same. Magnesium at the rate of 100 mg/100 gm of diet was believed to increase the solvent characteristics of urine for oxalates by increasing citric acid excretions. Acidification of the urine enhanced

the deposition of oxalates by decreasing the citric acid excretion in vitamin B_6 deficient diet.

Udupa and Bharadwai (1961) suggested the administration of vitamin C as a prevention of urinary calculi in man. The biochemical reaction of calcium and phosphorus were shown to be related to vitamin C. These reactions were restored to normal in the patients of urinary calculi.

Vitamin D may be a contributing factor to urinary calculi. Flock (1939) showed that the urinary calculi patients had a high calcinuria. Moderate doses of vitamin D increased considerably the calcium excretions in these patients. Similar results were quoted by Earle (1956). The calcium levels were increased on administration of vitamin D. Harrison (1955) demonstrated that the citric acid excretion was increased by administration of vitamin D. The increase in citric acid excretion is believed to prevent the calcium stone formation. The actual role of vitamin D in urolithiasis is not known.

Minerals and Salts

The nature and the amount of minerals may influence the occurrence of calculosis. Salts of acid phosphate seem to provoke the calculus formation while sodium-chloride is shown to prevent calculosis in cattle. Potassium acid phosphate may act directly on the excretion of calcium and magnesium, leading to the formation of calculi of phosphates of carbonates of calcium and magnesium. Salts of silica alter the crystalloid:colloid balance resulting in precipitation of colloids and crystalloids.

Puntirano (1955) studied the role of colloids in urinary calculi in sheep. He reported that salts of magnesium and silica had an important role in crystalloid:colloid balance and that an increased intake of

silicious material acted in two ways. Due to silicious material the crystalloid contents of urine increased. On the other hand silicic acid, a metabolic product of silica salt, increased percentage of non-protective or hydrophobic colloids. Swingle and Marsh (1956) supported these findings. They postulated that high concentration of electrolytes in urine suppressed the stabilization of silicic acid. Earle and Lindell (1951) studied this problem in the fattening lambs. Lambs ingesting larger amounts of silicates showed a marked increase in the plasma levels of magnesium, inorganic phosphorus and silica. Of the three groups, each containing 6 lambs, the group getting sodium silicate 1% of the basal diet developed calculi of magnesium phosphate. Lambs from other groups getting either 15,000 i.u. vitamin D or 15,000 i.u. vitamin D plus 1% sodium silicate developed only deposits in kidney. Silica intake was shown to influence the excretion of phosphates and magnesium by Settle and Saver (1960). They fed each guinea pig a single dose of 2 cc. of a solution containing 253.8 mg. of double silica oxide. In another group they injected 15 cc. of a material intra-peritonially in which each cc. contained 20 mg. of silica oxide. They demonstrated silicious deposits in the kidney after 48 hours. In their opinion, this proved that the soluble salt of silica when fed resulted into formation of an insoluble deposit in the kidney.

Keeler and Lovelace (1961) fed silicon in forms of Na_2, SiO_3, $9H_2O$, and SiO_2 to steers. Zinc implants were introduced in the bladder prior to the feeding of these minerals. Although the excretion of silicon in urine was considerably increased, they failed to demonstrate any appreciable deposit of silicon on the zinc implants in the bladder within 25 to 60 days. In their experiments histopathological examination for

deposits occurring in the kidney was not performed. Baker (1961) discussed silica calculi in sheep. He suggested that sheep consumed considerable quantities of silicious material. In the rumen of sheep, organic matter was broken down to nucleuic and perchloric acids. The insoluble residue was shown to be mostly opal phytoliths, known as allonthigenes. He postulated a relation between the phytoliths and opal zooliths and suggested that the soluble silicates, in their process of excretion, might precipitate as opal-zooliths. Some of the blood cells as lympocytes, phagocytes and R.B.C. were shown to be mineralized by amorphous silica. This gave rise to the microzooliths. Microzooliths were believed to be similar to phytoliths in nature and formed nuclei for the uroliths.

Magnesium is believed to play an important role in calcium and phosphorus metabolism. Gershoff and Andrus (1961) demonstrated that the high magnesium salt intake prevented the formation of oxalic acid calculi, although rats remained hyper-oxaluric. They also showed that the renal deposition of apatite ($3Ca_3\ (PO_4)_2CaX_2$) correlated inversely with the dietary levels of magnesium and directly with the levels of calcium. Magnesium was thought to be responsible for increasing the urinary silica solubility.

The greatest incidence of urinary calculi in cattle occurrs in the winter season. Less intake of water has been incriminated by some workers (Newsom, 1938; Swingle and Marsh, 1956). As the urine becomes more concentrated due to the less intake of water there may be an increased precipitation of the crystalloids. Udall and Roberts (1954) studied the effects of salt, feeds and sex on urinary calculi in a group of 100 lambs. They divided the lambs and studied the effects of several combinations of

corn vs. milo, males vs. females, and salt vs. no salt. The incidence of calculosis was highest in the group getting milo and no salt and was the least in the group getting milo with salt. They concluded that the salt in the ration increased the intake of water and resulted in diuresis and thus prevented calculosis. Scheel and Paton (1960) studied this problem on the range cattle confined to the feed lot conditions. They formed several groups of cattle, maintained on different levels of salts. The group receiving 0.5% of sodium chloride had the highest incidence of calculosis, whereas in the group receiving 10% sodium chloride (force feeding) there was not a single case observed. They concluded that 5% sodium chloride in the feeds of the cattle on feed lot could prevent the calculosis. The exact action of the sodium chloride, in their opinion, was unknown. They supported the theory of diuresis, by Udall and Roberts (1957), which suggested that the sodium chloride aided in flushing out the urinary tract, or in other words, keeping urinary total solids low. According to Lindley et al. (1953) diuresis was not an important factor. Their study was on consumption of water by rams. They reported that the rams with urine having the lowest total solids had the greatest incidence of urinary calculi. These rams were consuming larger amounts of water and also were passing greater amounts of urine than the non-affected group. Swingle and Marsh (1953) reported similar findings. They reduced the water consumption of steers to one-half the normal amount of water for the first week and then to one-third the normal amount for the rest of the experiment. The specific gravity of the urine increased from 1.046 to 1.055. The pH range was from 8.0 to 9.0 during the experiment. The urine was examined for any solids passed, but they were unable to demonstrate evidence of urinary calculi. According to them water

consumption was not an important factor in the etiology of urinary calculi. Although more cases are observed in winter the etiology still remains obscure and the role of sodium chloride in preventing the urinary calculi is not definitely established. Udall and Chen Chow (1963) showed that it was the chloride ion and not sodium ion that prevented calculi formation. They postulated that the mechanism was ion competition for cationic binding sites on the matrix material.

The intake of phosphates and carbonates may predispose calculus formation. Lindley et al. (1953) studied the effects of $CaCO_3$, $MgCO_3$ and $K_2H\ PO_4$ on blood and urine of rams. He observed that K_2HPO_4 apparently caused the calculosis in rams. The types of calculi he found were $Ca_3(PO_4)_2$, $Mg_3(PO_4)_2$ and $Mg\ NH_4PO_4$. Elam et al. (1956) maintained eighty cross bred sheep on 16 pelleted roughage concentrate rations for 124 days. The variables in the rations were phosphates, potassium and the beet pulp. They reported that the addition of potassium salts in the ration resulted in seven cases out of twenty sheep. One out of twenty sheep suffered from urinary calculi when only phosphorus was high, whereas twenty-eight out of forty animals developed calculi when potassium acid phosphate was added to ration. When phosphorus and potassium salts were added, nineteen of twenty sheep developed calculi. Urinary excretion of calcium was increased when phosphates were added, whereas magnesium excretion was increased when the carbonate of potassium was added. Similar results were observed by Elam et al. (1957) in sheep. They demonstrated eleven cases of calculosis out of fourteen sheep when potassium acid phosphate was added to ration. They suggested that the phosphates were responsible for the mobilization of calcium. Again Elam et al. (1959) studied this problem

in steers. Plasma levels of phosphorus and sodium were high in steers getting potassium acid phosphate. Increased phosphorus and potassium and decreased magnesium and chloride were observed in the urine.

Molebdenum deficiency is incriminated for xanthine stones. As stated by Bell et al. (1959) molebdenum forms an important constituent of the enzyme, xanthine oxidase, which converts xanthine to uric acid. In absence of molebdenum, xanthine is passed in urine as such. Free xanthine in urine is thought to predispose xanthine calculi.

Thus the salts of certain elements may predispose the calculi, however, this is probably not the chief factor. Excretion of phosphates or calcium does not necessarily cause calculi. In hyperparathyroidism in man and dogs, calcium excretion is very high but the incidence of calculi is not a common feature in these patients (Albright and Joseph, 1934).

Feeds

Feedstuff may play an important role in formation of urinary calculi. Feeds deficient in some important factor such as vitamins or minerals or in excess in some minerals are shown to cause concretions in the kidney. A sudden change from a roughage ration to a concentrate one may be a predisposing factor in urinary calculi. Scott (1924) observed an outbreak of urinary calculi in sheep and attributed a change in feeds from alfalfa hay to shelled corn and linseed meal as the triggering factor. Newsom (1938) reported heavy losses of sheep from urinary calculi when wheatbran was fed. On replacing wheatbran by corn and alfalfa hay, the incidence of calculosis was checked. He also reported a farm near Fort Collins with no incidence of calculi for 14 years, on which a change in feed from

alfalfa to wheat straw, cane, oats and corn resulted in heavy loss due to "water belly" in lambs. Changing the diet to corn and alfalfa apparently corrected the situation.

Udall and Hartman (1951) utilized 100 lambs and studied the effects of corn vs. milo, male vs. female, and salt vs. no salt in the ration. They found that the urinary mucopolysaccharides (nonprotective colloids) increased due to milo feeding.

Scheel and Paton (1960) conducted a study on range cattle. They found that the range cattle confined to a high roughage and a low concentrate ration underwent a sudden change in feed lot conditions. On range they received adequate calcium but in feed lot conditions they received low calcium and high phosphorus. A ration containing Ca:P ratio 0.5:1 was shown to influence urinary calculi more than a ration with 1.25:1 ratio. They further reported that the incidence was high in winter season when corn was replaced by milo. Evelth et al. (1948) blamed lack of proteins in feeds. Prairie hay, wheatbran and distilled water produced four cases out of four experimental animals, whereas only one animal out of twenty-four developed urinary calculi when soybean meal alone was fed. Whiting et al. (1958) observed that the prairie hay from ranges where urinary calculi was a problem produced urinary calculi; whereas the prairie hay from the urinary calculi free ranges failed to produce any case. This was supported by Forman et al. (1958) who fed sheep with Canadian Western range hay which contained 8.28% of silica. The pH of urine of the sheep on Western range hay was 5.5 and those on Eastern range hay was 8.2. The rate of polymerisation of silicic acid, as shown by Holt (1954), was inversely proportional to the square of the silica concentration and was most at 5.5-6 pH. Cornelius (1959) fed

weathers a calculi provoking ration of wheat straw 20%, dried beet pulp 30%, linseed meals 17%, oats 15%, wheat 15%, NaCl 0.5%, and $K_2H\ PO_4$ 2.5%. The ration contained calcium 0.18%, magnesium 0.37%, phosphorus 0.17%, potassium 1.82% and sodium 0.43%. Calculi developed within 15 days, however, no analysis of calculi was made.

Beet pulp has often been blamed to cause calculosis. Puntriano (1955) used 50% beet pulp, 25% rolled barley, 25% wheat straw and alfalfa free choice. Calculi were produced in sheep. The Ca:P ratio was normal in urine. He postulated that magnesium and silicon had some role in colloid:crystalloid balance.

Elam et al. (1956) produced urinary calculi in 26 out of 40 lambs on a ration containing 25% beet pulp. When phosphorus and potassium were added to the same ration in the further study, calculi occurred in 19 of 20 animals. These workers observed that excretion of phosphorus and calcium was increased when beet pulp was fed. Contrary to the above findings, Elam et al. (1957) reported that the beet pulp and the beet pulp ash had no influence on urinary calculi. Wheat straw, as shown by Clare (1959), influenced the plasma proteins and urinary calcium levels. Levels of plasma proteins and urinary calcium increased considerably when wheat straw was fed in high amounts producing calculi.

METABOLIC FACTORS

Biocolloids of Urine

In the past fifteen years considerable attention has been given to the biocolloids of urine with respect to their role in urinary calculi. Successful attempts have been made to produce calculi following disruption

in the colloidal balance. This theory seems to explain satisfactorily at least part of the etiology of urinary calculi. Although a recent theory, the importance of biocolloids in urinary calculi was first suggested by Ebstin in 1884, as cited by Butt and Hanser (1952).

The colloidal system is an intermediary between the microscopic system where the size of a particle is above 500 mμ and the molecular system where in the size of a particle is below 1 mμ. Thus size of the colloids varies from 1 mμ to 500 mμ. Colloids are broadly divided into two types, hydrophobic and hydrophilic colloids. The particles of hydrophobic colloids are held in suspension due to the repulsive charges on them. They have no affinity towards the liquid phase. The addition of electrolytes with the opposite charges neutralize them and thus result in coagulation. The hydropholic colloids are also called non-protective colloids. The hydrophilic or protective colloids have an affinity towards the liquid phase and do not precipitate on addition of electrically charged particles. Following ultramicroscopic studies of the urine of sheep and cattle, Puntriano (1954) reported bright minute discs of colloids and small crystals of crystalloids on a dry film. The colloidal particles appeared to coat the crystalloid particles and thus prevented crystallization.

The colloidal matter is composed of a mixture of many substances. These include nucleic acid, nucleotides, nucleosides, chondroitic sulphuric acid, glycogen, mucin and a complex amino carbohydrate as reported by Joly (1940) and as cited by Puntriano (1954). Several factors influence the blood and the urine levels of the colloids. Butt (1952) reported that a diet rich in protein, especially meat, resulted in an increase in urinary colloids. He further stated that the protective

urinary colloids were more prevalent in woman than in man, and were still more in pregnant women. Environmental stress was also shown to influence the concentration of colloids. Butt (1952) showed that the pathological increase in the non-protective colloids influenced the protective colloids. In a strong emotional stress, he demonstrated that the protective colloids disappeared. Puntriano (1954) cited the importance of surface tension of urine in calculosis. Increased surface tension was shown to decrease the colloidal activity.

Boyce (1955) studied 24 hour samples of urine from eight normal subjects, 14 patients with renal calculi and two patients in which bilateral cuteneous urethrostomosis had been performed. He measured dry weights of the residue insoluble in Molar 1 - NaCl solution, in other words, he measured non-protective colloids. In normal patients it varied from 38 to 56 mg. per 24 hours' urine and was constant. In the patients of calculous disease he found considerable variation from individual to individual and also from time to time in the same individual. While in normal animals the ratio of NaCl soluble mucoproteins to NaCl nonsoluble mucoprotein was found to be 1:1, in calculous disease patients it varied from 1:25 to 1:14. This insoluble portion was also designated as Tomm and Horsefall or T and H mucoprotein. The chemical composition of the mucoprotein from the calculous patients was found to be the same as normal subjects. Puntriano (1955), in his studies on the urine of sheep, suggested that the mineral content of the concentrates were responsible for the colloid-crystalloid balance in the urine and that hyaluronidase aided in the maintainance of a normal crystalloid-colloid balance. The Ca:P ratio in urine remained normal throughout the experiment indicating that the magnesium and silicon had a possible role

in crystalloid-colloid balance. Since magnesium was found infrequently in the urine sediment and since silicon was the main bulk of the calculi, it was concluded that silicon was the chief mineral involved in the colloid crystalloid imbalance. According to Swingle (1953) the uroliths formed due to the precipitation of silica by the mucoprotein in urine. He suspected that at least two factors were involved. One was a particulate nucleus and the other was the alteration of quality and quantity of protective colloids in urine. Puntriano (1955) postulated that the imbalance was due to the excess secretion of silicates increasing the urinary crystalloids. He further suggested that silicates changed into silicic acid (non-protective colloid) resulting in an increase in the proportion of non-protective colloids in the urine. Silicic acid was shown to be important as this non-protective colloid formed a jell which was suspected to serve a nucleus to other concretions. In concentrated urine, as stated by Swingle (1956), the electrostatic stability of silicic acid was suppressed by a high concentration of electrolytes. Silicic acid eventually precipitated out. Author (1961) demonstrated that the rate of excretion of urinary mucoprotein containing silicic acid was increased by 175% in the patients with urinary calculi.

Calcium and Phosphorus in Blood and Urine

The majority of calculi in man and animals contain calcium and phosphorus. In most of these cases calciuria and phosphaturia are common features. Calculosis as a secondary ailment is not uncommon in hyperparathyroidism. Albright et al. (1934) reported that the urinary levels of calcium and phosphorus increased by 23 times normal in the

hyperparathyroid patients with accompanying urinary calculi. In the serum the calcium levels remained high while the phosphorus levels were low. Hodjkenson et al. (1961) reported hypercalciuria in patients with crystalline calcium oxalate stones, however, hypercalciuria was not observed in patients having striated type of calcium oxalate stones. It was postulated that the crystalline stones were formed due to the crystallization of the salts in the saturated urine, whereas the striated stones were formed due to absorption of calcium salts on an organic matrix. Spargo and Sager (1955) studied effects of calcium:phosphorus ratio in the diet of rats. When rats were maintained on normal calcium and low phosphorus diets, concretions occurred in six days. As a result of the phosphorus deficiency calcium absorption increased thereby increasing the unbound calcium in the blood. The unbound calcium combined with citrate and precipitated in urine. What caused precipitation was not clear. Similar findings are reported by Reen et al. (1959). Rats fed on a high calcium and a low phosphorus ration developed citrate stones. They postulated that it was the low phosphorus and not the high calcium which was responsible for calculosis. Reen and his co-workers also studied the effects of dietary proteins on calcium and phosphorus in rats. With high levels of proteins less amounts of calcium and a high amount of phosphorus were excreted. With normal levels of phosphorus in the diet, high levels of calcium reduced absorption of phosphorus from the intestine and resulted in calcium phosphate stones. Keyser (1935) suggested a relationship between calcium, phosphorus and the pH of urine. According to him, various feeds have a considerable influence on the pH of urine. He blamed alkaline urine for the precipitation of calcium salts. He reported that milk aggravated calculosis in man as it furnished a rich

source of calcium and phosphorus and kept the urine alkaline. For calcium oxalate, triple phosphate and calcium carbonate stones in man, he suggested a high protein, low oxalate and low phosphate diet. Intense acidification of urine was also important.

In ruminants calcium and phosphorus have been shown to play an important role in urinary calculi. Lindley et al. (1953) studied effects of calcium, phosphorus and vitamin A in sheep. With a high level of phosphorus in the feeds, the excretion of phosphorus was increased and resulted in stone formation. The phosphorus level in urine was readily controlled by the addition of calcium and magnesium to the basal diet. Vitamin A had a similar effect on phosphorus level. With a high phosphorus level, the composition of the stones formed was $Ca_3(PO_4)_2$, $Mg_3(PO_4)_2$ and $MgNH_4PO_4$. In their opinion the pH of the urine had no role in stone formation. Cornelius et al. (1959) reported similar results in sheep on ration containing a Ca:P ratio 0.18:0.71. The urine excretion of phosphorus was 16.5 to 53.2 mg/100 cc. of urine. Calculi developed in 15 days in these sheep. Utilizing 80 cross bred lambs, Elam et al. (1956) demonstrated that the addition of phosphorus increased the incidence of calculosis. The addition of potassium and phosphorus to a basal diet resulted in 19 cases of calculosis out of 20 experimental animals. Urinary phosphorus and calcium were increased due to the diet containing beet pulp. Again in 1957 Elam and his co-workers demonstrated similar results with K_2HPO_4. They reported eleven cases out of fourteen sheep receiving K_2HPO_4. Reviewing the high incidence of calculosis in feed lot cattle, Scheel and Paton (1960) postulated that a low calcium and a high phosphorus in the ration was responsible for the calculosis. Calcium to phosphorus ratio 0.5:1 was thought to have a greater influence on calculosis than 1.25:1.

Urinary Citrates

Citrate is a normal excretory product of the urine. According to Shorr (1942) 0.2 to 1.2 gm. of citrate is excreted by man in a 24 hour period. The role of citrates in urinary calculi was first suggested by Kissui and Locks in 1941. They observed that the urinary citrate concentration was much lower in urinary calculi patients than that of normal individuals. The excretion of citrates was shown to be affected by many factors as hormones, proteins in diet and calcium and phosphorus levels in diet.

Shorr et al. (1942) studied the problem in man. It was suggested that citric acid was a product of endogenous metabolism or an intermediate product of carbohydrate metabolism. Factors influencing the excretion of citric acid were alkalosis, hormones and the intravenous administration of citrates or citric acids. The precursors of tricarboxilic acid series as succinic, fumaric and mallic acids also influenced the excretion of citrates in urine. In the menstrual cycle of women, they observed, that the level of citric acid was much higher at the middle of the cycle and was lowest at the time of menstruation. Following previous experiments in 1942 they reported that estrogen increased the excretion of citrates and that the testosterone decreased the same.

Shorr et al. (1942) investigated the role of calcium in the excretion of the citrates. The changes in the calcium levels as influenced by the citrate were well known. That the reverse was not true was demonstrated by Shorr in a case of hyperparathyroidism. The levels of citrates increased along with the calcium levels. When citrates were administered intravenously the citrate excretion was increased but the calcium excretion remained unchanged. They also studied two males with recurrent calculosis

and with noninfected urine. During the stone free intervals the patients were kept on a low calcium diet. Both had a fairly large excretion of calcium with a low level of citrate. Spargo and Sager (1955) stated the importance of calcium to phosphorus ratio in calcium citrate calculi. Normal calcium and low phosphorus diets produced urinary calculi within six days in rats. They postulated that the calcium absorption from the intestine was augmented in the phosphorus deficiency and that the citrate was a result of metabolic processes. The citrate combined with calcium and was precipitated in the urine. Harrison and Harrison (1955) suggested that the nature of the precipitate and its location depended upon the concentration of the phosphate in diet. They used diets with a Ca:P ratio similar to cow's milk and acetazoliamide to inhibit the excretion of the citrates. Precipitation occurred in the kidney, however, the nature of the precipitate was not reported. Reen et al. (1959) supported these findings. They did not use acetazoliamide, but a diet high in calcium and low in phosphorus was used in rats and resulted in the formation of calcium citrate calculi. Diets low in protein augmented stone formation. Schnider and Steanbock (1940), as cited by Reen et al. (1959), demonstrated calcium citrate calculi in rats on diet with 0.5% protein and 0.04% potassium.

Other factors that have been shown to influence the urinary citrate excretion are pH of the urine, acidosis-alkalosis and certain vitamins. Harrison and Harrison (1955) reported that the citrate excretion was increased when the urine was alkalized by the administration of sodium or potassium bicarbonates. Shorr et al. reported similar results in systemic alkalosis. Gershoff and Andrus (1961) demonstrated renal deposits of oxalates in the rats fed with a vitamin B_6 deficient diet.

Feeding of the deficient diet was accompanied by an increased excretion of oxalic acid and xanthuric acid and a marked decrease in the citric acid excretion. They also considered the role of magnesium in the citrate level. With addition of the magnesium the citrate level was increased in urine leading to an increase in the solubility of urine for oxalates. Similarly the acidification of urine resulted in the deposition of oxalate stones by decreasing the citric acid excretion.

ENDOCRENOLOGICAL FACTORS

Certain substances may be indirectly involved in the precipitation and eventual deposition of salts. These substances affect some of the physiological processes in the body and predispose calculosis. Hormones belong to this group. The sex hormones may affect the excretion of citrates and may also alter the colloidal system. Adrenal cortical hormones act on the selective excretary mechanism of the kidney and the decreased mitochondrial enzymes may initiate nucleus formation in the kidney.

Shorr (1941), while studying the role of citric acid in calculosis, observed that the excretion of citric acid was highest at the middle of the estrous cycle and was lowest at menstruation. Estrogen seemed to enhance the excretion of citrates. He also observed that the male sex hormone, testosterone, had an opposite effect. These findings were similar to those reported by Marshall et al. (1956) who found that the incidence of calculosis was more common in males than in females. McDonald and Hoffman (1957) introduced small zinc nodules in the bladders of male and female rats. Concretions formed over the nodules in the

bladders of male and female animals in a 2:1 ratio. They further reported that the incidence was higher in spayed female rats and in testosterone treated female rats.

Contrary to the above findings, stilbestrol was thought to provoke urinary calculi by Udall and Jensen (1958). They treated 300 feed lot lambs with 300 mg. of stilbestrol pellet implants. They found that 60 sheep (20%) showed evidence of urinary calculi in 30 days. A majority of cases occurred during the winter months. Similar types of experiments were carried out by Bell et al. (1954). They treated lambs with stilbestrol. Twelve out of 517 lambs were lost due to excessive swelling of the rectal and perineal regions. Symptoms similar to calculous disease were observed but there was no positive evidence of it. The symptoms were believed to be caused by blocking of the urethra due to a mucous plug. This mucous plug was a precipitated colloidal material. Henneman et al. (1957) observed three cases of urinary calculi in 51 fattening lambs treated with progesterone and estradiol. One case occurred out of 18 lambs treated with 100 mg. of progesterone and 10 mg. of estradiol. One case occurred out of 18 lambs treated with 125 mg. progesterone and 5 mg. of estradiol. Also one case occurred out of 15 lambs treated with 10 mg. of estradiol. In a lot of 700 lambs on fattening ration with 0.5 mg. of stilbestrol per pound of feed, Marsh (1961) reported that 70 lambs developed the "water belly" syndrome. No calculi were found in these lambs. The urethral occlusion was due to plugs of precipitated mucoproteins. It was presumed that affected lambs consumed more stilbestrol. However, these experiments did not give a positive evidence that stilbestrol was responsible for calculosis. The dose of stilbestrol was sufficient to cause other symptoms as inflammation

and swelling of the rectum and vulva. The mucous could be due to inflammation. Cornelius (1961) showed that the subcutaneous implantation of diethylstibestrol increased the concentration and daily output of salt soluble urinary biocolloids (protective colloids).

The adrenal cortical hormones help govern the functions of the kidney. Selye et al. (1957) showed that the selective calcification of the zona-intermedia of the kidney could be obtained within 12 days by administration of 1% NaH_2PO_4 as the only source of water. The lesion was minimal in the adrenalectomised rats and was maximum when large doses of desoxycorticosterone acetate (DOCA) were given. It was absent in the rats treated with cortisol acetate (COLA). COLA inhibits renal concretions by counteracting the selective effect of DOCA. It appears that the corticoids exert an important action on the activity of the kidney in the excretion of phosphates. Similar experimental work was done by Bois and Selye (1956). Unilaterally nephrectomised rats were given 1.2% NaH_2PO_4 solution in place of water. Calcium deposition was observed in the pars intermedia of the kidney. This effect of the phosphate solution was enhanced by desoxycorticosterone acetate and was inhibited by cortisol acetate.

According to recent literature the initiation of renal calculus formation requires the disruption of specific enzymes within the proximal tubular cells of the kidney. Such disruption results in death of the cells and cellular dysfunction. Engfeldt et al. as cited by Boyce and Kind (1963), reported on the changes which occurred in the renal cells of rats following parathormone therapy. The most striking changes were noted in the cells of the proximal convoluted tubules. Disruption of mitochondrial activity was reflected in decreased succine dehydrogenase

and phosphatase activity. The altered cellular metabolism resulted in intracellular mineral salt deposition, increased PAS-positive granules and appearance of apatite crystals. Shigematsu and Tanaka as cited by Boyce and King (1963) also reported similar changes in the cells of the proximal tubules of mice kidneys following the administration of lithogenic drug as thiacetazone and vitamin D_1. The most prominent changes observed were the dissolution and desquamation of the brush border, vacuolization, swelling and osmophilia of the mitochondrial with an accumulation of cellular debris in the lumen of the tubules. Concentrically laminated bodies, 0.1 to 0.2 in diameter are formed as the result of the debris. These ultra fine particles were observed throughout the nephron. Thus disruption of specific enzymes within the proximal tubular cells results in the death of the cells and initiates calculus formation.

INFECTION

Infection of the urinary tract is common in the dog, cat and man and is often associated with urinary calculi. This infection is usually secondary to other lesions in the body of the patients, as reported by Mosier and Coles, (1958). Rosenow and Meisser (1922) suggested a relationship of a primary lesion in the tonsils to urolithiasis. They isolated a strain of streptococcus from urine of dog showing renal colic due to urinary calculi. Teeth of healthy dogs were devitalized and infected with this strain. These dogs developed renal calculi. In a second experiment they isolated a strain of streptococcus from arthritic patients. Again the teeth of healthy dogs were devitalized and infected

by the arthritic strain. These dogs developed arthritis but not urinary calculi.

Along with the streptococcal strains, Hagar and Magath (1925) isolated Proteus ammoniae. They used urinary sediments for pure isolation. Irrigation of the bladder with 0.5 to 1 cc. of 0.1% solution of salicylic acid produced severe cystitis in guinea pigs. This was then superimposed by one ml. of broth culture of Proteus ammoniae. Of twenty-two guinea pigs, twenty-one developed cystitis and encrustation in bladder in four days to one month. On analysis these encrustations were found to be calcium phosphate and calcium carbonate. They concluded that the inorganic salts were deposited in the bladder in cases of cystitis and alkalinuria caused by Proteus ammoniae. Proteus ammoniae was believed to split urea by the enzyme urase into ammonia and carbon dioxide. The alkalinity caused by ammonia precipitated calcium and magnesium salts. The source of the organism, in their opinion, was from the intestine. Chutt (1938) supported their findings. He isolated Proteus bacillus, Nonhemolytic streptococci, B. influenzae and M. flavus. He reported that urea, when split, rendered the urine alkaline. The resultant depositions consisted of an amorphous material containing calcium and magnesium phosphate, triple phosphate, calcium carbonate, and calcium phosphate. Shorr et al. (1942) reported that infection predisposed urinary calculi by decreasing the citrate level. Citrates are believed to increase the solvent characteristics of urine. Nilsen (1956) isolated micrococci from the matrix of calculi. Cultures of these organisms were introduced into traumatized bladders of minks. Of 50 mink, 19 developed calculi. When the culture was introduced in the untraumatized bladders of 15 mink, seven of them developed calculosis.

Not all organisms recovered from urinary infection cause urinary calculi. Coles and Mosier (1959) produced nephritis by seven different types of organisms. Urinary calculi were not reported in their experiments. Also Mosier and Coles (1958) reported 32 clinical cases of urinary tract infection involving seven different types of organisms. The pH of the urine was a variable factor and urinary calculi were not reported.

DIAGNOSIS, TREATMENT AND CONTROL

Knowledge of the nature and composition of urinary calculi is of extreme importance in the treatment and control of urinary calculi. A successful treatment for phosphate type of calculi may be quite opposite to that for urate calculi. For proper therapy one needs to study not only the composition of the stone but also the environment in which they are formed. A complete classification of urinary stones as related to etiology is not available in a single literature source. For general consideration of diagnosis of the nature of the stones and the control of calculi formation the following factors may be considered.

The history of the patient provides information regarding previous incidence and the current symptomatology. Hematuria, renal colic, dysuria and frequent attempts of mituration are some of the symptoms that are generally observed. Recurrent calculi formation in a single patient usually results in the same type of urolith. Surgery on the urinary tract or an infection may predispose the incidence. Hereditary incidence of cystinuria in cystine type calculi must be considered.

Palpation and catheterization are valuable aids in diagnosis of urinary stones. Large vesical stones can be palpated in small animals. Rectal examination may help in case of vesical calculi in larger animals. Catheterization may reveal the location of a urethral stone. A metal catheter is often helpful in detecting a vesical calculi by percussion sounds.

Urine examination aids in diagnosis. The physical examination may be done for color, turbidity, reaction, specific gravity, and surface tension. Turbidity and surface tension provide information relative to the colloidal activity (Puntriano, 1954). The precipitated colloidal matter renders the urine turbid. A higher surface tension indicates lower colloidal activity and increased specific gravity indicates increased concentration of colloid/crystalloid matter. Information as to the pH of the urine is important in therapy. Phosphate, carbonate, oxalate and citrate stones are formed in alkaline urine while cystine, xanthine, silica and uric acid stones are formed in acidic urine. The urine should be checked for blood clots or mucous plugs. Microscopic examination of the sediment may reveal the presence of tubular casts, epithelial cells, leucocytes, erythrocytes, bacteria and crystals. Tubular casts indicate the presence of lesions in kidney while epithelial cells indicate cystitis.

Chemical tests for calcium and phosphorus contents are often helpful. The calcium to phosphorus ratio is a good indication of the state of health of animal. Specific tests for cystine, xanthine, cholesterol and organic and inorganic phosphate may be carried out.

Aseptically collected urine specimens should be cultured. When the urine is positive for micro-organisms, the animal should be examined for tonsilitis, infected teeth or other focal infection in the body since the urinary infection may occur secondarily (Mosier and Coles, 1958).

Radiographs may aid in diagnosis, however, some calculi such as the uric acid, urate and xanthine stones may be radiotranslucent. The radio opacity of various calculi decreases in the following order: calcium phosphate, calcium oxalate, calcium and magnesium phosphate, magnesium ammonium phosphate, calcium and magnesium urate and uric acid (Shea, 1925).

General treatment, either preoperative or postoperative, may consist of antibiotics, antispasmodics and relaxants. The use of a proper antibiotic is essential. The causative micro-organism should be isolated and tested for sensitivity for antibiotics. Vitamins with special reference to vitamin A, B_6 and C; mild diuretics and a balanced ration should be given. Fresh water must be made available at all times.

The reaction of the urine, the amount and nature of proteins will vary with the nature of the existing calculi. Maintenance of acid urine is essential in the patients with calcium phosphate, ammonium magnesium, phosphate calcium carbonate and calcium oxalate stones. This may be achieved by administration of ammonium chloride. Considerable controversy exists regarding the therapeutic value of pH management or urine of patients with oxalate stones. Gershoff and Andrus (1961) suggested alkalinization of urine. With acidic urine the oxalate deposition was enhanced. Keyser (1935) suggested intense acidification of urine. He further suggested that milk should not be given to the patients with oxalate stones as it tends to render the urine alkaline. Higgins (1951)

reported that excretion of oxalates was effective in a wide range of pH, from acidic to alkaline. Gershoff and Andrus (1961) reported the successful use of vitamin B_6 and magnesium at 400 mg. per 100 gms. of diet in rats with oxalate calculi. A diet low in ascorbic acid, oxalates and proteins containing amino acids as tryptophane, glycine and serine, should be fed. Ludwig (1963) reported that ascorbic acid, tryptophane, glycine and serine increased oxalate in urine.

Prieu and Walker (1956) had favorable results with acetyl salicylic acid in calcium phosphate calculi. They suggested a dosage of 10 grains to be given every eight hours. Salicylic acid increases glucoronic acid excretion which increases the solubility of phosphates. Citric acid and sodium citrate mixture was employed by lavage with some success in the dissolution of calcium phosphate stones (Albright et al., 1939). Care and Wilson (1956) suggested the use of sodium metaphosphate (1-2%) orally in drinking water. The mode of action was not clear.

Uric acid and cystine stones require intense alkalinization of urine and a low protein (purine) diet. Brodey (1955) suggested use of vegetables and fruits and elimination of liver, kidney and heart from diets. Pollock (1955) suggested a lavage of renal pelvis by an alkaline solution.

A supplement of molebdenum is very essential in the control of xanthine calculi. Molebdenum has an important role in intermediary metabolism of proteins that is the conversion of xanthine to uric acid.

The composition of feeds and their mineral contents are apparently very important in the development of bovine urinary calculi. A ration high in concentrates, due to its low calcium and high phosphorus contents, often predisposes calculosis. This is also true with the rations containing

high amounts of wheatbran, linseed meal, cottonseed meal, beet pulp and some other feed ingredients containing high phosphorus. The addition of calcium and the maintenance of Ca:P ratio at about 2:1 is important in prevention of urinary calculi in such cases (Scheel and Paton, 1960).

Certain feeds, such as prairie hay from the Western range country of Canada, may contain high silica salt, as reported by Forman and Sawer (1958). This predisposes silicious deposits in the urinary tract. Therapeutic alkalinization of the urine has been suggested in such cases.

Although the female sex hormone in physiological levels inhibits the stone formation as reported by Marshall et al. (1956), McDonald and Hoffman (1957), indiscriminate use in the ration may predispose calculosis; Udall and Jensen (1958). A proper dosage is therefore very essential. The use of hyaluronidase was suggested by Puntriano (1954). But Crookshank and his co-workers reported that they failed to observe any response to this therapy. They suggested ammonium chloride and phosphoric acid 80 gms. to prevent a high incidence of calculi. Sodium chloride at the rate of 5% of the total ration has been suggested by some workers (Elam et al., 1954; Scheel and Paton, 1960). The exact action of sodium chloride is not known. Acetazolamide was used in 12 steers by Baldwin (1960) with a significant response in eight. Actazoliamide inhibits the action of carbonic anhydrase and produces diuresis. 500 mg. intramuscularly followed by 2 gms. bid by mouth was suggested dose.

SUMMARY

Urolithiasis is of great economic importance because of its wide spread occurrence in feed lot cattle and lambs. It is also important as a disease syndrome in the dog, cat and man. Of a particular note is the

tendency for calculi to recur in all species. A review of the etiology of urinary calculi in man and animals reveals that there are numerous theories explaining the various concretions forming in the urinary tract.

Apparently there are two stages of the calculus formation. The calculus starts with the formation of a nucleus. This is followed by deposition or concretion. There may be alternate concretions of the colloidal and the crystalloid matters, producing a striated stone, or there may be a simple crystalline deposition. Nucleus may be formed by the death of the renal tubular cells due to the dysfunction of the mitochondrial system. This dead material is converted to microliths, which when retained in the urinary tract form nuclei for the concretions. It is also believed that desquamation of the urinary epithelium due to vitamin A deficiency, urinary infection and stilbestrol treatment in feed lot cattle have similar effects. The dead epithelium is thought to form nuclei for concretion. Salts of the uric acid, oxalate and phosphate may crystallise in supersaturated urine when the colloidal activity is decreased. These crystals form nuclei for the further concretions.

Concretions over nucleus may be formed in several ways. In feed lot cattle, where the incidence is very high, high phosphorus and low calcium contents of concentrate ration are incriminated. High phosphorus in ration interferes absorption of calcium and also increases excretion of the same. The increased excretion may precipitate in the urine. On some ranges prairie hay may predispose the incidence due to high silica content in the hay.

Striated calculi are common in all animals. The colloidal striations are primarily due to alterations in the biocolloids of urine with the precipitated colloids forming the striations. Adequate levels of magnesium and protein in the diet seem to increase the desirable (protective) colloids and thus prevent precipitation. On the other hand, testosterone, emotional or environmental stress will influence the hydrophobic colloids causing an elevation of these non-protective colloids and a decrease in protective colloids.

The pH of urine may be an extremely important factor in urolithiasis. Calcium phosphate, calcium carbonate, calcium ammonium and magnesium phosphate stones are formed in alkaline urine while uric acid, cystine, and silicious stones are formed in acidic urine. A high pH enhances the excretion of citrates and increases the ability of urine to retain the oxalates in solution. In an alkaline urine the silicates, xanthine and uric acid will remain in solution, while in acid urine the phosphates and carbonates are held in solution. Factors which affect the pH of urine are vitamin A deficiency, infection and the diet. Vitamin A deficiency is shown to influence the pH of urine of the dog, cat and man by rendering the urine alkaline. A simple change of the pH of urine to the acid state prevents phosphate calculi in vitamin A deficient dogs and rats. Certain infections cause alkalinuria. The single and the most commonly associated organism in infection of urinary tract with calculi is Proteus ammoniae. P. Ammoniae splits urea into ammonia and carbon dioxide and the ammonia renders the urine alkaline. An infection of the urinary tract is often associated with tonsilitis, infected teeth, or other focal of infection. A diet may be acid ash or alkali ash and thus render the urine acidic or alkaline. Bacon, wheat, corn, eggs, fish and rice render urine acid while cabbage, carrots, and milk render urine alkaline.

Cystine, xanthine and cholesterol calculi are usually formed due to metabolic disorders. Cystinuria is a hereditary condition and is due to faulty protein metabolism. Xanthine stones are formed in molebdenum deficiency. Xanthine is oxidised to uric acid in the presence of xanthine oxidase which contains molebdenum. In the absence of a sufficient quantity of molebdenum the xanthine is excreted unchanged. Very little is known about cholesterol calculi. Although cholesterol is not a normal constituent of urine, it may be observed in the urine of patients affected with nephritis.

In summary, a urinary stone is formed in two stages. The nucleus is formed first. This is followed by the deposition of an abnormal precipitation of colloidal or crystalloid material onto the nucleus. In uric acid stones, there may be a pure crystalline deposition. The striated calculi are formed due to alternate deposition of precipitated colloidal and crystalloidal matter. The exact cause of the alternate striations seems to be less well understood. It is postulated that the colloid striations absorb the crystalloid matter to form a crystalloid striation.

A diagnosis of urinary calculous is based on the available history, clinical symptoms and the physical examination including palpation and catheterization. A radiograph may aid in the diagnosis. Various laboratory tests for the urinary contents of calcium and phosphorus are helpful. Treatment may be aimed at combatting infections, inducing diuresis and restoring the normal physiological functions of the body. The diet should be corrected for deficiencies and be balanced.

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CURRENT CONCEPTS OF THE ETIOLOGY OF UROLITHIASIS IN MAN AND ANIMALS

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ABSTRACT

A review of the etiology of urinary calculi reveals that several types of urinary concretions are formed in the urinary tract. Although each one may be formed in a different environment, the basic mechanism of formation of various calculi is thought to be the same. A calcus starts as a microlith in the renal tubules. The nature of further concretions over the microlith depends upon its environmental factors. Vitamin A deficiency produces alkalinuria and keratinization of the mucosa of urinary tract. Keratinization of the cells will roughen the mucosa of the urinary tract and may predispose deposition of salts. Infections of the urinary tract may act in a similar manner. With the advent of alkaline urine the acid soluble salts such as the phosphates and carbonates tend to precipitate. Feeds have an important role in the etiology of ruminant urolithiasis. In some regions prairie hay may predispose calculosis owing to its high silica content. Feed lot animals on concentrated rations may develop a calcium deficiency. The high level of phosphates interferes with calcium absorption as well as increases the rate of calcium excretion through the urine. The biocolloids of the urine occupy an important role in maintaining a colloidal suspension of the various elements of the urine. Abnormal colloidal functions will result in the formation of a substance known as matrix substance A. This is thought to occur in all types of calculi. Of the two types of colloids, the increased hydrophobic colloids will precipitate certain minerals such as the silica salts. Hydrophilic colloids although more stable are found to be decreased in the urine of calculus disease patients. That the incidence of urinary calculi is lower in female than

male is explained by the fact that the colloidal activity is increased by estrogen. Estrogens also elevate the urinary citrate. The citrate is believed to increase the ability of urine to hold oxalate in solution and thus prevent crystallization. Enzymes of the mitochondrial system of cells are important since the cells die in their absence. Death of the cells may lead to the formation of microliths. A deficiency of molebdenum may affect the protein metabolism and predispose xanthine calculi. Cystinuria is a hereditary condition which leads to formation of cystine calculi.

The diagnosis of the urinary calculi is based on the available history, clinical symptoms and the physical examination as palpation and catheterization. A radiograph may aid in the diagnosis. Various laboratory tests for the urinary contents of calcium and phosphorus are often helpful. The treatment consists of combating the infection, inducing diuresis and restoring normal physiological functions of the body. Nutritional deficiencies should be corrected and the animal placed on a balanced diet.

A calculus originates as microlith in tubules of kidney. When a microlith is retained in the urinary system, various types of concretions may form over it to form an actual calculus. The type of calculi will depend upon the urinary environment and the several factors cited above.