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## Etiology of renal calculi

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ETIOLOGY OF RENAL CALCULI

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HISTORICAL

Renal calculus appeared with the dawn of civilization. The symptoms of this disease are described in the earliest medical writings. From the clearness of these descriptions it is probable they existed a considerable time before this.

The oldest kidney stone is believed to be some seven thousand years old. According to Shattock (77), the earliest calculus known was discovered by Professor Elliot Smith in 1901. It was found in the pelvic bones of the mummy of a sixteen-year-old boy in upper Egypt. This stone is believed to have formed about 4800 B.C., some generations before the advent of Menes, First Dynastic king. It is a uric acid stone.

Campbell (16) cites Shattock in describing a renal calculus found lying close to the second lumbar vertebra of a skeleton found in a tomb dating from the Second Egyptian Dynasty (about 4100 B.C.) It was composed of carbonate, phosphate, and oxalate of lime.

Every medical record makes reference to the subject of urinary calculi, according to Bowers (11) and every stone described is identical in composition with that of stones found today.

There is no mention of stone in the Ebers Papyrus which is probably the oldest medical treatise in existence.

Its date is about 1550 B.C.

Lithiasis has always been a prominent disease in India, according to McCarrison (56). It is mentioned in the earliest Hindu writings. The earliest documents known, the Rig Veda and Atharva Veda date from about the second millennium B.C., and are filled with incantations against this disease.

Charaka, Susruta and Vaghbata, who lived during the second, fifth and seventh centuries, respectively, were the first to write real descriptions of calculous disease and indications for treatment. The operation of suprapubic lithotomy was described in Indian writings about the beginning of the Christian era, which antedates those of the European surgeons who advocated this operation by fifteen hundred years.

A most important contribution by the Hindu writers was the first endeavor to classify stones by their character. They divided them into four types. The description of the first three types reminds one of phosphatic, oxalate and uric acid calculi, respectively. As for renal lithiasis specifically, little or nothing is to be found in Hindu writings.

Hippocrates, 460-370 B.C., recognized both renal and vesical calculi. Under the heading of "The First Disease of the Kidney," he gave a classical description of renal colic. He was a daring surgeon and he advised cutting down on the kidney when there was definite swelling in the loin. He opened the kidney when it was pyonephrotic, though he does not appear to

have removed renal calculi. Bowers (11) quotes Hippocrates as saying, "I will not cut persons laboring under stone but will leave this to be done by men who are practitioners of this work."

Although nephrolithiasis was known from the earliest times, and Hippocrates knew the character of the disease so well, the surgical treatment in the absence of swelling in the loin was absolutely nil and, with few exceptions, remained so until the latter part of the nineteenth century.

The first intentional nephrotomy for renal stone was probably performed in 1474 by Germanian Calot, according to Campbell (16). This is the famous and oft-quoted case of the Archer of Mendon, but the technique was not described and the entire episode is shrouded in such mystery that it has not been definitely accepted. Undoubtedly other nephrectomies were attempted and some performed, but it was completely without knowledge of an anatomical approach. Lau (48) states that, in 1560, Pierre France first removed a vesical stone by suprapubic lithotomy in a child ten years old. The kidney operations were done blindly and sometimes the stones were obtained, but often the kidney was not seen. The operation remained to be placed on a sound anatomical basis.

Riotan in the first half of the seventeenth century was the first to speak of renal calculi in a precise manner. He recognized their coral-like form and was aware of the position of the ureter, pelvis and calyces. What is more, he demonstrated

that one could expose the kidney without injuring the peritoneum. Following this, in 1670, Zambecarius began experimental nephrectomies on dogs, which work was carried on by Roonheysen (1672) and Blankart (1690) of Holland. These men showed by physiological experiments that life could be maintained after removal of the kidney (16).

Modern urological surgery commenced with Gustave Simon who first performed an intentional nephrectomy in 1869. According to Lau (48) and Campbell (16), nephrolithotomy was first performed by Morris in 1880. William Ingalls performed nephrolithotomy in the Boston City Hospital in 1873, but he did not publish his report until a year after Morris, so that Morris is given priority. In 1898, Morris reported thirty-four such operations with only one death. Czerny is also credited with performing a pyelolithotomy in 1880. Litholapaxy was introduced in 1878 by Henry J. Bigelow of Boston. Great impetus was given to renal and ureteral surgery by the introduction of X-ray as a diagnostic procedure for the recognition of calculi. Mac Intyre in 1896 produced the first X-ray picture of a stone after twelve minutes' exposure.

This newer type of surgery was rapidly taken up by the general surgeon all over the world and was practiced by them to a greater extent until the period of the World War. Their interest, with a few exceptions, was mainly in the development of an anatomical

approach and perfection of surgical technique. They concerned themselves with the removal of the stone and not with reasons for the production of the stone.

A new approach to the subject of renal lithiasis was initiated by the chemists in the latter part of the nineteenth century. They studied the stone itself, seeking its composition.

Urology had its inception with the introduction of the cystoscope by Nitze in 1877. As urologists developed newer diagnostic methods and performed more surgery, the conception of stone changed in that it is now considered a symptom of disease rather than the cause of disease. This attitude toward calculous disease has created, as paramount, the endeavor to restore the normal dynamics of the urinary tract rather than simple removal of the stone.

Because of this reversal of attitude by urologists, the causation of stone was sought for with more vigor by them, and in doing so they have concentrated the efforts of the chemist, bio-chemist, physio-chemist, pathologist, bacteriologist and clinician to weld their thought and discoveries into a concrete etiology with a practical clinical application for prevention of the stone formation.

Prior to the advent of surgery in the latter part of the nineteenth century, there were no means of dealing with renal calculi except with drugs. If drugs failed, the condition was incurable. This led to the concoction of many remedies known as



litholytics. The early Hindu literature contains many prescriptions for dissolving and disintegrating stones. Hippocrates evidently did not believe in them, for he advised that the organism be relieved of gravel by use of diuretics. According to Campbell (16), the prescriptions which appeared during the middle ages consisted of anything from diets of sparrows to pipe stems. During the eighteenth century when stones were exceedingly common in Europe and England, a prescription containing old tobacco pipes, egg shells, snail shells, soap, white onions and several vegetable extracts was bought by the English government in order that it might be made public. Chelselden spoke highly of it and Sydenham used it himself. These were all quack remedies and had no scientific basis, for the composition of calculi was not known.

Urea was not discovered until 1733 by Rouelle de Calet. It was first crystallized by Cruikshank in 1789 and synthesized by Mohler in 1828. Uric acid was first isolated by Sheeler in 1776 and found in urinary concretions by Wallaston in 1797. Phosphates had previously been discovered by alchemists. Lastly, cystine was discovered in certain calculi by Wallaston in 1810. Uitzman (16), in 1882 published a method of chemical analysis for calculi and classified them in accordance with their chemical composition.

COMPOSITION OF RENAL CALCULI

INORGANIC

(a) Uric acid and urates

Most common.

Pure uric acid calculi are rare. They are usually a mixture of sodium, ammonium, calcium or magnesium urates.

Moderately hard in consistency.

Surface may be smooth, finely granular or rough.

Color varies from yellow to brownish yellow.

Cut section shows concentric arrangement of lamellae.

As a rule are small.

(b) Oxalates

Usually calcium oxalate or ammonium oxalate. Seldom pure; often forms coating for urate calculi.

Very hard in consistency.

Surface is rough and granular like mulberry.

Color varies from dark brown to blank.

Occur singly, rarely larger than hazelnut.

(c) Phosphates

Usually a mixture of calcium, ammonium, or magnesium phosphate.

Found in alkaline and infected urine.

Seldom pure; often form covering for uric acid, urates or oxalate nuclei.

Surface is rough or finely granular.

Friable in consistency.

Greyish white in color.

Form and size are variable. They are usually round and small, although they may also be large enough to form a cast of the pelvis and calyces.

(d) Calcium carbonate.

Rarely pure. Occur in association with the phosphate group.

(e) Cystine calculi.

Form as result of hyperexcretion of cystine as a result of faulty metabolism of amino acids.

May occur in certain families. Appears to be an inherited factor.

175 cases on record.

When pure, cystine calculi are soft and yellowish.

Usually found in association with calcium phosphate.

(f) Xanthine calculi.

Very rare.

Color varies from yellowish brown to greyish green.

ORGANIC

(a) Bacterial.

Rare. Less than a dozen cases reported.

Made up of bacteria, usually colon bacilli arranged in concentric layers. In the outermost layers, the organisms may still be virulent at time of operation.

Color greyish yellow.

Elastic in consistency.

(b) Albumin or fibrin.

Rare. Nineteen cases reported.

Soft, round; pea to olive size.

(c) Amyloid albumin.

Rare. Three cases reported.

Pinhead in size with distinct amyloid reaction.

SIZE OF RENAL CALCULI

Varies from millet-seed to mass of several pounds.

Average weight: twenty to fifty grams.

Oxalate and uric acid calculi are seldom larger than a hazelnut.

Phosphatic calculi may attain enormous size.

SOURCE OF STONE-FORMING ELEMENTS

(a) Uric acid and Urates.

Endogenous.

Normal tissue catabolism produces 0.3 to 0.6 grams daily.

Not subject to external influence.

Exogenous.

Oxidation of purine bodies which come from nucleoalbumin: lean muscle, kidney, thymus and pancreas.

The methyl purines -theobromine, theine and caffeine- are eliminated chiefly as xanthine and need not be considered.

(b) Calcium oxalate.

Endogenous.

Bacterial fermentation of carbohydrates in the intestine.

Exogenous.

Foods such as spinach, rhubarb, tomatoes and asparagus.

(c) Phosphates.

Inorganic phosphates in vegetables do not influence phosphate concentration in the urine. Urinary phosphates are derived almost wholly from the conjugate-proteins.

Diet in no important way influences calculus occurrence.

(d) Cystine.

The presence of cystine in the urine means faulty metabolism of sulphur. It is normally excreted as sulphate.

Must decrease ingestion of meat and fish, subsist on milk, cheese and eggs.

ETIOLOGY

The discovery of salts of which calculi are formed gave great impetus to attempted dissolution of vesical stones with gastric juices, dilute nitric acid, salts of alkali metals and lead acetate. It was found that any acid strong enough to dissolve the calculus would destroy the mucous membrane. Many devices such as bags into which the acids were injected were made during the nineteenth century to enclose the stone and protect the mucous membrane.

In 1932, Randall (69) introduced phosphoric acid as a possible solvent for alkaline renal calculi. Using a solution of 1 gm./100 c.c., he injected the phosphoric acid into the pelves of dogs, and, although this solution has a p. H. of 1.6, there was no damage done to the epithelium. He stated that one could expect possible dissolution of small phosphatic calculi and prevention of recurrence after operation.

Albright, in 1939, cited by Campbell (16) suggested citric acid and hexametaphosphate which he proved could dissolve phosphatic vesical calculi, but no proof of renal calculus destruction has been advanced.

A diet high in vitamin A and acid-ash foods has produced a decrease in size or total disappearance of renal calculi in patients who refused operation, according to Higgins(35). In eighteen collected cases using this diet, the renal calculi underwent solution according to roentgenological evidence. In

experiments on rats, Higgins (35) noted dissolution of calculi in thirty instances when cod-liver oil (vitamin A) was added to the diet for from fifty to a hundred days. In other rats, he noted decrease in size of calculi.

Such neat results have not been duplicated by other urologists. In actual fact, Oppenheimer and Pollock (16), treating twenty-seven patients with the high vitamin A and acid-ash diet, noted an increase in size of the stones in five patients.

These attempts mentioned above are an example of the utilization of the knowledge of the chemistry of calculi. Medicine has faithfully followed in the wake of chemistry. We are indebted for much of our present knowledge of medical problems to chemistry and its branches, biochemistry and physical chemistry.

Following the solution of the simpler chemical problems of the chemical analysis of calculi, bio-chemists discovered the process by which certain ingested chemical substances are metabolized to form the excreted end-products--the salts which are found to make up urinary calculi. These discoveries led to many other fields of investigation.

The urologists now had something to work with--a far cry from the egg-shells and soap of Sydenham's day. They were able to approach the subject with a logical curiosity. Their thoughts turned to the possibility of stones forming because



of an excessive ingestion of certain foods which cause an over-abundant excretion of salts to produce the prevailing type of stone.

In 1923, Keyser (16) was able to produce calcium oxalate stones in experimental animal after the injection of butyl oxalate and calcium chloride. Again, in 1935, Keyser (43) caused experimentally-produced calculi by causing a hypersecretion of oxamide, calcium oxalate and calcium carbonate, and by excessive doses of parathyroid extract and viosterol. Joy (39) reports that in bone diseases where there is a decalcification of bone with a consequent increase in mobilized calcium in the blood there is a high incidence of renal calculi. Albright (2) states that the hyperexcretion of calcium in hyperparathyroidism is probably one of the most positive of all etiological factors in stone formation. He reports that 65.7% of the cases of hyperparathyroidism at the Massachusetts General Hospital had renal calculus.

Nor do the above factors constitute the complete story of the theory of hyperexcretion whether of endogenous origin or exogenous. The entire internal and external environment of human organism was surveyed.

The analysis of stones in large groups has been carried out in all parts of the world. These have shown a variation in the content of the calculi in different geographical sections.

Bowers (11) states that it was thought that an excessive intake of calcium and phosphorus by means of water and products of the soil was the key to calculus formation. The results of such though were negative as far as any direct relationship was concerned, for there are people who are pure vegetarians, living in a country of which the soil abounds in limestone, and those who all their lives have had well-water that is very high in mineral content, yet neither group producing calculi. In contrast, there are patients who were watched under the most careful supervision as to diet, even on distilled water, producing calculi from time to time.

India, China and Egypt appear to have the highest incidence of stone. Thompson (81) reports that in the Canton district where stone is quite prevalent, the drinking water is soft. The Chinese, moreover, take their water in the form of tea which is made with boiled water. He states further, in refuting the dietary factor in the etiology of stone, that in Switzerland where the water is hard there is practically no stone. Analysis of the stones in the Canton district showed that 78% were composed of uric acid and urates, yet the people live on a practically purine-free diet. Diet alone could surely not be accused as the sole cause of these particular stones. Joly (39) goes further by saying that in no case can stone formation be attributed to an excess of stone-forming substances

in the diet. Winsbury-White (84) believes it would be impossible to prove that the mixed dietary of a modern civilized community has any important bearing on stone formation.

During the nineteenth century stones were extremely prevalent among English children. In Thompsons series (81) of some twenty-five hundred cases nearly one-half were under sixteen years of age. Stone was comparatively rare in children of well-to-do families but exceedingly common among those of lower classes. McCarrison (56) published a graph showing the peak of incidence in India was in the first decade of life. Civiale, quoted by Desnos and Minet (20), reported that more than one-half the cases of stone in the middle of the nineteenth century occurred before twenty-years.

In the period between 1914 and 1924, Joly, cited by Campbell (16) reversed the picture and demonstrated calculous disease as a disease of middle life. This transformation has occurred through dietary changes and especially the administration of more and better dairy products. These facts coupled with the proofs presented in the preceding paragraphs indicated an "X" factor in stone causation.

The scope of investigation thus was widened. New theories begot differences of opinion, and differences of opinion

are as spurs in the flank of the scientist. He is goaded onward through a strange new field of science, seeking an idea that will integrate some of the divergent theories which drive him.

Mendel, Osborne and Ferry in 1917 found such an idea, according to Long and Pyrah (54). They first showed that rats fed on a vitamin-A-free diet develop calculi in the urinary tract. They were searching for an explanation for the occasional occurrence of calculi in their experimental animals. They found that those rats which developed calculi had been on an inadequate diet of fat-soluble vitamin. McCarrison, cited by Joly (39) showed in 1927 that lithiasis occurred in 30% of his rats if they were kept on a vitamin-A-deficient diet, and that if milk was given to the animals no stones occurred. Fujimaki (16) conducted similar experiments in Japan and reported similar results. The stones produced were phosphates, usually calcium and magnesium phosphate.

Higgins (34) in 1933 and again in 1935, repeated these experiments and produced calculi in 85% of the experimental animals. These calculi were phosphates. No oxalate or uric acid stones were detected. He noted three constant changes in the urinary tract of these animals that might be associated with calculus formation:

- (1) Keratinization of the epithelium was noted after

the diet had been deficient in vitamin A for a period of from eight to ten weeks. This involved the mucous membranes all over the body. Wolbach and Howe (85) found similar changes in the kidney pelvis of seven animal.

(2) Urinary infection was produced in a large percentage of these animals. Renal infection occurred in from sixty to ninety days.

(3) Alkalinuria was a constant finding in these animals. Addition of ammonium chloride to the diet caused a decrease in the incidence of calculus. Similarly, addition of vitamin A to the deficient diet caused the urine to become acid, and calculi were not produced.

Higgins concluded that vitamin A deficiency produced the essential conditions for calculus formation.

In a re-study of available data with regard to stone-formation in certain areas, Bowers (11) reveals that in the neighboring stone-free areas there was an abundance of vitamin A in the diet and a comparative absence of this vitamin in the stone-forming area, where the people subsisted on cereal foods.

Criticism has been directed against these experiments on the ground that the diets were deficient not only in vitamin A. but also in other vitamins. Higgins (34) experimented with other vitamins and found that eliminating vitamins B, C and D

did not result in calculus formation.

A more accurate measurement of the degree of vitamin A deficiency was made by Ezickson and Feldman (24). By using an apparatus that measured the patient's ability of dark-adaptation, they found that 91% of the patients with kidney stones had pathologic adaptation. After feeding these patients huge doses of vitamin A for from six to nine months, there was no improvement. They concluded that the avitaminosis is due to failure to assimilate or utilize the vitamin.

Higgins and Mendenhall (36) in 1939 reported that 25% of patients with stones who were given the biophotometer test showed vitamin A. deficiency.

The vitamin A theory did not, however, win unanimous acceptance. In these days when medical science seems to be going all-out for vitamins, there remain many authorities, more temperate, who are able to point out the short-comings of medical science's favorite child.

On the basis of recurrence of calculi with ten days in spite of high vitamin A therapy, Magoun and Sherman (55) conclude that they cannot see how vitamin A has any effect on stone formation.

Randall (70) makes it clear that calculi that form under conditions of avitaminosis are consistently made up of

those salts known to have their normal ratio disturbed, that is, calcium phosphate. Stones of uric acid, urates or even calcium oxalate do not precipitate at all. Also note the alkaline urine and the high incidence of infection--a not unusual medium for precipitation of phosphatic calculi.

Parmenter (63) points out that Higgins' experiments with vitamin A were conducted on rats and not on humans. Keyser (43) remarks also that rats are a species remote phylogenetically from human beings. He states that keratinization of epithelium of the urinary tract is not a common finding with stone.

Randall (66) believes that vitamin A deficiency plays a role only in determining the chemical composition of the stone.

The mechanism by which renal calculi are found in the presence of infection and obstruction is readily understood today. On this basis, Eisenstaedt (23) has divided renal calculi into two classes, primary calculi and secondary calculi.

Secondary calculi are those which form in the presence of some demonstrable pathological lesion, either an obstruction, a foreign body or in the presence of infection. For example, bacteria such as *Proteus* and *staphylococcus* are known urea-splitters. Their presence in urine rapidly causes the precipitation of alkaline salts, which in the presence of an obstruction, are sufficiently static to be coalesced by urinary colloids to form a stone, or in the presence of an ulcerated point of

attachment for the production of the incipient calculus.

Primary calculi, on the other hand, are those which develop in the absence of any demonstrable pathological change in the urinary tract as determined by clinical investigation. There is no obstructive uropathy, there is no sign of infection, there is no lesion whatsoever. A person who is apparently well suddenly develops a renal colic and passes a stone. Careful and thorough examination by every known urological diagnostic measure fails to reveal any abnormality. Eisenstaedt places uric acid, xanthine, calcium oxalate and cystine stones in the primary classification.

Eisendrath and Rolnick (22) consider infection of kidney pelvis after catheterization a common cause of calculus formation. They cite renal and ureteral anomalies as a cause of stagnation which favors hematogenous infection. Suppuration in other parts of body, they believe, bears some relationship to calculus formation in the kidneys. According to Eisenstaedt, urinary stasis is of the greatest importance, from whatever cause or wherever located, and infection of the urinary is subsequent to and dependent upon urinary stasis.

Infection, as a rule, states Blaustein (10), is indecisive in the etiology of stone, since stones appear in



consistently uninfected urine. He admits, however, to the belief that there is a direct relationship between general body disease and stone formation. He notes that the frequency of lithiasis in such patients is far too great to be mere coincidence. Certain peculiarities have been noted regarding these calculi. They are always found in the kidney or ureter; they have a great tendency to be bilateral; they may originate in any calyx, whereas calculi in non bed-ridden patients are as a rule found in the lower calyx or in the renal pelvis; finally, many of these calculi disappear when the patient has been on his feet for some time. These facts point to a rather common factor: immobilization, that is, the position in bed brings about a sluggish drainage of the calyces and pelvis.

Lazarus and Rosenthal (49) require the presence of a specific urea-splitting organism in the infection in addition to urosthesis. Higgins (35) observed that urinary infection was produced in a large percentage of his laboratory rats when they had been kept on a vitamin A deficiency diet.

Randall (70) discounts the influence of stasis in the etiology of stone. He states that although stasis is an active factor in certain cases, it fails as a theory when such stasis can be proved to be absent. Finding a stone in an hydronephrotic pelvis does not prove that stasis caused the stone. It may be that the stone came first and caused the

obstruction. By intravenous urography one can prove that calculi occur in pelves totally devoid of stasis. It is not a constant fact that very poorly draining pelvis, even if infected, will form a stone.

Immobilization is credited with being at least one factor in stone formation by Joly (40), and the poor drainage present in congenital anomalies such as a horseshoe kidney is considered the explanation for the very high incidence of calculi in such kidneys. He found, also, (39) that bilateral stones are most often secondary type, that is, due to infection. He explained that infection acts in two ways: one, it causes precipitation of phosphates and carbonates within the renal pelvis; and two, it provides a large number of potential stone nuclei.

According to Bumpus (14) renal calculosis is a deficiency disease enhanced by stasis. Rosenow (73), in investigating Randall's theory of calcification on the renal papillae, found evidence of infection present in 64.9% of thirty-seven cases. He suggests that these areas of calcification may have resulted from the infection.

Foci of infection, urostatics and localized infection in the urinary tract are the three factors which Bowers (11) considers sufficient to cause calculi. Foci of infection act as the source of infection of the tract or by lowering the

resistance of the body to allow the urinary system to become susceptible to infection.

Two factors have recurred repeatedly in the 126 cases observed by Winsburg-White (84) which he believes cannot be dismissed as unimportant. One is the pre-existence of dilatation in the upper urinary tract; the other is the presence of a chronic focus of infection in some pelvic organ, the prostate in the male and the cervix in the female. Sixty percent of his male cases showed inflammation of the prostate.

Higgins and Mendenhall (38) also found a definite relationship between local infection and foci of infection on the one hand and recurrence of calculi on the other. In one hundred cases, they found infection present in fifty-four out of seventy-two cases of unilateral recurrence and in twenty-three out of twenty-eight cases of bilateral recurrence. They found foci of infection in the prostate of twenty-seven, in the teeth of eleven, in the tonsils of sixteen and in the sinuses of three of the one hundred cases.

Infection accelerates stone formation rather than initiates it, according to Roche (71), and he states what many other opponents of the infection theory have also observed that calculi do form in sterile urine and that infected urine

without stone is common. He discounts also the value of obstruction as an etiological factor since seventy-five percent of ureteric stones are able to be passed naturally.

Dourmashkin and Solomon (21) found infection present in 19.1% of their cases, whereas Harrington (31) found no infection at all in twenty-six percent of all the urolithiasis cases at the University of California during the ten years between July, 1929 and July, 1939. Flocks (26) considers focal infection an important factor in the etiology of stone.

Experimental work under the infection theory culminated in the report of Rosenow and Meisser (72), where they infected the de-vitalized teeth of dogs and inoculated the pulp cavity with cultures of "specific" streptococci obtained from urinary calculi and obtained sixty percent positive results. This work has been neither corroborated nor challenged and disproved. It stands as probably the nearest approach to the clinical picture by purely experimental production of renal stone; though it is to be stated clearly that these authors do not actually show us how or where or why a calculus develops.

The theory assumes that such bacteria or their products act as the nidus about which crystallization forms a stone. It does not admit that stones occur in sterile urine nor does it agree with the modern belief that organisms do not

and cannot pass through the kidney without producing lesions. Experimental workers have not traced the complete story from infection to actual stone formation.

Randall(66) bases his theory as to the origin of renal calculi upon infection. He stated, in 1936, "That infection plays a far more important role in the causation of minor papillary or calyceal lesions in kidneys that are otherwise normal, and by so doing creates a focal point on which crystallization starts, is the crux of my hypothesis."

- (1) A central nidus to which crystals may adhere.
- (2) A supersaturated solution of the crystals in the urine which are to be precipitated to adhere to the nidus.
- (3) An adhesive something or other which causes these crystals to adhere in turn to the nidus and then to themselves.

A foreign body as a point of attachment can readily be understood. Rosenstein (74) reported a case in which a clot was found as the nucleus of a calculus fifteen years after a kidney injury. Muller (60) reviewed various theories for formation of stone following trauma and concluded that the pathogenesis has not as yet been fully explored. There is, however, abundant evidence that the condition follows trauma. Professor G. Nisio (61) reported numerous cases of stone having a history of trauma. He cites Illyes' case in

which a calculus appeared eighteen years after the injury.

Bacteria have been given a four-fold responsibility in the etiology of stone. Some investigators consider bacteria to be the nucleus around which a stone forms; other authorities have shown that the entire calculus may be composed of a clump of bacteria, while others consider bacterial inflammation to be most important; and finally, many investigators nominate bacteria as the chief etiological agent by virtue of their ability to split urea, resulting in the formation of ammonia and a favorable reaction for precipitation of alkali salts.

Stuart, Thompson and Krikorian (80) presented a case in which they found the *Bacillus alkaligenes faecalis* actually in the interior of the calculus. The organism, therefore, filled the part of the "generally accepted prerequisite of an organic nucleus", and it is their belief that on this nucleus there resulted a precipitation of calcium salts from an increased calcium content of the patient's blood.

According to Balustein (10), however, the theory that bacteria, bits of pus, muco-pus or desquamated epithelium are the nuclei of all kidney calculi not due to a foreign body is not at all satisfactory. Many stones fail to show any

central nucleus. The products of extensive inflammatory conditions in the urinary tract, such as renal casts, have existed in the calyces and pelvis without the formation of stones. Pieces of urinary calculi placed in the kidney pelvis of normal dogs do not grow at all, but may even decrease in size.

Ward (83) in 1926 described several cases of soft urinary calculi composed entirely of colibacteria. He mentions that the bacteria near the periphery of the calculi were in several instances still virulent at time of operation. These calculi varied in size from that of a bean to cherry. They were round or oval or tetrahedraform in shape. Eisendrath and Rolnick (22) describe such calculi as being exceedingly rare. These vary from a pinhead to cherry in size and are elastic.

Bacterial inflammation, according to Hellstrom (32), gives rise to secretion of an exudate which disturbs the normal relationship between colloids and crystalloids of the urine.

In repeated cultures of urine from the involved kidneys in recurrent cases of lithiasis, Lau (48) demonstrated coli, proteus or pyo-cyaneus in all cases.

The most important contribution to the influence of bacteria in the production of urinary lithiasis was made in 1926 by Hagar and Magath, cited by Barney and Jones ( 6). They demonstrated that certain stones were formed in the presence of a Gram-negative organism capable of breaking up urea into carbon dioxide and ammonia, namely, B. proteus.

Hellstrom (32) and Eisenstaedt (23) accept the theory that a urea-splitting organism is the most frequent cause of recurrent urinary calculi. They emphasized the role played by staphylococci. Joly (40) found staphylococci, proteus, B. coli and fecalis in fifteen cases of bilateral stone, and he makes a distinction between those bacteria which split the urea molecule and those which produce merely an alkaline urine. He states that stones occur more frequently in alkaline urine. He does not know of a single case in which a true stone developed in the course of a pure coli infection. He cites recent work by Dukes of St. Peter's Hospital in London that tends to show that B. proteus is the only organism that has the power to decompose the urea molecule. He found that the ordinary pyogenic cocci produced alkali, but that only proteus could decompose urea.

Urea-splitting streptococci and staphylococci in addition to B. proteus are credited with causing stones in laboratory animals, according to Keyser (43). Hellstrom (32)



has made the statement on several occasions that staphylococcus is the most essential cause of stone formation. He claims that in the presence of staphylococci with the absence of other factors, such as disturbance in metabolism, hyperparathyroidism, bone disease, essential phosphaturia, avitaminosis and congenitally inferior kidneys, renal calculi will form.

Higgins and Mendenhall (36) found that staphylococcus was the predominating organism in all their recurrent stones. Keyser (43) and Lazarus and Rosenthal (49) report incrustations in the urinary tract as a result of infection with alkaline urea-splitters.

Reporting on the prevalence and importance of urea-splitting organisms, Chute and Suby (19) stated that these organisms are the most common single cause of stone formation, accounting for fifty-four percent of all their cases. In ninety cases, seventy-five percent were infected with coli, staphylococci and proteus, the colon bacillus being most common. They observed that the urine in cases of urea-splitting infection is usually alkaline, and that the stones that occur are predominantly calcium phosphate and have a marked tendency to recur.

Birdsall (9) reported that urea-splitting infection was present in eighty-nine percent of his cases of lithiasis.

Albright, Dienes and Sulkowitch ( 3 ) showed that *B. influenza* can produce calculi in the kidney. This organism is a urea-splitter.

Barney and Jones ( 6 ) pointed out the difference in the locale of stone brought about by certain types of organisms. The following organisms seem to have a selectivity for invading the parenchyma and therefore form calculi which resemble the condition known as nephrocalcinosis, occurring in hyperparathyroidism. These organisms are *B. influenzae*, staphylococcus, streptococcus and *B. pyocyaneus*. The particular strains of these organisms which invade the parenchyma are, practically always urea-splitters. On the other hand, stones are produced in pelvis or calyx by coli, proteus and occasionally by staphylococcus and streptococcus. In one hundred carefully selected cases, urea-splitting organisms were found in forty-six percent.

Schade, cited by Alexander (75), was apparently the first to attempt coalescence of crystals with a protein material. He described certain conditions necessary to the formation of calculi, namely, precipitation of crystals from a supersaturated solution, together with some organic colloid material such as fibrin or mucin which can form the nucleus of minute calculi.

Although his evidence has been greatly criticized, it was an original step in the fabrication of the colloid theory.

The composition of the colloid in the urine has not been recognized, but it is known not to be albuminous. Urinary salts can be excreted in a highly concentrated form, in fact, in a much higher concentration than can be obtained in an aqueous solution. The ability of the urine to hold the urinary salts in concentration is attributed to the presence of the urinary colloids. The word colloids connotes two existing factions, one crystalloids, and two, true colloids.

Crystalloids are salts which go into watery solution and ionize to some extent at least. In the presence of a colloid some of the crystalloids go out of the solution and become absorbed by the colloid, while others remain in solution. The colloid will enlarge to a certain point to absorb a considerable amount of crystalloids so that the solution approaches the point of supersaturation. The crystalloids are not changed by this physical process and are not in solution, but in a state of colloidal suspension and can be seen as such with the ultra-microscope.

The maintenance of this state is attributed to a protective action of the "true colloid." It has been noted that in any such suspension, the suspended particles tend to accumulate at any point where the surface tension is increased. The normal mucous membrane of the urinary tract does not cause an increase of the surface tension, but it will be changed by the presence of a foreign substance such as an ulcerated area on the surface of the kidney pelvis. The colloid is then

precipitated in the form of a "gel," carrying enmeshed within it the crystalloids which have been liberated by the destruction of the protective action of the true colloid. In this manner a nucleus for a stone is formed.

Snapper (78) explained that urine is a supersaturated solution of many substances. Many of these are practically insoluble in water, but their solubility is furthered by the presence of hydrotropic substances. Hippuric, mandelic, and salicylic acids and urea possess this property.

Joly, cited by Bumpus (14), has held that the derangement of the colloidal mechanism by which stone-forming salts are normally kept in solution may be due to vitamin deficiency. He maintained that the urinary colloids are derived from the renal epithelium and any change in the renal epithelium will alter the colloid content of the urine. Such a change is known to occur in the presence of vitamin A deficiency.

When the urine is persistently alkaline, as in vitamin A deficiency, it is plausible to assume, according to Higgins (36) that the protective mechanism of the colloids is disturbed sufficiently to cause calculus formation.

A further refinement of the colloid theory was mentioned by Roche (71). He states that the urinary salts are held in solution by the stable colloids, chondroitin, and nucleic acids aided by hippuric acid, the calcium salts being especially rendered more soluble. These stable colloids also aid in keeping the labile colloids, fibrinogen, and mucin in solution.

Certain drugs, such as sodium benzoate, sodium salicylate and mandelic acid aid the stable colloids in restoring the normal hydrotropic balance when it has been upset. In this respect, these drugs act like hippuric acid. Blaustein (10) also subscribes to the colloid theory as presented above.

Opinion has been expressed that when the labile colloids of the urine preponderate over the stable colloids, precipitation of the salts present in supersaturated solution would occur. According to Snapper, Bendien, and Polak (79), a study of the complicated colloid frame which exists in every kidney stone proves that the development of a renal calculus does not start with the formation of a crystalline precipitate. On the contrary, the central nucleus found in every kidney stone is formed by colloids. This nucleus consists usually of a minute mucin, sometimes a fibrinogen, particle and now and then a foreign body.

This organic nucleus is then incrustated by one of the less-soluble urine compounds. On this incrustated stone-nucleus a new colloid precipitate develops. This layer is incrustated again, and in this way the stone grows successively by precipitation of concentric colloid layers which are incrustated in due course.

In experiments on rats, the last-named authors concluded that their efforts to prevent the precipitation of colloids by adding large doses of substances capable of increasing the stability of the urinary colloids were successful. Thus, sodium benzoate added to the diet prevented calculus formation in rats fed large amounts of calcium carbonate. They made similar obser-

vations on salicylates and mandelates.

In 1929, Meyer, cited by Eisenstaedt (23), bluntly stated that urinary colloids have nothing to do with the precipitation of salts from urine or maintaining them in solution. The author described a series of ingenious experiments made by Hellstrom. In order to determine the effect of bacteria on the precipitation of urinary salts, he dialyzed the urine. He found that precipitation occurred more often within the sac containing colloid. When precipitation did occur in the outer urine, it was completely cleared by restoring the pH. In fact, the behavior of both ran exactly parallel with the pH.

Higgins (33), in prescribing a diet designed to prevent recurrence and to dissolve existing calculi, based his treatment on the pH of the urine of the patient. Lazarus and Rosenthal (49), state that the pH of the urine plays a greater role than do the protective colloids in that the higher the pH the more likely it is that the crystalloids will precipitate out.

Twinem (82), minimized the influence of the protective action of the colloids. He observed that if stone were simply a matter of general metabolism and the crystalloid-colloid balance, then one would expect a much greater proportion of bilaterality than the actual ten to fifteen percent.

Randall (70), in rejecting the colloid theory, stated that this fascinating supposition lacks two essentials of tangible fact and unquestioned truth. It answers the recognized action of colloids to hold in solution the crystalloids of the urine, and more, to hold them in supersaturated solution. All infections

and epithelial degeneration are disturbers of the colloid mass, yet every infection does not bring forth a stone. We see people with chronic phosphaturia, oxaluria and cystinuria who live for years with this deranged metabolic balance, yet fail to form stones. This theory does not produce the experimental proof of the origin of the stone.

Metabolic disturbances, such as hyperparathyroidism and cystinuria, are now recognized as the definite etiological factor of a certain small number of urinary calculi. These calculi are uniformly composed of calcium phosphate which salt does not form the majority of stones and are therefore only a small part of stone etiology.

Albright, Aub, and Bauer (1), who have pioneered in this subject of hyperparathyroidism as related to renal calculus, found calculi in twenty-three out of eighty-three cases of hyperparathyroidism. In this disease, the blood calcium rises to abnormally high levels, and there is therefore an abnormal excess of calcium being excreted by the kidneys. Analysis of these stones showed they were consistently composed of calcium phosphate.

According to Chute (18), hyperparathyroidism is the etiological factor in about three percent of cases of urinary calculi. Braasch, Griffin, and Osterberg, (13), stated that hyperparathyroidism associated with stone is less than 0.2 percent at the Mayo clinic. This figure differs considerably from that reported by Albright and Bloomberg (2). They found 66.6% of their hyperparathyroid patients had renal calculi. Fourteen of these patients were suspected of hyperparathyroidism only

because they had renal calculi. Barney and Mints (7) have shown that approximately seventy percent of patients with this disease have renal calculi. Flocks (27) demonstrated that in this disease the urinary calcium is increased and the phosphorus decreased. Schneider and Steenbock (76) observed formation of urinary calculi in rats fed on a low phosphorus diet.

Barr, Bulger, and Dixon (8) reported the frequent occurrence of calcium stones in cases of osteomalacia. While the exact mechanism for formation of urinary calculi in osteites deformans is undetermined, according to Goldstein and Abeshouse (28), they attribute the lithiasis to an impairment of renal function in addition to the disturbance of calcium metabolism.

The theory of parathyroid hyper-function is probably the most positive of any presented, according to Randall (70). He stated that the sixty-five to seventy percent occurrence of calculi in hyperparathyroid patients demands consideration. He wondered, however, how a disease of calcium-phosphorus imbalance could play a part in oxalate, urate, or uric acid calculi.

Cystinuria is a disease of the young, according to Hammer and Thompson (30), who found in a study of all reported cases that seventy-five percent of the patients were under twenty-one years of age. They estimated this disease to be familial in fifty percent of the cases. Lewis (51) studied the occurrence of cystinuria in healthy young men and women and found one cystinuric person in every 320. He found that the incidence of lithiasis associated with cystinuria was less than 2.5%. Lewis (50) was able to produce cystine concretions by



subcutaneous injections of cystine in rabbits. Braasch and Andrews (15) point out that cystine lithiasis is very frequently unilateral.

Within the last two years, some attempts were made to explain renal lithiasis on the basis of liver dysfunction. Ezickson and Morrison (25) believe that liver dysfunction associated with vitamin A deficiency is the underlying factor which causes renal tissue change which result in stone. Lassen (47), on the other hand, fails to find any significance in liver dysfunction from the point of view of renal lithiasis.

Of very recent discovery is the renal lithiasis resulting from sulfonamide therapy. It does not play an important part in the interpretation of etiology of renal calculi as undertaken in this thesis. It will therefore be treated in a brief manner.

Pepper and Horach (64) were the first to describe sulfathiazole crystalline concretions in the renal tubules in 1940. Gross, Cooper, and Scott suggested the term urolithiasis medicamentosa be used to describe this type of lithiasis. Knoll and Cooper (45) reported in 1940 that 128 cases of urinary complications of both known and unknown etiology had been recorded in the literature as being associated with sulfonamide therapy.

Lindner and Atcheson (53) and Antopal (5) reported that these calculi are radiolucent. Hughes, Sayen, and LaTowsky (37) found calculi composed of sulfadiazine. The urine in every case was of acid pH. Prien and Frondel (65) stated that sulfanilamide, sulfaphiazole, and sulfapyridine are excreted in the urine partly unchanged and partly acetylated. They estimated that

thirty to seventy percent of sulfanilamide, not more than thirty percent of sulfathiazole and an irregular amount of sulfapyridine are involved in the urinary sediment in urolithiasis medicamentosa.

Renal calculi were in existence long before the discovery of the sulfonamides. Sulfonamide calculi may appear in the kidneys of patients using the sulfonamides, but such calculi cannot and do not appear in those not using the drugs. The cause and effect are obvious; therefore, such lithiasis need not be considered here.

Until the past few years no one has demonstrated a possible point of attachment for a calculus in the kidney pelvis. Ulceration of the pelvic mucosa occurs in avitaminosis, but in all these experimentally produced calculi, infection was a constant companion. This fails to account for the occurrence of a primary calculus without any cultural or histological evidence of infection.

The evidence of a denuded area in the pelvis of the kidney which might serve as the cause for the precipitation of the colloidal "gel" and its included crystalloids, and as a site for their attachment until a visible calculus has been formed was not presented until 1936 when Randall (66) published his paper on the origin of renal calculi. Two years before his paper appeared he let fall a hint as to what was in his mind when, in a public discussion following presentation of a paper by Joly in 1934, Randall stated that it was his belief that primary papillary ulceration was the basic cause of renal calculi.

The problem started in 1932 with a careful analysis of 117 urinary calculi, thirty-four of which were renal calculi.

From this study it was found that eighty-one percent of the stones occurring in this geographic area contained calcium oxalate, and that this salt predominated in those stones which could be classified as primary calculi. The predominate occurrence of this salt could not be explained by previously presented theories, for most stones heretofore developed experimentally were alkaline stones.

This created in Randall's mind a restless investigative attitude. He reasoned in this way: a stone is formed by salts in the urine. These salts exist in a supersaturated state. A stone will grow on any foreign body or foreign tissue. Stone must be a gradual accretion of crystals demanding a nidus for the seeding of such crystallization. Stone requires time to grow. Therefore it must be fixed in its beginning in order to gain clinical size. Thinking in this vein, Randall (70) formed the first postulate in his theory as to the origin of stone:

There must be an initiating lesion that precedes the formation of a renal calculus.

Now the question occurred to him, where? The pelvis and calyces have a simple epithelial lining, their resistance is high, their anatomy and physiology simple. The renal papilla, on the other hand, performs a complicated function, is open to multiple physiological variations and known to suffer recognized insults that lead to pathological changes. Thus the second postulate was formed:

The initiating lesion was to be looked for on the renal papilla.

Upon such a lesion, stated Randall (66), crystallization of a primary renal calculus first takes place, and its chemical

nature depends upon the salt in the urine which at that epoch is the most supersaturated one.

At about this time, Lieberthal and Huth (52), presented their demonstration of microscopic papillary lesions occurring in tuberculosis. Such a lesion would be an ideal spot for a stone to grow. From December 1935 to December 1937, Randall (70) studied 429 pairs of kidneys at the autopsy table. Seventeen percent showed hitherto unrecognized papillary lesions, consisting of deposition of calcium in the walls and intertubular spaces of the renal papillae. Twenty-eight calculi were observed growing upon the papillae. He described these papillary lesions as "milk patches" in another paper in 1937 (67). They varied in size from the tiniest possible dot to three millimeters.

In 1940, Randall (68) published additional evidence for his theory. In 1154 autopsies, he found 19.6% showed macroscopic calcium salt deposits and 5.6% showed visible calculi adherent to the papillae.

Rosenow (73) and Anderson (4), following Randall's lead, found identical deposits in the kidney. Rosenow mentioned that Caulk (17) in 1912 reported a case in which there was dense sclerosis and incrustation with calcium phosphate of the entire tip of a renal papilla. Caulk did not suggest that this had anything to do with formation of renal stone. deIllyes described a case in which uric acid crystals were deposited in the collecting tubules causing blockage and damage and consequent calculus.

As to the cause of the papillary lesion, the field is now wide open.

Randall believes poor blood supply to the renal papilla causes aseptic necrosis, and calcium is deposited in the form of a plaque which, when erosion of the papillary mucous membrane occurs, forms a rough surface upon which urinary salts are deposited, and stone occurs. Parmenter (63) suggests that bacterial toxius may play a role by causing cloudy swelling and desquamation of the epithelium of the convaluted tubules thus favoring calcium deposition. It may be this process which occurred when Rosenow and Meisser injected streptococci from calculi into the teeth of healthy dogs and obtained calculi from their kidneys eventually.

Moore (58) suggested that excessive doses of alkali as in treatment of peptic ulcer might cause irritation of the papillae and cause exudation of fibrin. Erickson and Morrison (25) claim the underlying factor which causes these tissue changes is largely liver dysfunction.

Rosenow found bacteria adjacent to or near the region of calcification of the papillae in twenty-four cases out of thirty-seven. On the contrary, Campbell (16) states that the absence of infection has been repeatedly demonstrated by special staining and by absence of round-cell infiltration.

Randall's theory of the etiology of renal calculi is receiving world-wide attention. Opposition is at present scant, but it has already appeared and will doubtless increase in volume as further investigations are made. From Denmark in the past few months came a paper by Njohede and Lassen (44). These authors stated that on the basis of Randall's theory, it would be reasonable to expect occurrence of calculi to increase with

age. They found that occurrence increases only until forty years of age. Further, they would expect, on the basis of Randall's theory, to find recidivation after every lithotomy or after every spontaneous passage, since some part of the lesion is bound to remain.

CONCLUSION

Many years have passed, each one with the knowledge of the existence of calculi, and each one has contributed its paragraph to the story of renal calculi.

Within our time we have seen the greatest advance of the knowledge of stone etiology, but the end is not in sight.

After preparing this thesis, I am quite convinced by Randall that the renal papilla is the site of the origin of a renal calculus. And I should like to try to reply to the objection raised by Kjolhede and Lassen, namely, that recidivation should occur after every lithotomy or after every spontaneous passage since some part of the lesion is bound to remain, by suggesting that such a calculus may behave like a dried crust on a healing lesion of the skin, and that when the lesion has completely healed, the crust peels off.

Randall has convinced me that the papilla is the site of origin. No one has as yet explained fully the etiology of renal calculi. It appears to me that the etiology must be looked for not in the urinary tract proper but in the kidney parenchyma or perhaps even in the body elsewhere.

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