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# Uremia

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# UREMIA

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## Definition

The term uremia, as used in this paper, is the name applied to the symptom comples which is characterized by the pathological finding of kidney failure, laboratory findings of nitrogen retention and the presence in the blood serum of xanthoproteic substances, and clinically by pallor of the skin, headache, mental and muscular weakness, nausea and vomiting, emaciation and sometimes convulsions. This term has been loosely used and much abused. From reading the American medical literature classified under this heading, the impression is gathered that any comatose or convulsive condition which can not be diagnosed definitely as some other clinical entity is put under the category of uremia. Blackfan (10) and Pollitzer (67) used the term to denote a convulsive state due primarily to brain edema and which may or may not be associated with kidney insufficiency. Alexander (1) and Evans (25) cite as uremic cases in which no kidney pathology is present and were primarily cardiac. Fishberg (27) defines uremia as"the symptom comples resulting from the retention of urinary constituents in the organism".

Apparently, there is at present no really satisfactory definition of the term uremia. Until such a definition can be coined and accepted by the medical profession as a whole or at least by those who chose to write on the subject, the present condition of chaos and misunderstanding will continue.

It is not the purpose of this paper to put the above definition forth as perfect or final; the definition is set forth in view of the later developments and work done in this particular field, a field which, apparently, is just being opened up and in which there is much work yet to be done. Uremia is terminal in about 7 per cent of the cases of benign hypertension, the majority of cases of malignant hypertension and in a large number of patients suffering from chronic renal diseases (27). A thorough understanding of the condition would enable those people so afflicted to live a longer, happier and more useful life. It is to be hoped that future research will give the medical profession that understanding.

## Physiology

The kidney is a tubular gland (69) whose chief functions are to regulate the salt and water balance in the blood, to aid in the maintenance of a constant pH of the blood, to excrete the end products of nitrogen metabolism, the threshold substances and excessive quantities of non-threshold substances and possibly living bacteria (57).

The structural units of the kidney are Bowman's capsule which is essentially a hollow sphere of delicate epithelium invaginated on one side by an intertwining tuft of capillaries, and a long tubule 1 to 3 cm. in length curled up in part of its course and closed at one end by Bowman's capsule and entering the collecting tubule at the other end (84). The epithelium of this tubule is roughly cuboidal or cylindrical (50). These two units, the capsule and the tubule, are known collectively as the nephron.

The blood supply of the kidney is derived from the renal artery by way of the pelvis. Arteries radiate to the cortex to divide into branches each of which becomes an afferent artery to a capsule and divides into a glomerular tuft. The efferent vessel leading from the tuft is smaller than the afferent vessel leading to it (84), so that the blood in the glomeruli has a slow velocity, high pressure and large volume (50). The efferent vessel, after leaving the capsule, runs but a short distance before redividing into another capillary net to surround

the tubules (41,84) where the blood pressure is relatively low (84). As both afferent and efferent vessels are under vaso-motor control, the capillary pressure of the capsule and that around the tubules may be regulated (50,84).

Richards and his co-workers (69) noted microscopically that in frog kidney not all of the glomeruli functioned all of the time and that often not all of the same glomerulus functioned all of the time. Experimental diuresis caused a larger part to become active. That such a thing occurs in mammals is to be inferred from the fact that dyes injected intravenously into rabbits are unequally distributed through the kidneys (84). Also, it is common knowledge that three-fourths of the kidney tissue may be destroyed without interfering with the normal kidney function (57). Some authorities claim that as little as one-seventh of the kidney tissue is functional at one time (22).

While claims have been made of the demonstration of non-medullated nerve fibres to the kidney tubules, the only proven nerve supply is from nerves of the sympathetic system which end on the blood vessels (41,84).

The process of urinary secretion is still in doubt. Bowman's theory advanced in 1842 and supported by Heidenhain in 1874 maintained that salt and water were filtered through the glomeruli while organic substances were secreted by the cells of the convoluted tubules. Ludwig

in 1844 claimed that all constituents of the urine were filtered from the plasma at the glomeruli and concentrated by absorption of water in the tubules (50,84). Much evidence for both theories has been advanced, but it was not until Cushney's monograph appeared in 1917 that the modern conception of urinary secretion was formulated. This theory, briefly, is that a process of ultrafiltration takes place in the glomeruli in which the filtrate is protein-free and is of the same molecular concentration as the blood and has the same amount of electrolytes. Then, in the tubules, the fluid is concentrated and certain substances are reabsorbed. Rehberg (69) has since, on the basis of experimental work, modified this theory somewhat, dividing the action of the kidney in the formation of urine into five parts: the formation of ultrafiltrates, the active reabsorption of water, the active resorption of threshold substances such as sugar and chlorides, the passive back-diffusion of all other substances in degrees varying according to the permeabilities of the tubule walls for each, with creatinine at one end as the most highly concentrated and alcohol at the other end as a substance which is not concentrated at all, and the secretion of substances not preformed in the blood. That such selective filtration should occur would require that a filtration rate of 120 to 180 cc. per minute or a total daily secretion of about

250 liters. Rehberg, after experimenting with creatinine, estimated that such a large amount of secretion was possible. Vimtrup calculated the number of glomeruli to be about one million and their total surface area to be about 1.5 square meters, an area sufficient, with the rich blood supply of the kidney and the filtration pressure on the capillaries, to account for the filtration (84).

Richard's work (69) on the frog kidney showed that the glomerular filtrate contained no colloids, was protein-free and had the same molecular concentration and contained the same amounts and kinds of electrolytes as did the blood. After passing through the tubules, he noted that the filtrate was concentrated many times over, that certain substances such as sugar and various salts were absent or decreased in amount and that certain other substances such as urea and creatinine were present in much greater concentration than in the capsules (84). While these findings cannot be transferred unquestionably to man, various experiments have been performed by Rehberg and others which tend to verify the physiology as found in the amphibian kidney.

## Abnormal Physiology

The kidney is the sole offender in cases of uremia and is the organ which sets off the chain of events which eventually leads to the symptom comples known by that name.

Accepting as true Cushney's theory of the excretion of urine, one is compelled to believe that kidney insufficiency such as results in uremia must be due to glomerular involvement. The possibility that the damaged tubules may reabsorb toxic products normally not returned to the blood stream must be considered (69), as some damage to the other functional elements will undoubtedly occur if one area is impaired in function. Certainly, one would not expect any pathological glomerular process severe enough to cause symptoms and yet in no way involve the tubules (54). When considering the abnormal or impaired function of the glomeruli, the fact that injury of renal function involves impairment of the ability of the kidney to excrete each and every urinary constituent must be considered (27).

The symptoms of uremia run in rather close parallel to the non-protein nitrogen concentration of the blood. While it is to be admitted that neither the urea nor the urea nitrogen of the blood is the cause of the uremic symptoms, the retention of these substances is, to a fair degree, an indication of kidney function. Although the

skin, lungs, gall bladder and bowel will attempt to eliminate these substances when their concentration in the blood becomes abnormally high, it is the kidney, by way of the glomeruli, which must remove these products. Any impairment of the ability of the glomeruli to carry on their normal function of filtration, if severe enough, will result in the retention of these products. This impairment of glomerular function may be brought about by any one or any combination of three mechanisms: by the reduction of the number of glomeruli and hence of the amount of glomerular surface, by changes such as thickening in the glomerular membrane, or by the reduction of filter pressure, either by reduction of blood pressure, increased osmotic pressure of increased intracapsular pressure (69).

Rehberg found a close relationship between the rate of filtration and the non-protein nitrogen content of the blood. As long as the filtration rate was more than 120 cc. per minute, he and his co-workers always found a blood urea concentration of less than 40 mgm. per cent, and serious urea retention did not occur until the filtration rate was decreased to about 60 cc. per minute (69).

In almost all cases of uremia the onset is marked by oligurea and by urine of low specific gravity which must be interpreted as an impairment of filtration by the glomeruli and reabsorption by the tubules.

## Etiology

Uremia occurs as the result of any of the manifold processes which cause renal decompensation. In considering the etiology of uremia, it is to be borne in mind that as long as one of the kidneys is functioning in a normal manner, with no obstruction of the urinary passage, uremic symptoms seldom develop. Upon removal of one kidney from active secretion of waste products the other, if normal, hypertrophies and takes over the function of the incapacitated organ. The promptness of occurrence of uremic symptoms may be dependent upon the amount of tissue destroyed (57). As stated previously, three-fourths of the renal tissue of dogs may be destroyed experimentally without the development of uremic manifestations. If the degenerative process develops slowly, an even greater amount may be destroyed (22). That tissue which remains hypertrophies and takes over the function of the incapacitated elements (57). In chronic renal disease, one often sees kidneys in which the glomeruli have largely disappeared, yet the patient has a history of a relatively normal life until, due to some sudden strain, the kidney has become decompensated and uremia has set in (27).

Renal pathology is the most common cause of uremia. Acute glomerulo-nephritis following angina, tonsillitis, measles, mumps, typhoid, influenza, and particularly scarlet fever, other streptococcus infections and wet and cold may lead to uremia (55).

Other acute nephropathies due to toxins or drugs may cause uremia, the severity of the symptoms being dependent on the amount of renal damage. The nephrosis resulting from chemicals is fortunately quite rare. When present, mercuric chloride is the most common offender (5). Lysoght and d'Abreu (17) report several cases of typical uremia with ulcerative colitis following the simple procedure of washing the bladder with oxycyanide of mercury. Other chemicals which can cause a similar picture are the uranium salts, chromium salts, arsenic, tartrates, phenol and the fluorides. An acute toxic nephrosis which develops in the course of severe toxemias such as peritonitis, jaundice, empyema, septicemias, toxic gangrene, pneumonias and malaria may give symptoms closely resembling those of the acute chemical variety (5).

Kaufmann (54) cites the kidney of eclampsia gravidorum with total cortical necrosis asbeing of unknown etiology, but it may be due to unidentified toxins.

Supperative processes of the kidney, septic kidney (4) and multiple abscesses of the kidney (47) have been reported, as have cases of sufficient multiple infarcts from bacterial endocarditis, to destroy enough kidney tissue to result in renal insufficiency and lead to uremia (27).

The chronic nephridities with nitrogen retention often result in a uremic death. Chronic glomerulonephritis most commonly leads to death by way of the uremic route as does malignant hypertension with renal

damage. Uremia is an uncommon termination of the amyloid contracted kidney or in the nephrotic contracted kidney (79).

Failure of excretion of urine may also be due to failure of the blood supply of the kidney. Obstruction of the blood supply may be either venous or arterial. Venous obstruction results in a passive congestion of the kidney with oliguria or anuria and retention of urinary products. Any condition such as pregnancy or other tumor masses which results in increased intra-abdominal pressure may occlude the renal vein. Thrombi, either blood or tumor, may occlude this vein, inhibiting return circulation, as may retrograde thrombi and emboli. Amyloid desease of the kidney with disturbance in kidney circulation has been known to cause obstructive emboli. An obstruction of the vena cava above the entrance of the renal veins may result in a similar condition (53).

Obstruction of the renal artery results in an anemia of the kidney with oliguria or anuria. As in the case of the renal vein, emboli or thrombi may occlude this blood vessel. Emboli from atheromatous plaques in the artery, erysipelis or from any other cause not infrequently lodge in the kidney (53).

Foord and Randall (28) report a rare form of renal insufficiency with multiple myelomatosis in which there was blockage of the glomerular capillaries by protein and by clumps of erythrocytes.

Uremia resulting from blockage of the urinary pass-

ages is not uncommon, and if diagnosed early can, in many cases, be treated with spectacular results. These obstructions cause back pressure on the kidney and decreased urinary output. The reported causes of obstruction are numerous and may be divided according to the location of the pathology.

Obstruction of the kidney tubules themselves due to hemoglobin casts following the administration of quinine with resultant hemoglobinuria has been reported. The case in question had a blood urea nitrogen of 344 mgm. per cent and creatinine of 16.2 mgm. per cent and terminated fatally (76). Death from black water fever early in the disease is due to this mechanism. Lipoid nephrosis is reported to result in the sloughing of the tubal endothelium with occlusion of the tubules. This condition is said to result in some cases from the use of morphine in susceptible individuals (86).

Obstruction of the ureters may lead to a condition closely resembling tubule blockage. The mechanics of both conditions are the same, back pressure resulting in decreased urinary excretion and pressure atrophy (57). Reaboff (71) lists a number of causes which he has found reported in the literature. Stones, either of the pelvis or ureter with resultant development of hydronephrosis, oliguria and uremia were reported, as was reflex anuria due to stones (36). Valves of the ureter sometimes develop,

inhibiting urinary excretion. Kinks in the ureters and reduplication are known to impair the passage of urine, as are abnormal insertion and renal ectopy. Cysts within the ureter are rare but have been reported. Accumulation of debris from renal necrosis may block the ureter, but in such a case it would be difficult, especially if a large part of the kidneys was destroyed, to tell whether the symptoms were due to ureteral blockage or to kidney necrosis. Pus plugs from suppurative nephritis, infected hydronephrosis or pyonephrosis or structures associated with renal tuberculosis have been demonstrated as etiological agents. Following trauma, the ureters have become obstructed by blood clots. Congenital stricture at the uretero-vesicular junction or occlusion by papillomata at the same location have resulted in uremia.

An entirely too common surgical accident resulting in anuria is legation of the ureters. Recurrent cancer, particularly of the fundus of the uterus, has caused anuria for variable periods of time. Aberrant blood vessels which cause pressure and blockage of the ureters, inflammatory masses of which appencial abscesses or acute seminal vesiculitis are probably the most common and also peri-ureteral sclerotic bands have been reported as etiological agents in uremia.

Neoplasms and stones of the bladder and cord bladder may act mechanically to cause back pressure, suppressing

urinary secretion. A retroverted uterus with the cervix pressing up on the neck of the bladder of a female may act the same as an enlarged prostate in a male, causing urinary retention and uremia (71). The prostate may be enlarged by benign hypertrophy, malignancy, chronic inflammation or abscess and thus be a cause of uremia.

There are about seventy cases of valves of the prostate urethra with symptoms of chronic renal insufficiency reported (87). Urethral stricture following infection, particularly gonococcal infection, is rather common. Congenital phemosis may rarely cause enough obstruction to give rise to uremic symptoms (71).

Other rather uncommon causes of chronic renal insufficiency are syphilitic sclerosis of the kidney and congenital cysts of the kidney (71). The kidneys of the patient with uremia due to aneurysm of the abdominal aorta reported by James (52).showed chronic interstitial changes and atrophy due to pressure. These kidneys had a decreased blood supply, also, as the renal arteries would barely admit the end of a small probe. Parathyroid disease has been reported by Bollin and Gershwin (7) as causing chronic kidney damage. The highest blood urea concentration in this case was 120 mgm. per cent, and this value dropped to 80 mgm. per cent following removal of the parathyroid tumor and remained at that level, probably indicating permanent renal damage.

The cases reported as uremic due to the etiological agents listed above did not have, in most cases, the acid test of the xanthoproteic reaction run on them; therefore they cannot be definitely called uremic in the most limited sense of the word. However, it is probable that at least a large percentage of them would have, under the most careful clinical and laboratory methods, been classified as truly uremic.

## Pathogenesis

Uremia is due to the retention of products normally excreted by the kidney and passed down the urinary tract and out of the body. Therefore, the symptoms must be due to the presence of one or more of the substances normally secreted by the kidney. The first substance to receive credit or blame for uremic symptoms was urea. In 1821, Provost and Dumas noticed an increased urea concentration in the blood of dogs following bilateral nephrectomy (57). Bright and his associates, Prout, Christeson and Babbington, noted an increase in the blood urea concentration of patients suffering from the disease bearing Bright's name (14). These men believed urea to be a powerful toxin and to it attributed the symptoms of the disease (30). Von Wilson, however, was probably the first to describe nitrogen retention and the uremic syndrome, which he attributed to urinary retention or to the chemical action of urea in the blood stream (58,71). As early as 1822 Vauquelin and Segal (58) injected urea intravenously into animals with no demonstrable toxic results. However, it was not until the work of Opler (33) under the direction of Hoppe-Seyler that the toxicity of urea was seriously doubted. Since then much work has been done with various substances, including urea, in an effort to determine the substance or substances causing the observed effects.

Hammond in 1888 interfered with the kidneys while injecting urea and got fatal results. Grehard and Quenquard in 1884 determined that urea may be fatal for dogs but that a blood urea concentration of 600 mgm. per cent was required before lethal results were obtained (46). Reiter and Wakeman killed dogs by injecting intravenously amounts of urea equal to one percent of the body weight. Leiter (58), by injecting an amount equal to 1.1 per cent of the body weight, induced in dogs a train of symptoms which he believed were entirely analogous to those found in convulsive uremia of man. On the basis of his work, he believed that convulsions and coma in the course of uremia were due to urea as such.

Hewlett and his coworkers (46) each ingested 100 to 125 gm. amounts of urea in an effort to determine the effect of this substance upon a normal human being. They noted the effects, their severity and the corresponding blood urea level. They found that the symptoms were most severe at the time when the blood urea level was highest. During the experiment they first noted nausea without vomiting, a symptom which disappeared before the development of maximum blood urea concentration and which might well have been due to gastric irritation by the large amounts of ingested substance. Diarrhea was noted in some but not all cases. Then,progressively, headache of a dull aching variety, dizziness, apathy,

drowsiness and finally an inability to do the customary work were noted. There was no increase in arterial tension during the experiment. From his observations he noted that symptoms were seldom present when the blood urea concentration was less than 100 mgm. per cent and seldom absent when the concentration was greater than 200 mgm. per cent, and that one gram of excess nitrogen raised the blood urea concentration about 2.5 mgm. per cent.

While some of these experiments would seem to point to urea as the etiological agent in uremia, there is clinical and biological evidence to the contrary. The elasmobranch fishes have a normal non-protein nitrogen concentration of something over 800 mgm. per cent (74). Dunnill (21) reports a case of a patient who, with a blood urea concentration of 350 mgm. per cent had a quite normal existence, although she was not as active as she was previous to her partial kidney decompensation. Administration of urea to patients suffering from Bright's disease does not seem to intensify the symptoms. However, the experimental feeding of chlorides and urea to uremic rabbits shortened their lives (79).

Whole urine has been held as the etiological agent of uremia. Dogs with veno-ureteral fistula died more rapidly than those with bilateral nephrectomy despite the normal function of the other kidney. If hydronephrosis of the anastomosed kidney was induced previously, jaundice

and acidosis appeared. The blood of such animals shows an increased non-protein nitrogen content and a strong xanthoproteic reaction before death. However, while Volhard (79) says that this phenomenon is hard to explain, he does not believe that the death is truly uremic, in spite of the increased non-protein nitrogen and strong xanthoproteic reaction of the blood serum.

Harlweck and Kerger (79) found that normal urine was not toxic to the isolated frog heart. In fact, they found it to be less toxic than physiological saline. What effect the urine had upon these hearts they attributed to an altered ratio of potassium to calcium. However, Bouchard is reported to have found that the blood of normal persons was more toxic to normal animals than was that of convulsive uremic patients, and Herter is reported to have later claimed to have verified this observation (32). Such a finding would lead one to suspect that there is retained in the uremic individual a substance or substances which is severely toxic and which is normally not present in sufficient amounts to cause symptoms. Working from such a hypothesis, Foster (32) calculated that if such a substance existed there should be sufficient of it in 200 cc. of the blood of a convulsive patient to kill a guinea pig. From such an amount of blood he was able, by a complicated chemical procedure, to extract a salt which, when injected into a

guinea pig, caused progressively dyspnea, twitchings or generalized convulsions, coma, and finally death within a short time after administration. Autopsy showed nothing but hyperemia of the kidney and brain. His controls showed no symptoms. Apparently no one has since confirmed or disproven this finding.

Hartman (45), just previous to Foster's work, announced the isolation of a yellowish oil with an empirical formula of $C_6H_8O$ which he thought might be a contributory factor in uremia. The symptoms produced by this substance were progressively nausea, headache, anorexia, twitchings, irritability of temper, mental dullness, and convulsions followed by a state of non-irritability. As in the case of Foster's work, there is apparently no confirmation or repudiation of this claim in subsequent literature.

Various other theories as to the etiological agents of uremia have been advanced. An increased creatin and creatinine concentration was found in uremic blood by Schatten in 1853 and by Jaccoud in 1867. Landois in 1891 produced convulsions in animals by direct application of creatin to the cortex. However, creatinine and the salts of creatin were revealed to be non-toxic by Feltz and Ritter (40).

Potassium chloride as a possible cause of uremia was championed by Feltz and Ritter in 1881 and by Limbeck in 1898 (58). Since this substance is highly toxic for

for animals, these workers believed it might well be the cause of the toxic symptoms of uremia. Bouchard injected urine into the blood stream of animals and got toxic symptoms which he attributed to the potassium salts. Herrington claimed a relationship between the toxicity of the urine and its potassium salt concentration (40). However, if potassium was present in sufficient concentration to cause toxic symptoms, one would expect to find an abnormal cardiac picture, a finding which is by no means constant (58).

Traube in 1860 advanced the theory of brain edema as the cause of uremic symptoms, but with inconstant clinical and anatomical findings the theory did not find general acceptance (58).

The blood of uremic patients with chronic nephritis was found by Straus in 1902 to have a depressed freezing point due to retention of organic molecules, a finding verified by Lindman (14,58). These men believed the symptoms were due to overcrowding of the blood with these organic molecules. Von Korange and Lindeman correlated the symptoms of uremia with a change in the osmotic pressure of the blood. However, this change is probably due to accumulation of easily diffusable urea and is of little significance other than relative to the injury caused to the ganglion cells by the increased molecular

concentration (79).

The action of ferments on urea in the blood stream with change to ammonium carbonate was blamed for the uremic symptoms by Frericks in 1851. Treitz considered the same change in the intestine as the etiological agent, but the discovery that the ammonium content of uremic blood was negligible brought a rather abrupt end to these theories (58).

In 1889 Brown-Sequard came forth with the theory that the kidney was an organ of internal secretion and that the lack of this secretion was the cause of uremia (58). In support of this theory, he states that animals with the ureters tied lived longer than those with the kidneys removed and that the injection of kidney extract prolonged the life of completely nephrectomized animals (40).

The theory of nephrolysins was advanced by Ascoli in 1903 and for a time it seemed to offer a satisfactory explanation of the observed phenomena. In 1909 Garrod (40) still considered the theory seriously. However, Pearce and Sawyer discredited the theories of both nephrolysins and of the kidney as an organ of internal secretion (58).

Senator was the first man to advance the theory of acidosis as the cause of uremic symptoms (31), and his theory has received the support of numerous other in-

vestigators. Jahsch in 1902 found decreased alkalinity in the blood or uremic patients. Straub and Schleger believed acidosis an important etiological factor, while Fischer in 1916 went so far as to call acidosis the cause of nephritis (58). McGavack, however, claims that in many cases there is no acidosis since failure of the kidney to excrete acids is compensated for by the acids leaving the body in the profuse vomitus of the uremic patients (62).

A low carbon dioxide combining power is a common finding among uremic symptoms. According to Volhard (79), there are three theories as to the etiology of this acidosis. In the first theory it is considered that the kidney may be unable to form ammonia. If this were the cause of the acidosis, one would expect relief from the use of a basic diet, but such a diet is without beneficial effect. Even after the administration of large amounts of alkali the acidosis recurs. A second theory is that retention of inorganic acid valences consequent to renal insufficiency with the result that a preponderance of the acid secretion exists. With this there may be a breakdown of the base preservation due to insufficient function of the kidney tubules. The third theory is that abnormal production and retention of organic acids may result in an increase in the undetermined fraction of the acid side of the plasma, a condition usually ob-

served in severe renal insufficiency.

A likely theory which has recently been brought forth by Becker and considered by Volhard (79) and Fishberg(27) concerns the products of intestinal putrefaction. Volhard states that he has seen no true uremia without elevation of the phenol values of the blood serum and a strong xanthoproteic reaction. The exact nature of these xanthoproteic substances is not known, but they are thought to result in free form due to the failure of the intestinal wall or liver to detoxify them as happens in a normal individual. These substances may be present in the blood in considerable concentration without the development of uremic symptoms, but, when the concentration becomes sufficiently great, they may pass through into the cerebrospinal fluid, at which time clinical uremia appears. The period of increasing concentration of these substances might well correspond with the so-called latent period between the beginning of impaired urinary excretion and the occurrence of uremia. While this theory of the pathogenesis of uremia is still highly theoretical, future research along this line may be very enlightening.

From the preceding discussion of the pathogenesis of uremia, it may be seen that opinion on the subject is by no means uniform. It may well be that the symptoms of uremia are due to a combination of the effects of

several of the various substances which have been discussed and that the condition of uremia is a disturbance of the whole organism rather than of the urinary system alone. Future work on this subject should clarify the present indefinite picture of the pathogenic phases of uremia.

## Signs and Symptoms

The signs and symptoms of uremia are somewhat dependent upon the different etiological factors involved. In all uremia there is a preceding latent period from the onset of renal insufficiency to the onset of symptoms (27). Dependent upon the cause, this latent period may be a matter of only days, during which the patient shows no marked symptoms of his renal insufficiency. On the other hand, cases in which the accumulation of products is slow, as in slowly developing renal insufficiency due to chronic nephritis, the latent period may extend over a period of months or even years. In such cases, it may be that the tissues themselves develop during the latent period a certain immunity to the retained toxins.

The onset of uremic symptoms is variable (57). Headache may be the first complaint of the patient, who, up to that time, may have had no idea that he was not in the best of health (29,71). This is one of the most common symptoms and may be of varying location and character (40). It is usually a dull headache and not violent, although it may be very severe at times. The symptom is by no means a constant one (79) and is often the result of hypertension or arteriosclerosis rather than of true uremic origin (27).

Patients suffering from uremia are usually very emaciated (72). This emaciation may be so marked as to

cause confusion with malignancy or other chronic wasting diseases, or it may be masked by the edema quite frequently found with renal insufficiency. The cause of the emaciation is not definitely known. Experimentally, removal of three-fourths of the kidney tissue results in an increased protein destruction which could account for at least a share of the emaciation. However, this increased protein destruction is not reflected in the basal metabolic rate of the patients, for the rate of body metabolism is not usually increased (27). Uremic patients show a marked anorexia (71,79), a rather common sign of the disease which could account for at least part of the emaciation. This dislike for food may be so severe that the mere sight of the same is sufficient to start nausea and vomiting. Meat is usually the food which is most avoided, but others may cause the same reaction. Even when food is taken, it may be promptly vomited.

Uremic patients frequently have a peculiar yellowish-brown tint to the skin (27,51,72) which is thought to be due to the presence of urochromogen in the blood (27). This urochromogen is normally oxidized to give the characteristic yellow color to the urine. In uremic patients it is believed to be retained by the kidneys in such quantities that is is deposited in the skin in sufficient amounts that, when oxidized, it gives the skin a yellowish-brown color (79).

Itching of the skin is another symptom which may become quite severe and be very resistant to treatment (71). It is thought to result from retained toxins of unknown identity. Rarely one sees uremic frost or the deposition of urea crystals on the skin. This would seem to be an attempt at vicarious elimination. Approximately 16 per cent of the uremic patients develop some type of a skin erruption. This erruption may be vesicular, papular, pemphygoid or purperal (27).

Pouches often form under the eyes of patients whose kidneys have decompensated.. These pouches would seem to be a type of local edema in the loose areolar tissue present at this location (6).

A rather characteristic odor variously described as fish (72), ammoniacal (27) or urinary (79) may be present on the breath. This may also be an attempt at vicarious elimination. The salivary secretions do show an increased non-protein nitrogen content which corresponds to the increased non-protein nitrogen of the blood of these patients. Microorganisms capable of breaking down urea to ammonia have been cultured from the mouths of uremic patients and it may be that the odor is due to the activity of these organisms.

Obstipation alternating with intractable diarrhea is frequently seen in uremia. The diarrhea is thought to be but another means of vicarious elimination of

retained metabolic products. It was probably upon this basis that the old clinical aphorism developed that uremic diarrhea should never be stopped (71).

The muscular twitchings and hyperactive reflexes so common in uremic conditions (79) are due to decreased calcium in the circulating blood (27,43,62,65). This decreased calcium is thought by Marriolt and Howland (58) to be secondary to an increased inorganic blood phosphorous. The reflexes, while hyperactive (79), are otherwise normal, and any abnormal reflexes indicate the development of complications (27).

While Bright included convulsions as the chief symptom of the uremic syndrome (33), it cannot in the present concept of the condition be considered common. Volhard (79) and LeComte (57) believed that they almost never occur. Fishberg (27) maintained that they are infrequent and that when they do occur they are in short attacks and occur terminally. He and Oppenheimer (65) found only two cases of eclampsia among fifty-one consecutive cases of chronic interstitial nephritis with renal insufficiency and nitrogen retention admitted to Mt. Sinai hospital. When the convulsions do occur, they are thought to be due to brain edema secondary to widespread peripheral vaso-constriction (65), although they may be due to toxins. The increased blood pressure which is usually present coincided with increased brain edema

and cerebral symptoms (10,65).

Other symptoms quite often found are dryness and burning of the mouth with dry, glazed mucous membrane which later may become covered with a thick, foul brownish or greenish coating. Ulcerative or gangrenous stomatitis may develop as may bleeding of the gums with loosening of the teeth (79). Excessive salivation with high non-protein nitrogen content is not uncommon. Extremely fetid breath is almost the rule. The larynx and hypopharynx have been observed in several cases to be covered by a grayish membrane removable with difficulty. The stomach may be the site of catarrhal gastritis. The non-protein nitrogen content of the gastric juices is as high or higher than that of the blood (27).

The gut shows changes from slight hyperemia to severe necrolizing and ulcerating lesions which rarely perforate (18,27,51,79). There seems to be no relationship between the severity of the lesions, the duration of the disease, the severity of urea retention or the gastrointestinal symptoms. Most commonly one finds at autopsy only swelling of the mucous membrane with superficial microscopic areas of necrosis. The submucoid vessels may be dilated and the mucosa may contain minute haemorrhages. Siegmund describes a pseudomelanotic pigmentation. In a minority of cases true ulcerative changes take place with the formation of pseudomembranes. There

may be dysentery-like changes with the contents of the gut being liquid and blood and having an offensive odor. Shreds of necrotic tissue may be present along with numerous bacteria. The cause of these lesions is questionable. Treitz thought at least the edematous lesions to be due to the action of ammonium carbonate formed from ammonia and carbonic acid resulting from the breakdown of the urea secreted into the intestinal tract by the intestinal glands. The ulceration and necrosis found so frequently may be due to the same substances, but they are probably due to haemorrhage into the submucosa which devitalizes the overlying tissue, predisposing it to the attack of the numerous microorganisms present. The initial haemorrhage is believed to be due to the haemorrhagic diathesis usually present in uremic patients. The colon and lower ilium are the most frequent sites of these lesions, but other areas of the gastro-intestinal tract from the esophagus to the anus are not spared. The vagina is frequently the location of similar changes (51).

Dyspnea is frequently seen in uremia, especially in the terminal stages of the disease (79). Kussmauds breathing is said to be due to retention acidosis (27). Cheyne-Stokes respiration is thought to be due to anoxemia and possibly some toxic action on the respiratory center (84). While usually a terminal symptom, Fishberg (27) states that it may last for weeks. Paroxysmal

nocturnal dyspnea may occur as the result of hypertension (27) or as the result of acidosis (71). Diffuse bronchitis is a common finding. Broncho pneumonia or pulmonary edema are often terminal (27) and may be the cause of intermittent breathing (84).

Chronic uremia is, except in rare cases of amyloid contracted kidney, almost invariably associated with hypertension and cardiac enlargement in all directions (27). The high blood pressure is thought by Garrad (40) to be due to a foreign substance in the blood stream, and he considers it to be a favorable reaction which shows that the heart musculature is able to compensate for the wide-spread vaso constriction so common in uremia. However, the hypertension throws an added load on the heart and the retained toxins probably injure the heart musculature. Myocarditis is common and areas of calcification have been noted. The electrocardiogram often shows myocardial damage and abnormal rhythm. There may be transitory extra systoles, auricular fibrillation or gallop rhythm. However, pulsus alternans is the most common irregularity found (27). In the terminal stages of uremia the blood pressure often drops, and this decreases kidney efficiency. True cardiac failure is not infrequently the immediate cause of death in nephritic patients.

Aseptic inflammation of the pericardium is not infrequent in the terminal stages of uremia resulting from contracted kidneys. There is usually little fluid, but

at times considerable quantities of a serous or bloody effusion is present. Usually, the condition causes no discomfort, but at times some precardial pain and dyspnea may be noted. There is usually a pericardial friction rub which may become loud enough to be heard several inches from the chest wall (27,79).

Fishberg (27) attributes most of the variegated psychoses of the older writers to cerebral artereosclerosis or acute functional disturbances of the brain. However, he admits that there are times when psychoses may be uremic in origin. Disorientation and terminal delusions are not uncommon (71). Depressed states have been known to result in suicide (40,71). Truly uremic excited states doubtless do occur (61,79), but they are fortunately infrequent. Terminally, mental weakness is the rule (71,79), although some cases remain clear to the end (27). Irritability and inability to sleep (71), vertigo, hiccoughs and neuralgic pains, the latter being very unusual, have been noted (27), as have thirst, langor, and diurnal drowsiness (72).

Uremic patients not infrequently complain of impaired vision (57). In coma, mystagmus and constricted pupils are often seen (71,79). However, the pupils may be dilated. Albumenuric retinitis is often seen but is not truly uremic in origin (71).

The blood of uremic patients always shows an increased non-protein nitrogen (5,71,79). The creatinine

and creatin concentrations are also elevated (71). The calcium is frequently lowered and the inorganic phosphorous raised. The chlorides may be elevated but are usually lowered except in obstructive cases. The blood serum has a peculiar rather fecal odor which is characteristic of the disease (79). It has an increased phenol content and gives a positive xanthoproteic or diazo reaction (3,27,79). In chronic cases the hemoglobin determination is roughly inversely proportional to the non-protein nitrogen content of the blood (5). In acute cases, this is not the case, the hemoglobin usually being normal and the non-protein nitrogen raised.

Kidney function tests show decreased kidney activity. Of the various tests used, the urea clearance test is probably the most accurate in the determination of renal damage. This test may show only 50 per cent normal before the blood creatinine, blood urea without relation to urea secretion, or phenolsulphonephthalien tests show any abnormality. It may be down to 20 per cent before these three tests are outside of normal variations. However, when improvement has started following acute nephritis, the phenolsulphonephthalien test may show a rise several weeks previous to any rise in urea clearance (78).

The urine, if any, in uremia is variable. In any condition where the urine shows a specific gravity of 1.015 or less, a night volume of 750 cc. or more and low salt and nitrogen concentration and where the kidneys

show low function tests, as when the phenolsulphone-phthalien test is 75 per cent or less, uremia is to be watched for (26). Patients whose uremia is on a basis of kidney pathology have urine which is characteristic of the etiological condition. In most cases oliguria with decreased specific gravity marks the onset of renal decompensation. The urine of acute glomerulo nephritis is decreased in amount and shows albumen and erythrocytes (88). The urinary volume is decreased and even completely depressed due to blockage of the capillaries, capillary damage resulting in the excape of blood fluid as edema, cardiac insufficiency or dehydration from vomiting or fever. The hematuria may be microscopic or gross. Macroscopic hematurea usually lasts for only days or at the most weeks, while microscopic hematuria may last for months, even in cases where the process is not becoming chronic. The albumenuria is usually not severe; it is usually in the range of from 0.2 to 0.4 per cent, but it may exceed 2 per cent. Rarely, albumenuria may be entirely absent or present only intermittently. Casts of any kind are apt to be found. Leucocytes also are usually present.

The urine in amyloid nephrosis is, previous to the onset of insufficiency, of low specific gravity and large volume. Albumen is usually but not always present in large amounts (27). Both volume and albumen content

decrease as insufficiency sets in (88). Casts, when present, are for the most part hyaline, although waxy, granular and epithelial casts are sometimes seen in smaller numbers (27).

During the compensation stage of chronic glomerulo nephritis, the urine output may amount to 2 or 3 liters per day. With the onset of uremic symptoms, this output is markedly decreased. Early in the disease, albumen may be present in copious amounts, but is is usually present in small quantities or absent entirely late in the disease. Hematuria may be gross but is most likely, especially in the late stages, to be microscopic. All types of casts may be found (27).

The secondary contracted kidney excretes a urine closely analogous to that of the chronic glomerular nephritic kidney (88).

The urine in kidneys of the type resulting from hypertension is usually small in amount and of low specific gravity with little or no albumen present. There may or may not be a few erythrocytes which, if present, have no sifnificance. Casts may or may not be present, their presence generally paralleling the albumen content (88).

## Diagnosis

The diagnosis of uremia is usually made upon the history of kidney disease, the peculiar pallor of the skin, puffiness under the eyes, headache, mental and muscular weakness, somnolence, nausea and vomiting, diarrhea, dyspnea, emaciation and sometimes convulsions. The onset is usually insidious and accompanied by oliguria with low specific gravity of the urine. A uriniferous odor on the breath is usually noted. However, even the best clinician may be led astray if he does not verify his diagnosis by laboratory tests. The most important laboratory procedure in the determination of uremia is the xanthoproteic reaction. While it may be negative in the very early stages of the condition (3), a well-developed case with symptoms shows a positive reaction for both spinal fluid and blood. No condition may be termed true uremia without these reactions being positive. The kidney function tests such as urea clearance, phenolsulfonephthalien and glomerular filtration may be of great aid in diagnosing renal insufficiency. A non-protein nitrogen concentration in the blood of less than 100 mgm. per cent rules out uremia, but one of more than that amount does not necessarily mean that the patient suffers from kidney insufficiency. An elevated blood nitrogen may be found in case of great loss of body fluids and depletion of electrolytes by means of vomiting,

bowel or skin. This point of differentiation is very important and proper evaluation of the etiology isoften the means of saving a life. Experimentally, a decrease of chlorides in the blood results in an elevation of the non-protein nitrogen and a train of symptoms which are closely analogous to those seen in uremia, so closely analogous that the differentiation may be possible only by quantitatively determining the blood chlorides. The chloride content may have fallen from the customary 500 mgm. per cent to a value as low as 200 mgm. per cent. Also, in such cases, the xanthoproteic reaction of the blood and of the spinal fluid would be negative. The administration of sodium chloride solutions in large quantities yields spectacular results in these cases.

Heart failure, particularly essential hypertension, with failure of the kidney to secrete because of lowered blood pressure, may result in uremic symptoms, although the failure is not renal but rather cardiac. This type of death has been termed uremic by some authors (1,25), although the primary pathology is not renal but is cardiovascular. Another circulatory accident which brings on a marked increase in the non-protein nitrogen of the blood is coronary thrombosis (71),. The continued high specific gravity of the urine along with clinical findings and other laboratory tests should serve to differentiate this condition from true uremia.

Twenty-six cases of diabetic coma with non-protein

nitrogen concentrations in the blood of more than 100 mgm. per cent were reviewed by Holmes (56). These cases were treated routinely with insulin and came out of the coma only to slip back and die an apparently uremic death. Casts, red blood corpuscles, and white blood corpuscles were found in the urine, the specific gravity and output of whichwwere not recorded. Progressive albumenuria with coma and progressively increasing non-protein nitrogen concentrations in the blood of from 100 to 300 mgm. per cent were observed. Since there is shock with lowered blood pressure, the circulatory failure with resultant impaired renal function along with the fact that there is a depleted blood chloride content amy account for the abnormal increase in non-protein nitrogen. There was also considerable microscopic kidney damage, due presumably to the acids and ketone bodies. Apparently no xantho-proteic tests were run, either in this series of cases or in any other series of similar etiology. Such a symptom complex would tax the skill of any clinician in making the diagnosis and determining the treatment of such a case.

Other causes of coma which may be confused are alcohol, opium, gas poisoning, epilepsy, apoplexy, ~~or~~ meningitis, encephalitis, and abscess or tumors of the brain or brain injury.

## Prognosis

It is not always possible to give a prognosis in uremia with any degree of accuracy since the prognosis is that of the underlying cause, and symptoms that are terminal in uremia due to one cause are not terminal when the condition is due to some other cause. Pericarditis usually precedes death by about a month. However, Fishberg reported a case in which the patient lived a year after pericarditis had set in. Hiccoughs usually indicate that the end is not far off, as do deepening somnolence, truly uremic convulsions, periodic or acidotic breathing, intractable vomiting, stomatitis, evidence of gastro-intestinal ulcerations and fall of temperature. Secondary infections are borne poorly by these patients and are very apt to be terminal (27).

The laboratory can usually be of great aid in determining the outlook for uremic patients. A blood urea concentration of 250 mgm. per cent or more is usually fatal within a period of a few days or weeks (27,71), especially when associated with a urea clearance of 10 to 20 per cent in the kidney function test. A high blood nitrogen content is not as bad a prognosis in acute cases as it is in chronic cases, for the acute condition may resolve and the obstruction may, in some cases, be removed (22,71).

A low hemoglobin is a poor prognosis, especially in

chronic cases. However, a high hemoglobin is not always indicative of a good outlook (78). Severe acidosis also gives a bad prognosis (26,79). Increased thyroid function hastens metabolism and the accumulation of metabolic products and thus hastens the end (71).

The diazo reaction, not positive in early uremia, becomes strongly positive late in the disease and indicates a lethal termination of the condition. Volhard (79) believes Becker's xanthoproteic test is the most reliable index to prognosis available at the present time. He believes that the symptoms of uremia parallel the xanthoproteic reaction of the blood rather than the nitrogen of the blood.

Rehberg (84) found that by comparing the urea output with the glomerular filtration test and Volhard's concentration test he was able to accurately draw conclusions both as to prognosis and therapeutics.

## Treatment

The treatment of uremia may be conveniently divided into prophylactic treatment and the treatment of the uremic state.

In the treatment of acute glomerulo nephritis, the most important single measure is bed rest, which should be continued until all edema is gone, the blood pressure normal, the urinary output normal in amount and showing no red blood corpuscles. The diet in this stage is usually not important, especially in mild cases. In severe cases, it may be wise to reduce protein consumption, but this should not be continued for too long a period as the patient immediately starts using his own protein when the protein balance is negative. With severe edema, salt and fluids may need to be restricted (5). Aldrich, as reported by Hardy (42), recommends that fluids be forced on the theory that oliguria in such cases is due not to the breakdown of the kidneys but to the abnormal action of the tissue cells. He believes that the water, by diluting the toxins, lessens cell injury, thus permitting more water to be released from combination with the cells.

In cases of anuria, hypertonic solutions intravenously may lead to return to urinary excretion. For this purpose Bannick (5) recommends 500 cc. of 20 per cent dextrose or 350 cc. of 30 per cent dextrose or 400 to 500 cc. of 25 per cent sucrose. These solutions are

hydroscopic and may relieve kidney edema allowing the return to normal function of the organ. If this treatment is not successful, decapsulation of the kidneys may, in selected cases, result in renewed kidney activity (5, 71).

Foci of infection should be removed at the earliest possible time. In this country, it is the general practice to wait until a good clinical improvement has taken place. In many European countries the foci are removed during the active stage of the disease, if the operative risk is not too great.

While it is probable that few people die of true uremia during the process of acute nephritis, there is danger of the condition becoming chronic and eventually leading to a uremic death.

Chemical nephrosis is rare and seldom leads to true uremia unless the assimilation has been of very large quantity or has continued over a long period of time. Treatment of chemical poisoning is quite fruitless. The source of the chemical should be eliminated and every effort made to remove the toxic substance from the system of the patient. If large doses are swallowed and a sudden poisoning is feared, the gastro-intestinal tract should be as thoroughly washed as possible and the balance of the toxin neutralized with antidotes. Lately, sodium formaldehyde sulphoxylate has been recommended as an antidote for mercuric chloride. The oliguria is treated

as in acute glomerular nephritis (5).

The acute toxic nephroses are best treated by removing, if possible, the underlying etiological cause. During the period of oliguria, the salt and protein intake should be restricted. Diuresis should be attempted in the same manner as in acute glomerular nephritis. Since this condition is always secondary to some severe systemic disorder, this etiological disorder should receive the attending physician's utmost attention (5).

The chronic nephridities are the most common causes of the uremic syndrome and may develop insidiously or following acute nephritis which becomes chronic or which apparently heals and then turns up years later in the chronic stage. The treatment of chronic nephritis is not curative. Often, however, by proper care, the patient may be able to lead quite a long and useful existence. In general, the treatment of chronic nephritis is dependent upon whether or not there is nitrogen retention with or without edema or edema with or without nitrogen retention. Uremia is concerned only with those cases in which there is nitrogen retention. For the treatment of edema, the general rule is to employ diuretics and restrict salts and fluids. In the case of nitrogen retention, there should be no restriction of salts or fluids and no use of diuretics, but protein should be restricted. The only cases which ever lead to uremia are those concerned with nitrogen retention with

which edema may or may not be associated.

Chronic nephritis with nitrogen retention and without edema should have a restricted protein diet but not so much restricted that the patient utilizes his own tissue, that is has a negative nitrogen balance. McGavack (62) states that the high non-protein nitrogen of the blood may be lowered by striking a balance between nitrogen intake and excretion. A positive nitrogen balance is normal only during growth and during convalescence following tissue destruction. At any other time a greater intake than excretion means that there is nitrogen retention, that is, that the kidney is unable to excrete the proper amount of nitrogen which consequently accumulates in the various body tissues.

When decreasing the protein consumption in an effort to lower the retained nitrogen, one should always bear in mind the fact that it is easy to do far more harm than good by the stringent reduction. Permanent bodily injury more deleterious than that caused by the nephritis may result in earlier death than in the case of untreated patients. When cutting down protein consumption, the protein deficit must be replaced by protein saving foods. High carbohydrate, medium fat and low protein diets are used for this purpose. McElroy (61) recommends for this purpose the low protein, high carbohydrate diet of Chase, followed by a banana and cream diet. The effect of such a diet is dependent upon the rate of filtration of the

glomeruli. When filtration is so slow that even the products of minimal protein metabolism cannot be removed, even the lowest protein diet will, of course, result in nitrogen retention (69). However, when there is sufficient filtration, a compensatory polyuria will often prevent for a long period of time, even with retention of the products of protein metabolism, the symptoms of uremia (61). With this object in view, the water intake should be increased, care being taken to avoid kidney fatigue and cardiac decompensation. Diuretics are to be avoided because of kidney damage and danger of fatigue. In cases of anuria or oliguria, 1500 cc. of 20 per cent glucose for 2 days and 3000 cc. of Fischer's solution daily for the next 3 days has been recommended (71). Rehberg's creatinine concentration test will give a good idea as to the results that follow such treatment (69).

Voit's experiment in 1868 showed the value of an increased urinary output in cases of retention of metabolic products. He found that he could feed dogs large amounts of urea without injurious results if the dogs were given large amounts of water simultaneously. However, if water was withheld, vomiting, lethargy, and ataxia developed (33). Since the kidney is unable to concentrate the substances excreted normally, more urine must be excreted in order to carry off these products (30).

In the treatment of chronic nephritis with edema and without nitrogen retention the problem is more difficult.

The protein may be only moderately reduced since severe reduction would not only cause catabolism of the patient's tissue but might also cause a decrease of serum albumen with consequent increased edema. Salt should be rigidly restricted and the fluids moderately restricted except when the symptoms are severe. Salyrgan and other irritative diuretics are contra-indicated, as are the ammonia diuretics which are apt to produce nitrogen retention. Potassium nitrate is also contra-indicated when the non-protein nitrogen concentration is over 100 mgm. per cent, since a potassium retention is apt to occur and toxic symptoms result. Alkali and xanthine diuretics should be tried, but they are usually of no avail. 500 cc. of 25 per cent sucrose may give the desired diuretic effect. Transfusion may be tried for the anemia and azotemia (5).

The general condition of the patient must be watched in all nephritic cases. Increased weakness and cardiac decompensation may be the result of lowered protein consumption, in which case the protein in the diet must be raised. Other cardiac symptoms should be treated by strophanthines or digitalis. Surgery is contra-indicated for these patients, as it may bring about renal decompensation (27,83). Should surgery be imperative, Berri (9) recommends 500 cc. of isotonic dextrose solution during the operation, 400 cc. of 4 per cent sodium chloride intravenously after operation and 300 cc. of 4 per cent

sodium chloride intravenously 2 and 3 days following the operation if the chloride content of the blood and urine are not sufficiently high.

When uremic symptoms have once set in, they should occupy the physicians chief attention. Bed rest is obligate (7). The water consumption should not be limited unless the kidneys show fatigue or the heart shows signs of decompensation. Edema in this stage is not an indication for limitation of fluids as they probably dilute the toxins present (27).

The anorexia of these patients may be a very troublesome symptom. By this time, no definite benifit can be expected from a rigid limitation of protein (42), so a diet of the patient's liking should be given. Fantus (26), however, recommends even in the uremic stage a diet such as the Chase high carbohydrate,,low protein diet followed by the banana and cream diet for uremic acidosis.

If the patient is comatose, stuperous, severely dyspeptic or anoretic, the giving of a diet or of fluids by mouth may be difficult. When such a condition exists, 10 per cent glucose may be administered by proctoclysis or by stomach tube (61).

Opinion varies as to the use of diaphoresis as a means of ridding the body of toxins. Sweat contains usually from 60 to 200 mgm. per cent of non-protein nitrogen, but ordinarily only about 2 gm. of nitrogen daily can be removed by this means (27), a quantity which

would be of little value in this condition. Hardy (42) claims the procedure is contra-indicated as it adds to the patient's weakness and does no good. Fishberg,(27), however, says that the patients feel better after such treatment and that the procedure may be tried unless contra-indicated by weakness or cardiac conditions. In any case, the treatment should, he says, be discontinued if the patient becomes weak or uncomfortable. While giving the treatment, fluid lost should be replaced by hot drinks, possibly to avoid concentration of toxins which may be the cause of the aclamptic seizures which sometimes follow.

Venisection in chronic uremia has very few indications since the patients are already anemic and weakened (27). McElroy (61) has tried transfusion and plasmophoresis to combat the ill effects of blood letting with indifferent results. Fantus (26) does not recommend transfusion following venisection, while Reaboff (71) recommends the replacement of any blood withdrawn by transfusion. The effect of blood letting is largely to relieve embarrassment to an overburdened heart and may be life saving in sudden cardiac failure. The detoxifying effect is probably nil as the non-protein nitrogen concentration of the blood may actually raise due to the rushing into the blood stream of tissue fluids following venisection (27), the tissues having a non-protein nitrogen concentration much higher than that of the blood (35).

Constipation may be very severe when present. It should be combated in an effort to do away with intestinal putrefaction and the absorption of putrefactive products (27). Saline laxatives may be used and act not only as a cathartic but also as a means of elimination of urea (42). A condition of diarrhea should not be maintained as it tends to weaken the patient (26). To prevent the severe diarrhea often encountered in uremic patients, astringents or even opium should be used (42). Prolonged colonic irrigation with two or three gallons of 2 per cent sodium bicarbonate solution may be helpful (26). However, if the patient is not too debilitated, the diarrhea should be allowed to continue (57).

Persistent hiccough is usually a terminal symptom and therefore there is no reason for withholding morphine. However, some men like to try stimulating applications to the epigastrium such as fomentations of mustard leaves and such drugs as nitroglycerine, gr 1/100, liquid extract of ergot in dram doses and carminatives such as oil of turpentine mixture in capsules before trying such drastic measures (42).

Paroxysmal dyspnea or uremic asthma is most effectively treated with morphine, but, since it is sometimes thought to be a manifestation of acidosis, sodium bicarbonate, gr. LX, at 4 hour intervals may be tried, as may oxygen inhalations (42). Volhard and Decker (80) claim that this dyspnea may be due to absorption of

occult edema and recommend that the patient take no fluid after midday, sleep in a sitting position or have his legs treated for passive congestion.

Itching of the skin which sometimes becomes intolerable and breaks out into a true dermatitis is best treated by warm alkaline bath and sedation by such drugs as the bromides (42). Lumbar puncture may give relief (26).

The irritative nervous symptoms are most effectively handled by morphine, but chloral hydrate, gr. V-XV, with a bromide salt, gr. XV, orally, may be tried (42).

The persistent headache may be treated with aspirin, phenacetin, or other analgesic drugs. Intravenous one per cent magnesium sulphate, vena section, or lumbar puncture are helpful when the condition is associated with hypertension (22).

The uremia resulting from chronic renal disease is invariably fatal (83), therefore, the duty of the attending physician is to relieve the suffering and ease the death of the patient.

## Summary

1. Taking into consideration recent advances in the study of renal insufficiency, a definition of uremia is advanced.

2. The various theories of kidney function are discussed with special reference to Rehberg's modification of Cushney's theory.

3. Abnormal kidney functions which may lead to uremia are brifely reviewed.

4. The various substances and conditions to which the symptoms of uremia have been attributed are listed and their probable relationship to the uremic condition briefly evaluated.

5. The various causes which may lead to kidney decompensation and uremia are surveyed.

6. The more common signs and symptoms of the uremic state are discussed.

7. The absolute requisites for a diagnosis of uremia are listed and differential diagnosis touched upon very briefly.

8. Terminal and near-terminal symptoms of the uremic condition are discussed.

9. Treatment is divided into two sections: prophylactic treatment of conditions which may lead to uremia, and the treatment of the uremic condition after it develops.

## Conclusions

At the present time there is little agreement among American writers relative to the meaning of the term uremia. Definitions vary as do claims as to etiology and pathogenesis. However, the work of several of the later investigators seems to be drawing a semblance of uniformity from this previously chaotic field. Modern work in the field of intestinal putrefaction with absorption of these products by the blood stream seems to be a step in the right direction. This work has been noted only very recently in this country. Consequently but little in American medical literature has been written on the subject. The close correlation between the uremic symptoms and the concentration of these xanthoproteic substances in the blood stream and spinal fluid cannot be disregarded and the further study along this line may be fruitful.

Since it is thought that the free phenols and related products of intestinal putrefaction may be closely associated with the uremic syndrome, one naturally wonders why these products are not detoxified as they are in normal humans. Since the liver is the great detoxifying organ of the body, it is strange that this organ did not come up for consideration in uremia some time ago. However, it is no longer neglected as work as yet unpublished is being done along that line.

The studies made by Foster and by Hartman with specific toxic substances from the blood of uremic patients have apparently been neither confirmed nor denied. While the value of the isolation of a specific toxin as the cause of symptoms of uremia would probably be largely academic, it would at least be a point from which to work. However, the research which has been done up to the present time points more to a combination of causes than to any single cause.

Many prominent men consider as uremic conditions which are truly extra-renal in etiology but do have a train of symptoms closely analogous to true uremia. It is difficult to evaluate the relationship of these conditions to true uremia.

The signs and symptoms of uremia are quite uniform and rather characteristic. However, there are other conditions which have clinical symptoms so closely analogous to uremia that diagnosis is almost impossible without laboratory aids. For this purpose the non-protein nitrogen determination and the xanthoproteic reaction are most valuable.

Prophylactic treatment to prevent the occurrence of uremia should always be undertaken in threatening cases. When uremia has developed in chronic nephritis it is always terminal and treatment is symptomatic and paliative.

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