Should the patient survive two years or more the kidneys gradually assume the appearances that will be described under the heading, Secondary Chronic Interstitial Nephritis.

Pathological Histology.—Microscopically the lesions affect the glomeruli, the tubules, and the intertubular connective tissue (Fig. 3066). On account of the intensity of the lesions in the glomeruli the process has been spoken of as *chronic glomerular nephritis*. The

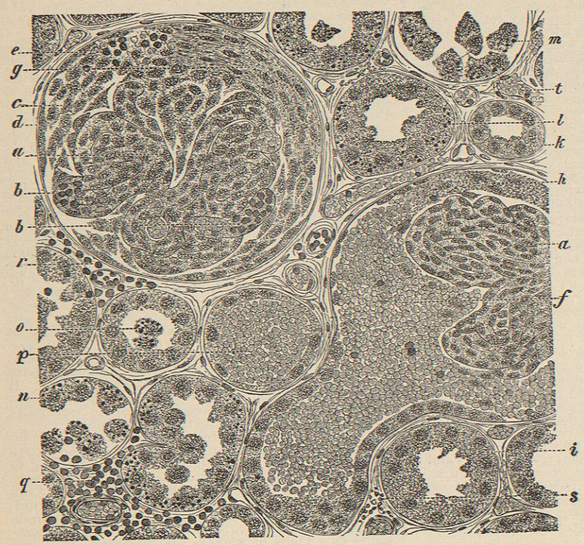

FIG. 3066.—Chronic Hemorrhagic Nephritis. *a*, Normal coil of capillaries; *b*, capillaries filled with leucocytes; *c*, desquamated glomerular epithelium; *d*, capsular epithelium; *e*, exudate consisting of leucocytes, erythrocytes, and granular material; *f*, hemorrhage in one of the capsular spaces and extending into the beginning of a uriniferous tubule; *g*, granular and lamellated exudate containing nuclei of the desquamated glomerular epithelium; *h*, disorganized blood enclosing desquamated glomerular epithelium; *i*, convoluted tubule; *k*, looped tubule; *l*, uriniferous tubule containing pigmented and fatty degenerated epithelium; *m*, pigmented epithelium desquamating; *n*, fatty and in part desquamated cells; *o*, desquamated and fatty epithelium in the lumen of a normal uriniferous tubule; *p*, tubule filled with blood; *q*, perivenous, *r*, pericapsular, cellular exudate; *s*, pigment in the connective-tissue stroma; *t*, capillary filled with blood. × 300. (Ziegler.)

changes in the glomeruli, which vary much in intensity in different cases, in general resemble the changes found in acute nephritis, being both proliferative and degenerative in character. The proliferative changes involve the epithelium as well as the cells of the vascular tuft, and in consequence the cavity of the Malpighian body becomes more or less filled with an exudate similar to that present in acute nephritis. The degenerative changes consist of fatty and hyaline transformation of the epithelium and the endothelium of the capillaries. In consequence of these alterations the glomerulus usually is rendered completely functionless—a process that is accomplished also by the so-called adhesive glomerulitis, recently described by Engel. Amyloid degeneration of the vascular tuft also is quite common. The conspicuous lesion in the tubules is fatty degeneration, which involves especially the epithelium of the convoluted tubules, although the epithelium of the straight tubules is usually affected also. In addition, the other retrograde alterations mentioned in connection with acute nephritis are present to some extent. The lesions may be uniform throughout the kidney, but they are commonly focal in character. It is in consequence of the marked fatty degeneration of the epithelium and of the anæmia induced by the pressure exerted on the blood-vessels by the desquamated and degenerated cells and detritus in the obstructed tubules that the pale and fatty color of the kidney is brought about. The changes in the connective tissue do not differ essentially from those present in acute nephritis. In the one case there is considerable fatty degeneration and infiltration, in the other considerable hemorrhage; but both are present in varying degree in all cases, especially in the chronic hemorrhagic nephritis and in acute exacerbations of chronic nephritis. As the disease advances the cellular exudate becomes converted into newly formed fibrous connective tissue which by contracting leads to atrophy of the glomeruli and tubules. The earliest formation of such new fibrous connective tissue is usually about the capsule of Bowman. With increase in the formation of such fibrous connective tissue the appearances to be described under the heading, Secondary Chronic Interstitial Nephritis are brought about.

Symptoms.—In some cases, clinically as well as anatomically, chronic diffuse non-indurative nephritis develops out of acute nephritis, the symptoms of the acute disorder, especially pallor, dropsy, and albuminuria, persisting. In the majority of cases, however, the chronic disease develops insidiously. Commonly no date can be assigned as the time of the onset of the disease, and the symptoms at first scarcely suggest the renal lesion. Thus the patient may complain of indigestion with periodic attacks of nausea and vomiting, or of headache, or of pallor, or of weakness on slight exertion, or of gradual failure of health with loss of flesh, etc. Finally, swelling of the feet or ankles may attract his attention; or an observant patient may notice that his urine is cloudy and reduced in amount; or puffiness of the eyelids may suggest to the physician the wisdom of examining his patient's urine; or the albuminuria may be detected in an examination for life insurance, etc. As in acute nephritis, so in chronic nephritis, the characteristic signs consist of œdema and of changes in the urine. At first the œdema is slight and present in the seats of predilection of renal dropsy—in the eyelids, about the ankles, in the pretibial regions, in the hands, etc. Except about the eyelids, the œdema is often absent in the morning after a night's rest, and it develops or increases during the course of the day. In some cases it increases gradually until it becomes extreme; in other cases it suddenly becomes extreme. In either case it may be associated with effusions within the

serous cavities of the body; though it varies much in different cases and in the same case at different times, it is always obstinate; and, having disappeared, it is extremely likely to recur. In some cases œdema is absent—the chronic hemorrhagic Bright's disease without œdema, of Wagner.

The urine is reduced in amount and, as remarked, this may be the first symptom to attract attention. Usually the daily amount varies between 300 c.c. and 700 c.c.; only rarely and then during uræmic attacks, in acute exacerbations and shortly before death, is there such marked oliguria as frequently occurs in acute nephritis. With improvement in the condition of the patient, especially coincidentally with the absorption of marked dropsy (as well as with the advent of secondary chronic interstitial nephritis), the daily amount of urine increases and may reach two litres or more. In addition the urine is acid in reaction, though it soon becomes neutral or alkaline on standing; it is turbid and of increased specific gravity (1.018–1.025), though it is lower when large amounts are voided. It varies in color, depending largely upon the concentration and the amount of blood that it contains. It always contains a considerable amount of albumin—sometimes as much as one-half or three-fourths by bulk after the boiling-and-acid test, one per cent. to three per cent. by weight, or 15 to 30 gm. in the twenty-four hours. The amount excreted is usually greater during the day than at night. The excretion of urea and other solids is always deficient. On standing, the urine deposits an abundant sediment that consists of erythrocytes and leucocytes (generally in large numbers); epithelium from the uriniferous tubules, the pelvis of the kidney, and the bladder; hyaline, epithelial, fatty, leucocyte, and sometimes erythrocyte casts; compound granule cells, free fat droplets, cell detritus, bacteria, etc. In associated amyloid disease waxy casts also are encountered.

In general, the other symptoms are similar to those encountered in acute nephritis (which have been already detailed). Uræmic manifestations are common, more particularly the chronic nervous and gastro-intestinal symptoms which frequently persist for some time, being subject, however, to remissions and exacerbations. Attacks of acute uræmia are less common than in acute nephritis and in chronic indurative nephritis. When they do occur coma rather than convulsions is likely to be observed. Debility and anæmia are usually pronounced, and both, but especially the anæmia, seem to bear some relationship to the rapidity of the course of the renal lesions—being more marked the more rapid the course. The pulse usually is of increased tension, and after the lapse of some time arteriosclerosis develops. Usually also hypertrophy of the heart supervenes. The recognition of this may be rendered difficult by the presence of considerable dropsy, but a displaced and forcible apex beat and an accentuated aortic second sound, together with the increased pulse tension, serve for its recognition, even in the absence of demonstrable percussion evidences of enlargement of the heart. Albuminuric neuro-retinitis is quite common. It is sometimes unattended by subjective symptoms, a fact readily explicable when we remember that the location rather than the extent of the retinal lesions is of significance. Involvement of the macula lutea leads to destruction of sight, and less serious lesions are commonly manifested by dimness of vision and restriction of the fields of vision.

Diagnosis.—The diagnosis of chronic diffuse non-indurative nephritis, suggested by the history of the case, the extreme pallor, and the presence of œdema, is based upon the results of an examination of the urine. The diagnosis of the disease, therefore, is easy, but the recognition of the condition of the kidneys is commonly attended by some difficulty. The large red kidney, chronic hemorrhagic nephritis, may be suspected when the urinary sediment contains a relatively large number of erythrocytes and blood casts, whereas the presence of large numbers of fatty casts, free fat droplets, and fatty or compound granule cells suggests the large white kidney. In some cases of large white kidney, in the absence of hemorrhage, the presence of considerable fat may give to the surface of urine that has stood for some time, a distinct oily lustre. The differential diagnosis between chronic diffuse non-indurative nephritis and amyloid disease of the kidneys is always difficult and sometimes impossible. Amyloid disease, however, is suggested by the etiological factors of amyloid disease, the associated enlargement of the liver and spleen attributable to amyloid disease, relatively slight œdema, slight or no hypertrophy of the heart, relatively few casts, those present being of the hyaline, waxy, and granular varieties, and the absence of uræmia and neuro-retinitis. Sometimes, however, the etiological factors of amyloid disease result in chronic diffuse non-indurative nephritis rather than in amyloid disease, and in many cases attempts at differential diagnosis can be of academic interest only since the two diseases are associated. Retardation in the excretion of methylene blue is said to occur in chronic nephritis and some diagnostic significance has been attributed to it. The means of distinction between the large white kidney and the small white kidney—the secondary chronic interstitial nephritis, will be referred to presently.

Course and Prognosis.—Chronic diffuse non-indurative nephritis manifests a tolerably uniform course, although remissions and exacerbations of the symptoms occur from time to time. The duration varies from two to three months in the cases commonly designated subacute to one and a half to two or two and a half years in the more chronic cases. Some patients, however, survive a longer period, the kidney assuming the characters of the secondarily contracted kidney. The prognosis is always bad, since death is the inevitable result. A few cases of recovery especially in children have been reported, but it is extremely doubtful that these were cases of well-developed chronic diffuse non-indurative nephritis. The prognosis is the more serious the greater the amount and persistence of the albuminuria and the œdema, the less the excretion of the urinary solids, and the more marked the cardio-vascular and retinal changes. Death is hastened by persisting and recurring uræmia and by the development of certain complications, such as intercurrent infections, inflammation of the serous membranes, catarrhal pneumonia, œdema of the lungs, etc. Under favorable circumstances contraction of the kidney occurs, the secondary chronic interstitial nephritis develops, and the subjective condition of the patient materially improves temporarily—he may even be in apparent good health.

Treatment.—In general the indications for treatment are similar to those mentioned in connection with acute nephritis, our endeavors being directed toward favoring the elimination of accumulating waste products, and improving the condition of the blood. Special symptoms are to be treated as they arise. The general hygienic and dietetic rules detailed in connection with acute nephritis are applicable in the chronic form of the disease, and the same rules govern the use of diaphoretics, cathartics, and diuretics. In combating the anæmia and the œdema Basham's mixture, Trousseau's diuretic wine, or Grainger Stewart's mixture of scoparius, digitalis, and potassium acetate will be found of much service. Strontium lactate, diuretin, sparteine, adonidin, oxygen (as recommended by Dujardin-Beaumetz), etc., may be found useful in different cases and may be employed from time to time. Probably the best results attend the use of general hygienic and dietetic measures, free daily evacuation of the bowels, a daily tepid bath, an occasional Turkish bath, the administration of iron, quinine, and strychnine, and from time to time a strictly milk diet.

(*b*) CHRONIC DIFFUSE INDURATIVE NEPHRITIS.—*Etiology and Pathogenesis.*—Three forms of chronic diffuse indurative nephritis (chronic interstitial nephritis, sclerosis of the kidney) may be distinguished: 1. Secondary chronic interstitial nephritis (the secondarily contracted kidney, the pale granular kidney, the small white kid-

ney) that develops as a sequence to the large white kidney. It has been suggested, however, that, contrary to the prevailing opinion, the small white kidney is not always preceded by the large white kidney. 2. Primary chronic interstitial nephritis (the primarily contracted kidney, the red granular kidney, the gouty kidney); and 3. Arteriosclerotic nephritis. *Secondary chronic interstitial nephritis*, being a late stage of chronic diffuse non-indurative nephritis (the large white kidney), the etiological factors in the two cases are the same. These have already been mentioned. *Primary chronic interstitial nephritis*, on the contrary, is an independent disorder. It develops in a kidney previously healthy and consists of a slowly progressing atrophy of the renal parenchyma and its replacement by newly formed fibrous cicatricial connective tissue. It is especially common after the fortieth year of life, but it may occur after the twentieth year, and it has been observed even in children. Twice as many men are affected as women. In many cases no etiological factor can be determined upon. In some cases, cases in which the disease affects the members of several generations of the same family, heredity plays a more or less important rôle. In the majority of cases the disease may be looked upon as the result of the exigencies of modern life, as the penalty of the strenuous life. The hurry and the cares, the worries and the anxieties of modern life, the nervous tension and the mental strain inseparable from large undertakings and heavy financial responsibilities, an irregular mode of life, over-eating of rich and highly seasoned foods, excessive indulgence in alcoholic beverages, and insufficient muscular exercise, combined tend to produce imperfect metabolism—the products of which being eliminated by, give rise to a progressive deterioration of, the chief emunctories of the body—the kidneys. In many cases the disease is directly attributable to certain autogenous and exogenous intoxications, of which the most important are alcohol, lead, and uric acid and the other metabolic poisons associated with gout. Although one can scarcely doubt that alcohol is an important etiological factor, it is likely that many of the cases attributed to the influence of alcohol are due rather to the excessive consumption of rich and highly seasoned foods. Certain disturbances of metabolism, especially such as are associated with certain functional disorders of the liver and are sometimes vaguely described under the caption, "lithæmia," are believed to lead to the disease. The disease also follows certain well-known infective diseases, especially syphilis, malaria, etc., and it is said to be provoked at times directly by scarlet fever, acute articular rheumatism, etc. *Arteriosclerotic nephritis* is very common in this country. Its etiology is the etiology of arteriosclerosis. Thus, while it occurs in both sexes, it is especially common in men past the fortieth year of life. It is prevalent in alcoholics, syphilitics, lead workers, those accustomed to hard manual labor, and "good livers," as well as in those subject to the exigencies of modern life. Although it constitutes the condition known as the *senile kidney*, it is by no means confined to advanced life. It is especially common in those having a tendency to arterial degeneration in whom it frequently develops early in life, being hastened by the etiological factors already mentioned.

Pathological Anatomy.—The kidney in chronic diffuse indurative nephritis varies somewhat in appearance, depending upon the variety of the disease. In the *secondary chronic interstitial nephritis* the kidney is sometimes slightly enlarged, sometimes normal in size, and sometimes considerably reduced in size; it varies in size depending upon the stage of the process. When reduced in size it is usually much increased in consistency, and the capsule is thickened and markedly adherent. When stripped of the capsule the surface of the kidney is granular, pale yellowish in color, or mottled with reddish areas. Usually many cysts varying considerably in size and filled with a clear watery or viscid fluid project from the surface. On section the cortex is much diminished in thickness, yellowish in color or mottled, and reveals many foci of fatty-degenerated epithelium. The pelvic fat is usually considerable. In the *primary chronic interstitial nephritis* the kidney is usually embedded in a large mass of firm adipose tissue. Having been extricated from this it is found to be very much reduced in size, being frequently but one-third or one-half the normal size; sometimes both kidneys together weigh less than 50 gm. The capsule is much thickened, puckered, and intimately adherent to the kidney tissue, and the blood-vessels are considerably dilated, on account of their vicarious action. On stripping the capsule the surface of the kidney is found to be markedly granular, the granules varying in diameter from 1 to 5 mm. The elevated portions are usually dark reddish-brown in color (whence the term red granular kidney), whereas the depressed portions are paler and grayer in color. Usually a number of cysts, varying in size from that of the smallest granule to that of a chestnut, and filled with clear amber-colored watery or viscid contents, project from the surface. The kidney is very firm, hard, and dense, and extremely resistant to the knife when it is sectioned. The cortex is much reduced in thickness, sometimes being scarcely 2 mm. thick. It is usually dark reddish-brown in color or mottled, paler grayish areas alternating with the darker red areas. At times small cysts are found—sometimes projecting from, and sometimes entirely within, the cortex. The pyramids are usually reduced in size, and they are darker in color than the cortex. In cases of gouty kidney uric-acid infarctions or striations of uric acid or sodium urate may be found in the pyramids. On account of the thickening of their walls the small arteries of the kidney are more or less apparent to the unaided eye. The contraction of the pyramids sometimes results in enlargement and elongation of the calices. In *arteriosclerotic nephritis* the kidney can scarcely be distinguished from the red granular kidney.

Pathological Histology.—In chronic diffuse indurative nephritis, although the lesions are widespread and involve all the structures of the kidney, the most conspicuous lesion is a considerable overgrowth of fibrous cicatricial connective tissue. In the *secondary chronic interstitial nephritis* the lesions already mentioned in connection with the large white kidney reveal the changes consecutive to overgrowth and cicatrization of connective tissue—atrophy of the secreting tissue of the kidney, more or less obliteration of the glomeruli, considerable increase in the connective tissue especially about the capsules of Bowman and about the blood-vessels, more or less arteriosclerosis and obliterating endarteritis, distended and occluded uriniferous tubules, etc. The lesions are usually focal, and small areas of extreme fatty degeneration of the renal epithelium are sometimes conspicuous. In the *primary chronic interstitial nephritis* the most conspicuous lesion is the overgrowth of cicatricial connective tissue (Fig. 3067). This is a replacing fibrosis—the result of gradual atrophy of the renal parenchyma. The connective-tissue overgrowth is usually more marked in the cortex than in the medulla; in the cortex it is usually focal in character, small areas of the kidney being successively involved, whereas in the medulla it is more diffuse. In all stages this newly formed connective tissue contains a considerable number of small round cells, but as the process advances it becomes markedly fibrillar and frequently encircles the capsules of Bowman in a lamellated fashion and spreads to the adjacent intertubular tissue. In some places granules of blood pigment the remains of previous hemorrhages may be apparent. The glomeruli reveal all grades of alteration from moderate fibrosis to complete obliteration and hyaline metamorphosis. The less marked changes consist of hyaline degeneration of the vascular tuft, proliferation of the epithelial and connective-tissue cells of the Malpighian bodies, and the formation of new connective tissue. These progress until the Malpighian body is represented by a functionless, roundish hyaline mass. The tubular changes consist of more or less atrophy of the epithelium. This varies in degree and is usually most marked where the connective-tissue new formation and cicatrization are most marked. In some places the

epithelium may have entirely disappeared. At the surface of the kidney in the granular projections hyaline and fatty degeneration of the epithelial cells, dilatation of the uriniferous tubules due to connective-tissue constriction and occlusion by tube casts, desquamated epithelium, cell detritus, etc., may be apparent. The cysts already mentioned result from occlusion of the tubules and the Malpighian bodies. The arteries reveal varying degrees of sclerosis—usually advanced sclerosis. Endarteritis frequently progresses to complete occlusion of the lumen. The changes in the adventitia are often very marked, leading to more or less atrophy of the muscularis, and spreading to the adjacent intertubular tissue. In *arteriosclerotic nephritis* the changes in the blood-vessels are the primary event, the changes in the renal parenchyma being the result of defective nutritive supply. The changes in the blood-vessels, therefore, are most conspicuous, and the areas of atrophy may be seen to bear a direct relationship to the blood-vessel alterations. In many respects, however, the arteriosclerotic kidney is scarcely to be distinguished from the kidney of primary chronic interstitial nephritis; indeed, some observers decline to make any distinction between the two.

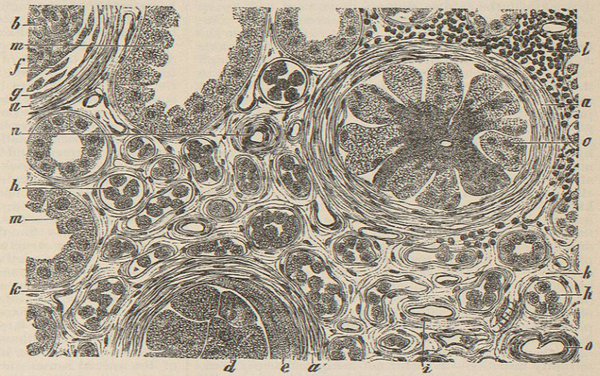

FIG. 3067.—Chronic Diffuse Indurative Nephritis with Atrophy of the Renal Tissue. *a*, Thickened and fibrous Bowman's capsule; *b*, normal glomerular vessels; *c*, glomerulus with partly impermeable and homogeneous vascular loops and almost entirely devoid of epithelium; *d*, obliterated glomerulus; *e*, homogeneous coagulation mass with nuclei, exudate, and epithelium; *f*, desquamated glomerular epithelium; *g*, capsular epithelium; *h*, collapsed urinary tubule with atrophic epithelium; *i*, collapsed tubule devoid of epithelium; *k*, hyperplastic connective-tissue stroma; *l*, collection of small round cells; *m*, normal, but somewhat dilated, urinary tubule; *n*, afferent vessel; *o*, vein. × 250. (Ziegler.)

In addition to changes in the kidneys characteristic changes occur in the heart and in the blood-vessels: in the heart, hypertrophy especially of the left ventricle, and in the blood-vessels, sclerosis. Chronic diffuse indurative nephritis thus is not merely a local disease affecting the kidneys; in most cases it is a widespread disease affecting the kidneys and the entire vascular apparatus—the heart and the arteries especially, but sometimes also the veins. In the majority of cases doubtless it commences in the kidneys, but it speedily implicates the heart and the blood-vessels; in some cases analogous lesions have been found in structures as remote as the liver, etc. In some cases it is likely that the lesions commence simultaneously in the kidneys and the cardio-vascular apparatus. A conspicuous feature of many cases is the development of miliary aneurisms that involve especially the arteries of the brain, and that, by rupturing, frequently lead to a fatal termination.

Symptoms.—It is sometimes impossible to recognize *secondary chronic interstitial nephritis* clinically—to differentiate between the large white kidney and the small white kidney. Presumptive evidence of secondary contraction of the kidney, however, is afforded by long duration of the disease (more than a year); lessening in the amount of dropsy; lessening in the amount of albumin in the urine, increase in the daily quantity of urine and decrease in the specific gravity; the presence of hypertrophy of the heart, accentuation of the aortic second sound, and increase in the arterial tension,—in a word, by the advent of symptoms characteristic of primary chronic interstitial nephritis. In many cases, without a knowledge of the previous history of the patient it is impossible to make a differential diagnosis between the secondary and the primary form of contraction of the kidney.

As might be expected from a knowledge of the nature of the process, the symptoms of *primary chronic interstitial nephritis* develop as insidiously as do the pathological lesions in the kidney. The disease may exist for years entirely devoid of symptoms. Indeed, in the majority of cases the early stages of the affection are altogether overlooked, unless they be discovered accidentally by the routine examination of the urine, as, for instance, for life insurance, or for patients ill with other diseases. When finally, after a number of years, the disease does produce obtrusive symptoms, these are usually of such a nature that they are likely, for a time at least, to be attributed to disorder of some organ other than the kidney. Thus, while the patient may present himself to his physician with the idea that he is suffering with diabetes on account of the large amount of urine that he voids, he is just as likely to complain of dimness of vision the consequence of albuminuric neuro-retinitis; or of one of the many manifestations of chronic uræmia, such as dyspnœa or asthma; or of gastro-intestinal derangements, such as gastric catarrh, gastric hemorrhage, or diarrhœa; or of headache, hemicrania, tinnitus aurium, or vertigo; of neurasthenia, pains in the muscles or joints, or eczema; of palpitation of the heart and precordial distress: or, the patient in apparent good health, may suddenly develop a severe and even fatal attack of cardiac failure, or he may pass into uræmic coma or convulsions, or he may suffer an apoplexy and die. The initial symptoms of the disease, therefore, are extremely variable.

In whatever manner the disease manifests itself the diagnosis depends upon the results of an examination of the urine and of the cardio-vascular system. The urine is increased in amount—1,800 c.c. to 4,000 c.c. daily—whence the common complaint of frequent micturition and sometimes of increased thirst; it is acid in reaction, pale in color, of low specific gravity (1.002–1.015). It contains a slight amount of albumin; usually only a trace, and at times no albumin at all. Albumin may be absent for days and even weeks at a time; it may be missed in the early morning urine and be present in that voided later in the day; and it may be present only after exercise, emotional and other excitement, or after eating, especially after eating proteids. The urine deposits a