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Review of intercapillary glomerulosclerosis

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A REVIEW OF

INTERCAPILLARY GLOMERULOSCLEROSIS

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INTRODUCTION

In 1936 Kimmelstiel and Wilson (1) described their findings in eight patients with diabetes of peculiar spherical hyaline masses in the central portions of the glomerular lobules of the kidneys. They interpreted these findings as a sclerosis or hyalinization of the intercapillary connective tissue. This connective tissue was described as originating near the hilum and extending into the periphery of the lobule.

The above authors went further and discussed what they felt was a clinical syndrome associated with the particular lesion in the kidney. The essentials of this Kimmelstiel-Wilson syndrome were the presence of a long-standing diabetic state in combination with the development of albuminuria, hypertension and edema. The eight patients in their series all (except for one) had been diabetics who showed development of severe and widespread edema. The patients were relatively old, had benign hypertension, and showed large amounts of albumin in their urine. Indications of heart failure and renal failure were present and apparently were complications of the initial lesion.

There have been since Kimmelstiel and Wilson first

described the lesion in the glomeruli of the kidney, many conflicting opinions as to the specificity of the syndrome of diabetes, hypertension, edema, and albuminuria for that particular lesion. (3) There have also been varied opinions as to the exact position of the lesion itself, and the question is raised as to whether there is an intercapillary connective tissue in which the lesion could occur. It was suggested that the pathological changes more likely occured in the walls of the glomerular arterioles. (2)

Additional interest arose in the exact morphology of the glomerular lesion and resulted in the description of two types of intercapillary glomerulosclerosis; that is, a nodular type and a diffuse type. (4)

It is the purpose of this paper to review some of the original and current thinking on the subject of intercapillary glomerulosclerosis or the so-called Kimmelstiel-Wilson syndrome.

INCIDENCE

General

Zins (5) cites the incidence of intercapillary glomerulosclerosis as found by other authors. (See Table 1.) The figures indicate a wide range, but even the lowest percent incidence indicates that intercapillary glomerulosclerosis is not an uncommon complication of diabetes.

Table 1. Incidences of Intercapillary Glomerulosclerosis in Diabetics.

Author	Year	Per Cent
Siegal & Allen	1941	33.3
Allen	1941	33.0
Horn & Smetana	1942	22.9
Bell	1942	20.5
Spuhler	1943	50.0
Laipply, et al.	1944	63.5
Goodof	1945	44.0

Also, the incidence of diabetes in cases of proven glomerular sclerosis was noted by Kimmelstiel and Porter (6) to be very high. Since the lesion is rare in those not having diabetes, its presence has been considered a post-mortem aid to the diagnosis of a pre-existing diabetic condition. (5)

When the kidney lesions were differentiated into a nodular and diffuse type, Bell (4) described nodular

lesions in 12.4% of 688 diabetic males and in 19.4% of 777 diabetic females. When the diffuse lesions were included, the total incidence of glomerular sclerosis was 19.5% for diabetic males and 30.0% for diabetic females.

Incidence and Age

Rifkin (7) states that at first it was felt that intercapillary glomerulosclerosis was a complication of the older diabetic, occurring most usually in the fifth and sixth decade. Others (12), in general agreed, stating that the lesion was most common in the age group of from 50 to 79 years of age. Laipply, et al. (8) observed the lesion in the same age group of patients with advanced vascular changes such as arteriosclerosis. In dealing with the lesion in the younger patient, it was found (4) that in patients under the age of 50 years the glomerular involvement was much more common in hypertensive patients, but after the age of 50, the relation to hypertension was much less.

The incidence of diabetic nephropathy, in general, is greatest in the severe diabetic of youthful onset. (10) Others (9) have found this complication relatively common in children and adolescents when their diabetes was of ten or more years duration.

Bell (11) correlates the incidence of the inter-

capillary lesion with age and sex and concludes that there are few lesions in patients less than 20 years of age. He also found that in patients 40 years of age, the lesions were twice as frequent in females than in males, and he associates this fact with the increase in incidence of renal arteriosclerosis in females of that age.

Zins (5) attempted to relate the age of the patient to the degree of intercapillary glomerulosclerosis. His conclusions were that there was little or no direct relation between age and the severity of the lesion.

Incidence and Sex

Zins (5) noted no preponderance of the lesion in either sex. In his series females were 48% of all the diabetics examined while they composed 54% of those patients presenting the intercapillary lesion. Rifkin (7), too, saw no correlation with sex.

Bell (4) found nodular lesions in 19.5% of the males and in 30% of the females.

Robbins, et al. (12) felt that intercapillary glomerulosclerosis was more apt to occur in women on the basis of the increased incidence of diabetes in women over middle age.

Incidence and Severity of Diabetes

Zins (5) found no apparent correlation with severity. (See Table 2.)

Table 2. Degree of Intercapillary Glomerulosclerosis in Relation to the Severity of the Diabetes.

Degree of Diabetes (Read down)	Degree of Sclerosis (Read across) Minimal	Moderate	Advanced	Total %
Mild	8 cases	7 cases	4 cases	46.3%
Moderate	7 "	9 "	0 "	39.0%
Severe	2 "	4 "	6 "	14.7%

Others (10) felt, however, that diabetic nephropathy had a greater incidence in severe youthful diabetics.

Incidence and Duration of Diabetes

One author's series (5) indicated that the chances of developing kidney disease increased with each year of diabetes.

Goodof (13) and Bell (4) also correlated incidence of the lesion with the duration of diabetes. Rogers, et al. (12) showed that with increasing duration of diabetes there was a definite rise in the incidence of the kidney lesion. In their series 14% of the patients having diabetes for less than 4 years had renal lesions,

while there was a 64% incidence of intercapillary glomerulosclerosis in patients having their diabetes for 10 to 14 years.

In general, the above figures do seem to favor a direct relationship between the duration of the metabolic disorder and the incidence of the intercapillary lesion.

Incidence and Control of the Diabetes

Root, et al. (15) and Jackson, et al. (16) state that good control of the diabetic condition postpones or prevents the intercapillary lesions. Dolger (17) and Larsson (18) feel that such is not the case.

Incidence and Hypertension

Zins (5) and Laipply (19) found no correlation between hypertension and the incidence of the glomerular lesion. Bell (4), however, felt that in the younger diabetic the lesion was present more often in a hypertensive patient.

ETIOLOGY

Porter and Walker (20) felt that mild diabetics frequently had accelerated vascular changes which were often pronounced in one area; therefore, they suggested that the capillary changes of intercapillary glomerulosclerosis represented another instance of predilected degeneration.

Laipply (19) stated that since the lesions were present in the same age group of patients with advanced sclerosis, the sclerotic condition was probably contributory to the development of the kidney lesion, although not the sole etiologic factor. Others (11) have cited work indicating that the lesion is merely an extension of the arteriosclerotic process into the glomerulus.

However, Bell (4) described a series of 148 cases of severe arteriosclerosis in which 32.3% of the cases showed no glomerular lesions at all.

Pearl and Kandel (20) correlated the degree of peripheral arteriosclerosis (as measured by the occurrence of gangrene with the degree of involvement of the kidney by intercapillary glomerulosclerosis. Diabetics without the glomerular lesion showed a 22% incidence of gangrene. Diabetics with the kidney lesion showed a gangrene incidence of 24%. With severe kidney involvement the incidence of gangrene was 25%. It was concluded that if mere vascular disease were a prominent etiologic factor, one would expect a high incidence of gangrene with advanced intercapillary glomerulosclerosis; therefore, the basic assumption that arteriosclerosis and arteriolosclerosis cause intercapillary glomerulosclerosis seemed most unlikely.

Another author (22) felt that the whole process may be due to a metabolic difference different from ordinary diabetes and caused by a factor other than the failure of production of insulin by the pancreas.

Rifkin (9) felt that a disturbance of the lipid metabolism as well as an alteration in the metabolism of complex mucopolysaccharides was involved in the genesis of this syndrome.

Another cause, adrenal hyperfunction (21) possibly associated with a B_{12} deficiency, might be related to the development of the kidney lesion.

Zins (5) cited (but disagreed with) Spuhler (23) who stated that insulin might cause intercapillary glomerulosclerosis.

PATHOLOGY

Types of Lesions - Diffuse and Nodular

When the lesion was first described by Kimmelstiel and Wilson (1), the changes were felt to be a hyalinization of the connective tissue between the capillary loops of the glomeruli. However, Allen (2), Laipply (8), and Bell (11) felt that the changes were a result of a splitting of the capillary basement membrane and that the sclerotic process was intramural.

The difference of opinion depended on whether one

accepted the presence of intercapillary connective tissue at the periphery of the normal glomerular lobule.(14) Kimmelstiel and Porter (6) cited Zimmerman (24) as having demonstrated such an intercapillary connective tissue.

Bell's argument (11) against Kimmelstiel and Wilson's description of the lesion was that the capillary loops are held together only by glomerular epithelial cells and that there is no connective tissue cell between them. By studying early lesions, coarse fibrillar structures contributing to the intercapillary mass were seen to be derived from a splitting of the intercapillary basement membrane.

Bell (4) in microscopic studies of the kidneys from 1465 diabetics went further in his description of the kidney lesions and designated two different types of hyalinization; one type was diffuse in nature and the other type was a more localized nodular lesion. He felt that the nodular lesion was always associated with diffuse lesions, but in about one-third of the cases only diffuse lesions were formed. He stated that nodular lesions developed from diffuse lesions and no sharp separation could be made between the two types. He felt the destruction of the glomerulus was due more often to the diffuse lesion than to the nodular type.

The exact origin, chemical composition, and specific staining properties remain as the main problem yet to be solved in describing exactly this lesion. There is no agreement as to whether the apparently hyaline deposit actually arises in the mesangium or in the capillary basement membrane. Also, nephrosclerosis, glomerulonephritis, glomerulosclerosis, fibrosis, and axial thickening all affect the mesangium of the glomeruli and the basement membrane of the capillary tuft and thereby appear to occupy an intercapillary position. Therefore, in a descriptive sense all are intercapillary glomerulosclerosis.

The Nodular Lesion

1. Histogenesis and Morphology: The microappearance of the kidney glomeruli indicated that the hyalinization was confined to the center of the glomeruli. The appearance of the mass was suggestive of amyloid, but its staining properties were not characteristic. In the original description (1) of the lesion it was stated that the capillary basement membrane was either delicate or thick, but it was never wrinkled or split. The number of glomerular capillaries seemed decreased apparently because they were buried in the central hyaline mass, (this mass representing a broadening of the intercapillary

connective tissue). As the hyaline mass spread, it took on a laminated appearance, the capsular space eventually becoming very narrowed. The process worked further and further peripherally, indicating it to be degenerative in nature.

Zins thought that the early lesions seem to be a fibrosis of the intercapillary connective tissue. This stage can be regarded as a lesser involvement which can progress to a spherical lesion. (5)

Bell (11) describes the nodular lesion as being spherical in shape and at the center of the glomerular lobule. The diameter ranges from 20 to 100 microns and appears homogenous. The basement membrane of the inner capillary walls is not recognized, apparently, because they are fused with the central hyaline mass. The fully developed lesion gives the impression of being intercapillary in origin. The size and the number of the lesions vary in different kidneys. Others (14) agree with the concept of a focal lesion with intact capillary loops.

The normal or enlarged size of the glomerular tuft in intercapillary glomerulosclerosis is not so in the hyalinization associated with other diseases where there is a decrease in size. Wilens and Elster (25) feel this is due to abnormal deposits of fat in the glomeruli.

Additional histologic criteria of the nodular

lesion as described by Robbins, et al. (26) listed the following: (a) the presence of one or more peripheral eosinophilic hyaline masses in the apparent axial stroma of the glomerular tuft, (b) the presence of a peripheral capillary forming a partial or complete halo about the hyaline mass (best seen in kidneys congested with blood, for the capillaries containing rbc's appear to have aneurysmal projections into Bowman's space), (c) no evidence of significant endothelial cell or epithelial cell proliferation of the glomerular tuft.

Root (15) mentions that the lesions show mucopolysaccharide characteristics and demonstrate lipid involvement as determined by staining techniques.

Diabetic nodular lesions must never be confused with the central hyaline masses characteristic of chronic glomerulonephritis. The nephrotic lesions are uniform throughout the glomerulus and never appear as separate discrete nodules as do the diabetic lesions. (11) Allen (2) mentions certain qualitative aspects of the hyaline material which help to differentiate it from types of hyaline found in other nephropathies.

2. Pathogenesis: Newberger and Peters (27) felt that the development of the lesion was due to a widespread arterial and arteriolar degeneration. Yet, Segal and Allen (28) differed on this point in that they found the

lesions in diabetics without renal arteriosclerotic vascular complications.

Figures tabulated by Bell (11) concerning the association of intercapillary glomerulosclerosis with arteriosclerosis showed that in one series of 148 cases of severe arteriosclerosis 32.3% showed no glomerular lesions at all.

Some alteration in the metabolism of lipids was suggested as a factor in pathogenesis by workers (25) using Sudan IV stain and demonstrating that the amount of fat in the lesion was proportional to the severity of the lesion and, therefore, could be etiologically related to the development of the lesion.

3. Specificity of the Lesion: Allen (2) found the lesion in 33% of diabetics over the age of 40 years and concluded that a new and reliable criterion was available for the postmortem diagnosis of diabetes.

Warren and Lecompte (14) in an attempt to confirm Laipply's et al. (8) findings of an incidence for the typical lesion of 63.7% studied various glomerular changes in diabetics as well as non-diabetics, and concluded that it would be difficult to be certain of the specificity on the basis of the minimal changes required by Laipply as criteria for the lesion.

Robbins and Rogers (4) studied 100 proven cases

of intercapillary glomerulosclerosis. All 100 had diabetes even though some were not apparent at first.

Segal and Allen (28) found the renal lesion rare in people who did not have diabetes. They discovered only one case out of 200 non-diabetics studied.

Horn and Smetana (29) made different findings in 81 cases of intercapillary glomerulosclerosis taken from 550 diabetics. In its advanced form, the lesion was always associated with diabetes, but less severe glomerulosclerosis was found with equal frequency in cases of arteriolonephrosclerosis without diabetes. These findings were true in glomerulonephritis too. Therefore, these authors concluded that the clinical signs and symptoms are not specific for this lesion and that the lesion is found in conditions other than diabetes.

Zins (5) agreed with the above to the extent that the lesion is not 100% specific. In a series of 50 known diabetics he found the lesion in 42 of the cases. This, however, does indicate a significant degree of specificity of the lesion for diabetes. Zins felt that the diffuse lesions were least specific. Bell (4) stated that when chronic glomerulonephritis is excluded, the diffuse lesions are as specific for diabetes as the nodular lesion. Rifkin (9) agreed.

The nodular lesion is almost always pathognomonic for diabetes and Bell (11) found only two cases where the typical lesion was present without the diabetic condition.

Associated Kidney Changes Outside the Glomerulus

1. Afferent Arteriolar Changes: In nephritis there is rarely any change in the afferent arterioles and intercapillary lesions are evenly distributed through the glomeruli. In diabetes there is always hyalinization of the afferent arterioles and the intercapillary lesions are variable in shape and size. (4, 10) Renal arteriosclerosis and arteriolarsclerosis are associated with intercapillary glomerulosclerosis. (9) Warren and Lecompte (14) feel that glomerulosclerosis is also associated with sclerosis of efferent arterioles as well as afferent arterioles. It was this arteriolosclerotic process that Bell suggested extended into the glomeruli giving rise initially to the intercapillary glomerulosclerotic lesion. (4) Nephrosclerosis is considered to be a concurrent condition with intercapillary glomerulosclerosis. (26)

2. Capsular Changes: The parietal layer of Bowman's capsule shows a wax-like material beneath the epithelium with capsular wall thickening. (32) Initially

it is homogenous, but later becomes fibrillary and organized by connective tissue. These capsular lesions are felt to be specific for diabetes. (1, 30)

3. Tubular Changes: McManus describes thickening of the tubular basement membranes. (31) Kimmelstiel and Wilson (1) in their original paper described tubular changes to which they attached little significance. These changes were a striking deposition of fat and doubly refractile lipoid in the tubules and interstitial tissues. They had also seen these changes in arteriosclerosis.

Associated Changes in Other Organs

1. Pancreas: Occasionally some lipomatosis and interstitial fibrosis is seen (32) The association of hyalinization in the Islands of Langerhans with intercapillary glomerulosclerosis is felt by some to be inconsistent. (14) Striker (33) saw ten cases of severe intercapillary glomerulosclerosis without any evidence of hyaline changes in the "islands". In contrast, he has seen varying degrees of kidney lesions with inconsistent changes in the islands.

2. Retina: The question is raised whether the capillary aneurysms associated with the kidney lesions are related to the retinal aneurysms noted in patients having intercapillary glomerulosclerosis. This relation-

ship was suggested by Friedenwald (21) and others (9). Kimmelstiel (30) felt that they were not due to the same process on the basis that the retinal aneurysms are saccular and the glomerular aneurysms are fusiform. He felt there was no proof in humans that the glomerular aneurysms antecede the formation of spherical nodular lesions in the kidney.

Retinopathy was present in every instance of Kimmelstiel-Wilson's Disease studied by Ashton. (35) He also demonstrated microaneurysms in the glomerular tufts in patients with the disease.

Dana (22), in a review of 190 cases, found retinal aneurysms associated with 90% of Kimmelstiel-Wilson's Disease. These lesions occurred in only 10% of the control group. He felt the retinal aneurysm to be an intrinsic part of the same entity as Kimmelstiel-Wilson's Disease since aneurysms are often found near the glomerular lesion in the kidney. Therefore, he concluded a common pathogenesis for the changes in the renal and retinal vessels. Rifkin refers to the recent realization that the capillary microaneurysms in the retinal vessels of diabetic patients is the morphologic and biochemical counterpart of the intercapillary hyaline glomerular lesion. (7) Freidenwald reported the hyaline in

the glomerular nodule and that in the retinal microaneurysm are tinctorially identical. (21)

Warren and LeCompte (14) cite work by Henderson, et al. (34) showing a striking correlation (68.8%) of the lesions of intercapillary glomerulosclerosis and retinal changes. Kimmelstiel and Porter (6) found retinopathy in 86% of cases with advanced lesions. They also found the retinal changes without an associated glomerulosclerotic condition and, therefore, they concluded that the retinal lesion is not a result of the renal disease. Friedenwald (21) states that although all patients with specific renal lesions have retinal microaneurysms, only 58% of patients with aneurysms have intercapillary glomerulosclerosis.

Volk (36) describes the diabetic retinopathy as capillary microaneurysms, venule varicosities, small deep hemorrhages, and sharply demarcated exudates. He states that while the specific renal lesion occurs late in the course of the disease, the specific retinal changes may occur early in the course of the diabetes and need not be associated with hypertension and arteriosclerosis and do not in themselves mean a bad prognosis.

Experimentally Produced Lesions

Rich (37) has produced lesions in the rabbit kidney that are similar to the lesions of intercapillary

glomerulosclerosis but are not the same. (30) Alloxan diabetes predisposes kidneys to lesions produced by Cortisone. (9) Mann and Goddard (38) described the lesions produced in alloxan diabetic rats.

Lukens and Dohan (39) achieved similar lesions in dogs that had been diabetic for five years and had been treated with anterior pituitary extract.

Other methods of producing in animals lesions suggestive of human diabetic glomerulosclerosis have been by partial pancreatectomy and by parenteral injection of substances such as adrenal cortical steroid combinations, homologous serum globulins, and vitamin B_{12}. Similar lesions have also been produced by choline deficiencies. (7)

As to partial pancreatectomy, Foglia, et al. (42) produced lesions in 88% of their male and female rats by extirpation of 95% of the gland.

The experimentally produced lesions, though similar, are not histologically characteristic of the human renal lesion. No retinal aneurysms have yet been experimentally reproduced by any of the above methods. (7)

CLINICAL ASPECTS

Specific Syndrome

Newberger and Peters (27) described four cases of intercapillary lesions and considered the disease a distinct entity. Bell (11) criticised their conclusions on the basis that their criteria for the syndrome required the presence of only slight albuminuria and slight edema and not a full-blown picture of a nephrotic syndrome.

Anson (41) felt that intercapillary glomerulosclerosis could be anticipated if the patient had hypertension and mild diabetes. There were others who agreed with the specificity of the syndrome. (42)

Zins (5) found the clinical syndrome not recognizable as frequently as the kidney lesion and, thus, felt that the glomerular changes did not always occur in a nephrotic, hypertensive patient.

Bell (4) stated that the clinical symptoms bear relation to the intensity of the glomerular lesion, but not to their histologic type. The complete nephrotic syndrome may develop when only diffuse lesions are present. This speaks against specificity of the typical nodular lesion for the so-called Kimmelstiel-Wilson Syndrome.

Rogers and Robbins (43) felt that since Kimmelstiel

and Wilson's description (1) of intercapillary glomerulosclerosis had been mainly from a pathologic standpoint, there had never been a sharply defined clinical entity. In an attempt to determine whether a clinical entity could be distinguished, these authors reviewed the clinical records of 229 diabetic patients and evaluated them on clinical grounds for "possible" and "probable" presence of intercapillary glomerulosclerosis. Correlation of the diagnoses with autopsy findings showed 41 cases selected as having the specific glomerular lesion as compared to 28 cases actually having the lesion. This was a 32% error. Thirty-eight anatomic instances of the lesion were not chosen clinically because of the absence of symptoms (albuminuria, hypertension, and edema). On the basis of the above findings, these authors concluded that even in the presence of diabetes mellitus, no clear-cut syndrome could be said to exist in association with intercapillary glomerularsclerosis. Furthermore, diabetics not having the lesion may present the so-called classic features of the lesion. Other authors (4) concur with the above findings.

Clinical Picture

Root and White (10) divided the clinical course into the following stages:

Stage I - Nephrotic

Stage II - Anemic

Stage III - Salt losing

Stage IV - Uremic

Stage V - Acidotic

Stage VI - Cardiac failure

Stage VII - Encephalopathic

A picture of amelioration of the diabetes may occur. Glycosuria and even hypoglycemia may disappear with the onset of renal insufficiency in intercapillary glomerulosclerosis. (31) Others (12) noticed a marked decrease in the glycosuria as compared to the amount of hyperglycemia. Amelioration, however, is not a unique finding of intercapillary glomerulosclerosis. It also occurs in a variety of other non-specific renal lesions. This amelioration has been considered to be due to a marked decrease in caloric intake associated with increased illness.

The onset of this disease is often not apparent. All of the features typical of the full-blown disease may not be present at first or be only minimally present. For example, a mild diabetic with moderate hypertension and a trace of albuminuria may show edema which at first is thought to be of cardiac origin rather than nephrotic. The patient may go rapidly into uremia before the exact

etiology is realized. (7)

Rogers, et al. (12) discussed how often the symptom triad (albuminuria, hypertension and edema) occurred together in an individual to produce a recognizable syndrome. In a series of 100 patients with intercapillary glomerulosclerosis, only 25 showed the triad of symptoms. Furthermore, the clinical triad was absent in over 50% of those patients having the most severe lesions. These authors concluded that many, if not most, of the cases of intercapillary glomerulosclerosis do not present the classical triad of clinical findings. For this reason they felt the entity to be more often missed clinically than misdiagnosed.

1. Hypertension: In diabetics under the age of 50 years, intercapillary lesions are much more frequent in hypertensive patients, but after the age of 50 the relation to hypertension is much less. (4)

Dolger (17) also noted a 50% association of glomerulosclerosis with patients having hypertension and albuminuria. Others (7, 8, 34) find hypertension common but not constant. Segal and Allen (28) found lesions in 12 of 50 diabetics without hypertension.

Adams (44) in a study of 1001 cases of diabetes at the Mayo Clinic found no clear-cut evidence that diabetes promotes hypertension. He found that the incidence

of hypertension was 16.2% in males and 26.7% in females. These findings would at least favor the idea that a complication of diabetes (such as intercapillary glomerulosclerosis) must be added to the diabetic condition to create the hypertension. Hypertension is felt to have no part in the etiology of the kidney lesion, however.(14)

Most authors find that the incidence of hypertension and glomerulosclerosis is from 50 to 60 per cent. (6, 25, 33, 34)

2. Proteinuria: Newberger and Peters (27) found early proteinuria present in varying degrees. As the lesion progressed, the proteinuria became profuse.

Zins (5) saw no apparent correlation between the degree of the lesion and the amount of proteinuria except in markedly advanced lesions when proteinuria reached 3 to 4 plus.

Striker (33) felt albuminuria was a constant finding and that the degree correlated with the severity of the intercapillary glomerulosclerosis.

Bell (4) states that glomerular lesions may be present when proteinuria is mild or completely absent, but a severe amount of proteinuria suggests the presence of glomerular lesions particularly in young diabetics. Conversely, he found that 50% of diabetics with normal

glomeruli showed albuminuria varying in degree from one to four plus. He felt that the presence or absence of albuminuria does not substantiate or exclude the diagnosis of intercapillary glomerulosclerosis.

3. Edema: Severe edema in the diabetic under 50 years of age is usually of renal origin and strongly suggests the presence of intercapillary glomerulosclerosis. In the older diabetic, edema is of a much less diagnostic significance with respect to the renal lesion since the edema is usually due to cardiac failure or to other causes. (4, 48)

The edema associated with the renal lesion may precede the onset of the albuminuria. (10)

Complications

1. Acidosis: Rifkin's studies (7, 9) indicate that young diabetics are prone to frequent episodes of acidosis and coma prior to the onset of the Kimmelstiel-Wilson Syndrome.

Dana (22) found acidosis rare. This may have been because his criteria for the glomerular lesion required only the presence of "a lumpy loop of hyaline mass in the glomerulus", and there may have been some discrepancy on his part in picking actual cases of intercapillary glomerulosclerosis. However, Zubrod (47) also felt that acidotic coma was rare in the syndrome.

2. Renal Failure and Nephrotic Syndrome:

Kimmelstiel (30) felt that in the young diabetic with intercapillary glomerulosclerosis the nephrotic syndrome was the most prominent aspect of the clinical picture. The mechanism for the development of the condition is on the basis of renal insufficiency due to decreased glomerular filtration, renal blood flow, and tubular excretory capacity. (7, 45)

Zins (5) found the nephrotic syndrome (proteinuria, hypoproteinemia, hypercholesterolemia, and universal edema) present in 12.2% of diabetics with kidney damage. He believes it to be a late sign of intercapillary glomerulosclerosis.

Bell (11) states that the nephrotic syndrome rigidly defined (proteinuria two plus or more and edema two plus or more) developed in 45.6% of 57 cases of intercapillary glomerulosclerosis in subjects under 50 years of age and in 14.9% of those beyond that age.

DIAGNOSIS

Clinical Diagnosis

Rogers, et al. (12) feel that hypertension, edema, albuminuria, and cardiac failure occur with sufficient frequency in diabetics to make these findings of limited value in distinguishing intercapillary glomerulosclerosis.

Others (33) agree.

The clinical diagnosis of glomerular sclerosis can be made with reasonable accuracy in any diabetic by the demonstration of renal insufficiency not due to pyelonephritis or hydronephrosis. (4)

In diabetics less than 50 years of age the presence of glomerular sclerosis is strongly indicated by proteinuria, severe edema, hypertension, and retinitis. After the age of 50, these symptoms and signs have less of a diagnostic significance. (4)

A hinderance to making a clinical diagnosis is the fact that the onset of the disease is often not apparent due to the signs not being present or being present only minimally. The older, mild diabetic who is moderately hypertensive and shows only a trace of albuminuria may develop edema which at first is considered to be on a cardiac basis rather than on a nephrotic basis. (7)

Chronic heart failure in diabetics with arteriosclerotic or hypertensive cardiovascular disease or chronic pyelonephritis are often indistinguishable from diabetic intercapillary glomerulosclerosis. (7)

Amelioration of the diabetic state on the basis of insulin requirement and decreased glycosuria often herald the involvement of the kidney by intercapillary glomerulosclerosis. (12, 31)

Root and White (10) consider the following as a diagnostic clinical picture of glomerulosclerosis: (a) persistent albuminuria, (b) retinal lesions, i.e., aneurysms, hemorrhages, and waxy exudates, (c) benign edema, and (d) development of nitrogen retention.

Another author (33) would suspect interglomerular lesions on the basis of a patient showing diabetes associated with albuminuria, hypertension, renal insufficiency and mixed vascular and diabetic retinopathy.

Laboratory Aids to Diagnosis

1. Microscopic Exam of the Urine: Examination of the urinary sediment in Kimmelstiel-Wilson disease will show doubly refractive lipoid droplets in epithelial cells or casts containing cholesterol esters in addition to neutral fats. These appear yellow when viewed under ordinary light, but they have a maltese cross appearance when viewed under polarized light. The urines must be studied daily since the amount of anisotropic material varies. One must use fresh acid urine.

Doubly refractile lipids are also found in other causes of the nephrotic syndrome such as nephrotic glomerulonephritis, renal amyloidosis, lupus nephrosis and occasionally in diffuse vascular disease. They are generally not found in generalized arteriosclerosis and hypertensive renal vascular disease, with or without dia-

betes, in the absence of glomerulosclerosis. Therefore, if one can rule out nephrotic glomerulonephritis which is the chief diagnostic consideration in younger diabetic patients and rare in patients past the fifth decade, then careful examination of the urinary sediment becomes an important yet simple diagnostic aid.

Hyaline, waxy, and granular casts are noted in the urinary sediment with varying constancy. Occasionally red blood cells and white blood cells are seen. Red blood cell casts and hemoglobin casts are never seen. If the latter are noted, the diagnosis is of glomerulonephritis, malignant nephrosclerosis or renal infarct rather than of diabetic renal disease. (7)

2. Biochemical Alterations in Urine, Blood, and Serum: Serum and urinary proteins were studied by means of the Tiselius apparatus and paper electrophoresis. (52) In intercapillary glomerulosclerosis there is noted a low serum albumin and an increase in the serum alpha-2-globulins. The latter change is also noted in other conditions associated with the nephrotic syndrome and terminal uremia. It probably reflects prolonged proteinuria.

The urinary proteins show an increase in albumin and alpha-1-globulin with relatively normal concentrations of both beta and gamma globulins.

Mucopolysaccharides and lipid substances were

studied in the blood and urine. Higher levels than normal were noted in diabetics with retinopathy and nephropathy. There was no definite causal relationship since renal insufficiency, per se, as well as tissue destruction lead to elevation of levels of these substances. The Sf 12-50 class of lipoproteins (corrected for cholesterol) was elevated in the fully developed syndrome. Again this change may be related to the degree of renal insufficiency. The Sf 12-50 are not characteristically raised with retinopathy. Diabetics of long duration but without vascular complications showed normal Sf values.

Complicated diabetics showed elevated total lipids, lipid phosphorus, and serum cholesterol. Normal values were found for all three of the lipid classes in uncomplicated diabetes. Relatively normal levels of serum cholesterol and lipid phosphorus but increased levels of total lipids were found in diabetics with retinopathy but without renal insufficiency. (7, 48)

3. Renal Function Tests: Renal hemodynamics proved disappointing as a diagnostic tool in this disease. (49) The mechanisms of renal function changes are similar to those involved in glomerulonephritis, that is, a pattern of diminished filtration associated with a loss

of tubular secretory function.

4. Renal Biopsy: A positive biopsy is, of course, diagnostic, but a negative biopsy does not rule out the disease. (7)

Differential Diagnosis

1. General: Robbin, et al. (26) and Herbut (32) cited the condition of intracapillary glomerulonephritis which was described by Fahr. (53) In acute stages of the latter there is present an inflammatory exudate that renders recognition easy. In chronic stages, however, differentiation may be difficult. Pathologically, in intracapillary glomerulonephritis there is a blurring and reduplication of the basement membrane, but in intercapillary glomerulosclerosis the membrane is intact, discrete, and single.

Intercapillary glomerulosclerosis, chronic glomerulonephritis, and amyloidosis all have similar pathology because in all a large part of the glomerulus consists of a homogenously staining substance. Also, all three can lead to the clinical end result of azotemia and the nephrotic syndrome. (7) There are, however, differentiating points. (34

2. Chronic Glomerulonephritis: Nodular lesions are rare in this condition, but the diffuse type is common. Distinction between the interglomerular lesions of

chronic glomerulonephritis and those of diabetes is reasonably easy. In nephritis there is rarely any hyaline in the afferent arterioles and the intercapillary lesions are evenly distributed in the glomerulus. In diabetes there is always hyalinization in the afferent arterioles and the intercapillary lesions are variable in size and shape. (4) Chronic glomerulonephritis also causes widespread destruction of the kidney. (33)

Some additional clinical signs of chronic glomerulonephritis are a severe anemia, increase in blood urea, and a decrease in urine specific gravity and in serum proteins. (33) An Addis count showing hematuria is also indicative of chronic glomerulonephritis. (6)

3. Amyloidosis: The staining characteristics of amyloid and of the hyaline of intercapillary glomerulosclerosis are different. (14) Also, amyloidosis is associated with involvement of the spleen, adrenals and other organs. (33)

Laboratory-wise, renal amyloidosis is associated with an increase in serum and urinary gamma globulins whereas these substances show normal values in glomerulosclerosis. (9)

4. Heart Failure: Congestive heart failure in diabetics with arteriosclerotic or hypertensive cardiovascular disease is marked by dependent edema, dyspnea,

orthopnea, cyanosis and venous congestion. In intercapillary glomerulosclerosis the edema is widespread rather than dependent and the other symptoms mentioned above are likely not present. (33)

TREATMENT

General

Attention should be directed toward the general nutritional status of the patient and symptomatic relief of the edema. A high protein diet with additional calories to maintain the nutritional level should be given. The diabetes is usually controllable with small amounts of insulin.

Active Treatment

Root and White (10) divide treatment into four parts: (1) chemical control, (2) correction of infection, (3) avoidance of ketoacidosis and (4) proper diet.

Under chemical control they discuss treatment on the basis of the seven stages which they recognize in the progression of this disease.

Stage I - Nephrotic: Treat with diuretics such as ammonium chloride, Diamox, Mercuhydrin, etc.

Stage II - Anemic: Treat with multiple small transfusions of packed rbc and with iron or copper (as the sulfate).

Stage III - Salt losing: Remove salt restriction and administer NaCl with caution.

Stage IV - Uremic: Diet protein to be restricted.

Stage V - Acidotic: If acidosis occurs, treat with Na lactate, M/6 solution I.V. Use aluminum hydroxide if serum phosphorus increases. Use Ca gluconate, 10% solution, if tetany occurs.

Stage VI - Cardiac failure: Bedrest, restriction of fluids and digitalization.

Stage VII - Encephalopathy: $MgSO_4$ (2 cc of a 50% solution) I.M. as necessary; hypotensives and anticonvulsants; therapeutic lumbar puncture.

Infections such as pyelonephritis are managed with suitable antibiotics. As to ketoacidosis, the authors found this complication particularly in younger patients in whom many attacks of ketoacidosis had characterized their past history. Ketoacidosis as well as renal acidosis have been one of the severe problems in management of such cases in the past few years. Handling the situation was discussed under Stage V.

The diet that Root and White discuss is, in general, one that is adequate in high value protein (1½ to 2 gms/kg) and a selection of fats of vegetable origin that are easily digestable. During the nephrotic stage, the patient should receive little sodium (less than 1 gm),

1 to 2 gm of protein per kilogram, and an acid ash type of diet (restrict milk and basic vegetables, and prescribe acid forming foods such as meats, fish,eggs, and cereal). During the uremic stage one must enforce moderate restriction of protein, a low sodium diet, and the administration of the majority of calories in the form of carbohydrates.

To the above diet recommendations, Rifkin (7) adds that with poor renal function, the protein intake should not exceed 30 to 50 gms per day and that calories should be kept adequate to prevent malnutrition especially in the presence of severe proteinuria. Fluid intake should be enough to produce 1200 to 1500 cc of urine output per day; otherwise nitrogen retention would result.

Associated with the amelioration of the diabetic state that occurs in advanced intercapillary glomerulosclerosis (31), there is a progressive susceptability on the part of the patient to insulin hypoglycemia, and the patient's insulin requirements fall. This condition is felt, possibly, to be due to inadequate food intake, poor gastro - intestinal absorption, or even edema. (10)

More Radical Therapy

Adrenalectomy was discussed by Martin and Wilson (50) as treatment of diabetic vascular disease. Following adrenalectomy replacement therapy with cortisone (50 mg daily) was initiated. No significant changes in the

urinary protein excretion were noted following the operation. Better results were noted by Green (51) who used DOCA for replacement therapy. Green noted improved blood pressure levels and improved renal function. In Martin and Wilson's work, death from adrenal insufficiency with hyperkalemia and ascending paralysis occurred when the cortisone was reduced from 50 mg to 25 mg in order to relieve the malignant hypertension resulting from the medication.

Prophylaxis

Root and White (10) feel that prevention of this disease depends on (a) early diagnosis of the diabetes, (b) early control with insulin, and (c) a diet including adequate calories, vitamins and minerals. These and other authors (15, 16) feel that good control postpones and/or prevents the kidney damage of intercapillary glomerulosclerosis. Dolger (17) and Larsson (18), however, do not feel that good control of the diabetes helps prevent the occurrence of the glomerular lesion.

PROGNOSIS

Rifkin (9) stated that the average life duration following the onset of the syndrome is 6 to 7 years with a range of from 2 to 13 years. Fishberg (45) described the patient's course as downhill.

As to the cause of death, Rifkin (9) described 22 cases at necropsy. Nine died of uremia, seven died of heart failure, and two died of acute coronary occlusion. Henderson, et al. (34) described 61 cases. Thirty-two died of cardiovascular complications, fourteen of congestive failure, ten of gangrene, five of CVA, two of myocardial infarct, and one of cardiac dilitation. Only one died of renal failure. Fishberg (47) described 15 cases, five of which died of renal failure. Death due to acidotic coma is rare.

CONCLUSIONS

Since 1936 when Kimmelstiel and Wilson first described a peculiar sclerosing lesion of the kidney glomerulus and related to that lesion a syndrome consisting of hypertension, albuminuria, and edema, there have been many varied opinions as to the actual morphology of the glomerular changes and the specificity of a syndrome for the lesion. It has been the purpose of this paper to review some of the original and some of the current thinking on this subject.

The incidence of the lesion has been reported to be from 20% to as high as 60% in all diabetics. Even its lowest incidence rate indicates it to be a reasonably common complication of diabetes. The wide range of incidence is most likely on the basis of varying degrees of specificity involved in determining morphologic criteria of the lesion. The more strict the morphologic standards, the lower the incidence of the lesion.

The age of the patient seems to have little effect on the incidence. Those who feel there is a relation between the glomerular changes and arteriosclerotic changes elsewhere in the body think that the older diabetic is more prone to the lesion because of the increased arteriosclerosis in his age group. However, the lesions have even been demonstrated in children and adolescents who

have had long-term, severe diabetes.

Sex has been considered to have some bearing on the incidence of this complication of diabetes. Again, on the basis of increased vascular changes in the female beyond middle age, it was felt that intercapillary glomerulosclerosis would be more prevalent in the elderly female diabetic. These assumptions were not born out by statistics based on clinical and pathologic studies.

Severity of the diabetic condition based on its controllability with insulin and proper diet could not, just as with age and sex, be correlated with the incidence of the lesion.

Correlation of duration of the diabetes and the incidence of Kimmelstiel-Wilson's Disease was another story, however. Nearly all patients developing the syndrome give a history of diabetes of long duration. Statistics support an increasing prevalence and severity of the glomerular lesion in direct proportion to the increasing duration of the metabolic disorder.

As to the etiology of the condition, there are many theories. Some feel the changes to be due to a localized and predilected type of vascular degeneration. Others associate the lesions with arteriosclerotic processes at least to the extent that such a condition is contributory to the lesion even if not the sole etiologic

factor. A direct extension of the sclerotic process into the glomerulus from outlying vessels was suggested. Still others have cited such possible factors as disturbances of lipid metabolism, adrenal hypofunction and even insulin intolerance as possible causes of the pathologic changes. On the basis of such varied concepts of etiology, it seems possible that none of them or all of them are in some way connected with the development of the lesion.

The exact pathology of the lesion itself has some unclear aspects. The original investigators felt the lesion to be a result of hyalinization of the connective tissue between the capillary loops of the glomeruli. Others described a splitting of the capillary basement membrane and felt that the changes were occurring in the capillary wall. The exact origin, chemical composition, and specific staining properties remain as the main problem yet to be solved in describing exactly the lesion.

Progress has been made in distinguishing two general types of glomerular sclerosis, i.e., diffuse and nodular. The nodular lesion, which is merely a more localized deposition of the hyaline substance in the glomerulus, is considered specific for intercapillary glomerulosclerosis. The diffuse lesion has been noted with a variety of kidney lesions and pathologic processes affecting the kidney and is not felt to be specific for the

Kimmelstiel-Wilson Disease. However, the nodular lesions are possibly an advanced stage of the diffuse lesions, and the latter are considered specific for diabetes when other renal pathology can be ruled out. It is not impossible that there are even two different types of diffuse lesions; one type that is associated with and would eventually develop into the nodular lesion of intercapillary glomerulosclerosis, and a second type that is a result of other renal pathology and would never develop into the typical nodular lesion. Again, an answer to this awaits more precise investigative techniques.

Chronic glomerulonephritis is probably the most commonly encountered kidney pathology that must be differentiated from intercapillary glomerulosclerosis, although there are several other disease processes that must be considered, too. In general, the former is characterized by an extensive but uniform involvement of the glomeruli by a diffuse type of lesion; whereas glomerular sclerosis demonstrates a less uniform involvement of the glomeruli with discrete, but irregularly sized nodules.

Pathogenesis of the lesion is questionable. Are the lesions a result of a specific metabolic defect? Are they a result of arteriolar degeneration or possibly an extension of an arteriosclerotic process? These questions cannot be answered at this time.

Specificity of the nodular lesion was discussed for the so-called Kimmelstiel-Wilson syndrome. The advanced, unmistakable, severe, nodular lesions could be closely correlated with the advanced syndrome of Kimmelstiel-Wilson's Disease. As the nodularity of the lesion became less prominent, i.e., when it was more diffuse in nature, it became less specific for intercapillary glomerulosclerosis and was seen in association with other renal pathology.

Some characteristic pathology outside the glomeruli was noted in intercapillary glomerulosclerosis. Hyalinization of the afferent and the efferent arterioles, thickening of the parietal layer of Bowman's capsule, and deposition of fat in the basement membrane of the tubules with resultant thickening were some of the changes noted.

Changes in other organs were also considered. The pancreas showed no consistent changes associated with intercapillary glomerulosclerosis. The retina, however, showed changes which some investigators felt were an intrinsic part of the same entity involved with development of the typical glomerular lesions. The aneurysms of the retinal vessels appeared much the same as those noted in the vessels near the glomerulus in intercapillary glomerulosclerosis. The retinal changes were considered to be an early and characteristic finding in this syndrome.

Attempts in animals at experimentally producing lesions in the kidney of the same type as those found in Kimmelstiel-Wilson's Disease in humans have been unsuccessful. The lesions are similar but are histologically not the same.

The clinical aspect of the disease was considered first from the idea of specificity of the clinical syndrome. This again varied with the different sets of criteria for the syndrome. If only mild hypertension, a trace of albuminuria, and minimal edema were considered to be the necessary clinical signs for diagnosing the K-W syndrome, then the specificity was low and other causes were often found for the same clinical picture. On the other hand, if the criteria for the syndrome were the presence of proteinuria (grade two) and edema (grade two) plus marked hypertension and advanced retinopathy, then the syndrome became more specifically a result of intercapillary glomerulosclerosis. On the whole, however, the syndrome was not felt to be specific. Instances of nephrotic syndrome developing in the presence of only diffuse glomerular lesions and a series showing a 32% error in attempts at picking on clinical grounds those patients having the specific renal lesion were findings that did not favor specificity.

The clinical picture of the full-blown disease was probably best approached by dividing it into stages. These were, in order, nephrotic, anemic, salt losing, uremic, acidotic, cardiac (failure), and encephalopathic. These stagings make one aware of the impending complications. An amelioration of the diabetic state on the basis of decreasing insulin requirements was mentioned as a sign of kidney involvement. The onset of the disease is often not apparent since the signs are absent or only minimally present. The condition is more often missed clinically than mis-diagnosed.

Hypertension, which is not caused by diabetes and does not occur with increased incidence in diabetes, is associated with intercapillary glomerulosclerosis. Its incidence is from 50 to 60% and it is apparently a result of the diabetic complication.

Proteinuria of any marked degree seems to be a late sign, and it is indicative of severe kidney involvement, especially in the younger diabetic. However, even in severe lesions the proteinuria may be mild, and its absence does not rule out the diagnosis of intercapillary glomerulosclerosis.

The presence of edema is most diagnostic in the patient under 50 years of age. Over that age it is more often due to cardiac failure. Edema may precede onset of

proteinuria.

As to complications of the disease, the nephrotic syndrome seems to be the most prominent complicating feature of the full-blown entity especially in the younger age group of diabetics.

The clinical picture that is felt to be diagnostic for this syndrome is the combination of these signs: (a) hypertension, (b) albuminuria, and (c) edema. In the patient over 50 years of age, signs of chronic heart failure may be an associated finding, and in the patient less than 50 years of age, we should look for retinopathy as an associated sign. Also, try to rule out other causes for renal insufficiency such as pyelonephritis.

Laboratory aids to diagnosis consist of daily examination of fresh acid urine for doubly refractive lipoid droplets appearing in the sediment. Under polarized light these have a characteristic maltese cross appearance. A finding in the urine of rbc or hemoglobin casts immediately rules out diabetic nephropathy and suggests a glomerulonephritis.

Biochemical alterations of the blood, urine, and serum are of additional diagnostic significance. Serum albumin falls and urine albumin rises. Mucopolysaccharides and lipids show increased values in the blood and urine. Increased lipid phosphorus and serum cholesterol

have been noted in complicated diabetes whereas these findings were not present in uncomplicated diabetes. These biochemical changes are likely on the basis of renal insufficiency and tissue destruction as well as some metabolic alteration.

Renal hemodynamics have proved unsuccessful as a diagnostic tool in this disease. Renal biopsy is diagnostic only if the biopsy is positive, and there is a certain amount of hazard involved in doing it.

Differential diagnosis is centered mainly around intercapillary glomerulosclerosis, chronic glomerulonephritis and amyloidosis since all progress to azotemia and the nephrotic syndrome. Clinically chronic glomerulonephritis is usually associated with severe anemia, increased blood urea, decreased urine specific gravity and decreased serum proteins. Amyloidosis usually shows signs of splenic and adrenal involvement and laboratory-wise, shows increased urine and serum gamma globulins. Heart failure must be differentiated from nephrotic edema. The former is characterized by dependent edema, dyspnea, orthopnea and cyanosis.

Treatment in general is symptomatic. A suggested approach is as follows: (a) chemical control, (b) correction of infection, (c) avoidance of ketoacidosis, and (d) proper diet. Then by approaching the disease on the

basis of its progressive stages, nephrotic, anemic, salt losing, etc., one can have a good understanding of the necessary therapeutic measures that should be taken.

A proper diet seems to play an important therapeutic part. Maintain adequate nutrition. Keep the calorie intake up. Supply protein to offset tissue destruction, yet do not overload the depressed kidneys and cause nitrogen retention. Maintain an adequate urine output at all times.

Prophylactic measures consist of (a) early diagnosis of the diabetes, (b) control with insulin, and (c) maintainence of proper diet and nutrition. Every diabetic should be considered a potential candidate for the development of intercapillary glomerulosclerosis.

Prognosis indicates a uniformly downhill course. The average life duration is quoted at 6 to 7 years. Death is most often due to uremia, with heart failure and other cardiovascular complications being common, too.

SUMMARY

The purpose of this paper has been to review the original and the current thinking on the subject of intercapillary glomerulosclerosis.

The entity was first described in 1936 by Kimmelstiel and Wilson who, also, related to the kidney lesion a clinical syndrome consisting of hypertension, albuminuria, and edema (Kimmelstiel-Wilson Syndrome).

Varied opinions are expressed as to the exact morphology of the lesion. Whether the lesion arises from intercapillary connective tissue or from the basement membrane of the glomerular capillaries is still uncertain.

The incidence of the lesion, it was noted, correlated best with the duration of the diabetic condition. No correlation was noted between incidence and the age or sex of the patient or the severity of the diabetic state.

The glomerular lesions have been pathologically divided into two types; (1) diffuse and (2) nodular. The nodular lesion is felt to be pathognomonic for diabetes.

The diffuse lesion is discussed from the standpoint of its being a probable precursor of the nodular lesion.

Chronic glomerulonephritis and amyloidosis were mentioned under differential diagnosis as being conditions able to produce a clinical picture and even similar glomerular lesions simulating intercapillary glomerulosclerosis.

Characteristic changes in the retinal vessels were felt to be associated findings in intercapillary glomerulosclerosis that appeared early in the course of the disease.

It was noted that a clinical diagnosis is often difficult to make since the classical signs may be absent of only minimally present.

Hypertension is secondary to the development of intercapillary glomerulosclerosis.

Proteinuria correlates well with typical lesions only in cases of severe kidney involvement and even then may be absent.

The presence of edema is most diagnostic in the patient who is under the age of fifty years. Over the age of fifty years, cardiac failure confuses the picture.

Daily microscopic examinations of fresh acid urine samples looking for doubly refractive lipoid substances is an easy and fairly diagnostic laboratory test.

The biochemical alterations of the blood, serum, and urine are discussed from a diagnostic standpoint and are felt to be helpful aids.

Treatment consists essentially of four points: (1) chemical control, (2) correction of infection, (3) avoidance of ketoacidosis, (4) maintainance of a good diet.

The disease is approached and treated on the basis of its clinical stages which are (1) nephrotic, (2) anemic, (3) salt losing, (4) uremic, (5) acidotic, (6) cardiac (failure), and (7) encephalopathic.

Prophylaxis consists of (1) early diagnosis of diabetes, (2) control with insulin, and (3) maintainance of proper nutrition.

Prognosis, generally, is poor with a downhill course. Death usually results from uremia or cardiac complications.

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