REVIEW OF LITERATURE
DEFINITION - WHAT IS DIABETES?

Diabetes mellitus is a disease of the intermediate metabolism of carbohydrate, protein and fat. There is decreased cellular glucose due to a lack of effective insulin and subsequent long term degenerative changes, mostly in the vascular system of the body. This
definition is not sacrosanct, and present day basic research, if fruitful, could make it obsolete (Krall 1965).

Diabetes does not occur overnight. It starts at birth or earlier as a Mendelian recessive trait (Joslin 1959). It is provoked by the long term stresses of aging, obesity, acute stresses such as infection, pregnancy and other factors and is eventually diagnosed as overt or clinical diabetes.

**GENERAL REVIEW**

Egyptians as far back as 1500 BC or probably 3000 BC described a disease associated with marked polyuria. Arethaeus, the famous Roman Physician (AD 30 to AD 90), first used the name "diabetes", which means "to pass through" and it was considered to be a weakness of the kidney because of polyuria.

Avicenna (A.D 1000), the great Arab Physician, described diabetes with great accuracy including some of the complications like diabetic gangrene, furunculosis and phthisis, and remarked on the presence of honey-like material in the urine of diabetic patients.

Many centuries before Avicenna, Chinese, Japanese and Hindu writings indicate that a disorder associated with a sweet urine was known to these people.

In India, Charaka, Samhita and Sushruta in Ayurveda (fifth century) described diabetes or "Madhumeh" as one of the urinary disorders, resulting from provocation of the body humors. Glycosuria was described as follows:
"Person who passes urine which is exceedingly sweet, cool and slightly viscid, turbid and resembling the juice of the sugarcane, owing to the provocation of the Kapha, suffers from glycosuria. The importance of heredity and obesity as predisposing factors in the causation of diabetes were also recognised."

Sushruta considered that an important characteristic of diabetes was that "if walking, he would like to stand, if standing, he would like to sit, if sitting, he would like to lie down, and if lying down, he would like to sleep (Tulloch 1962).

It was Thomas Willis (1621-1675) who differentiated diabetes mellitus from diabetes insipidus, and it was William Cullen (1710-1790) who was the first to add the adjective "Mellitus".

Cawley in London (1788) first suggested a causative relationship between the pancreas and the diabetes mellitus. Before him, Brunner in 1682 had observed polyuria and polydipsia after removal of the pancreas in experimental animals.

Claude Bernard (1813-1878) propounded the theory that hyperglycaemia was due to over production of sugar from glycogen in the liver. Another spectacular discovery made by him was that the puncture of the floor of the 4th ventricle rendered an experimental animal temporary diabetic. In the year 1894, Pavy was the first to develop a blood sugar method and established a relationship between hyperglycaemia and glycosuria.
Naunyn, the foremost authority on Diabetes in Germany, in the nineteenth century was the first to introduce the term "Acidosis" by which he meant accumulation of Ketone bodies.

In 1857 Petters first noticed acetone in diabetic urine and Kussmaul first found acetone in blood in 1874. Stadelman, Minkowski and Kulz later identified B-oxibutyric acid in diabetic urine.

In the early part of the twentieth century, Allen propounded that diabetes is a disorder of the metabolism as a whole and not of carbohydrate alone and he advocated starvation regime, which became famous all over the world in the pre-insulin era.

Joslin, the doyen of specialists in diabetes has written that in spite of dietary restrictions of all kinds, the diabetic patient especially the juvenile, had a very unfavourable prognosis, because the fundamental problem of diabetes remained unsolved, as the cause of the disease was unknown.

In 1869 Langerhans discovered the islets in pancreatic tissue. Von Mering and Minkowski (1889) demonstrated that pancreatectomy in dogs caused hyperglycaemia, glycosuria, ketosis, coma and death and this was the first experiment which showed a definite relationship of diabetes with pancreas. This discovery was accomplished in Naunyn's Clinic in Germany.
Brown-Sequard (1889) was the first to coin the word internal secretion, and the experiments of Vassale in 1889, Opie (1901) Schulze & Sobolev in 1902 and Lydia Dewitt in 1906 conclusively established that the ligation of pancreatic duct caused the acini to degenerate, but the experimental animal did not become diabetic because the islets were not touched at all, and thus found that the antidiabetic effect of pancreas was localised to the islands of Langerhans.

Till 1920, the famous text books of Macleod & Starling did not mention the existence of internal secretion of the pancreas. It was only as recently as 1920 that Banting proposed that it was quite possible that the active principle produced by islet was destroyed by the external secretions of the pancreas and working on this hypothesis Banting & Best finally isolated insulin in 1922, in Macleod's Department in Toronto, Canada.

Beef pancreatic extracts were the first commercially available source for clinical use. Collip further purified and concentrated these extracts.

Banting, Best, Collip, Cambell and Fletcher published their first clinical paper on Insulin in 1922, and concluded the chain of evidence by their epoch-making discovery of insulin in 1921.

Abel of Johns Hopkins made the first Crystalline Insulin in 1926 and Scott confirmed that the crystals were the zinc salt of the Insulin protein. Hagedorn introduced
the first long-acting insulin by adding protamine to insulin. Bauman developed globulin-insulin, Hagedorn N.P.H. and Hallas-Moller lente-insulin, in which zinc along, without protamine causes the desired slowing of absorption.

Houssay, a renowned physiologist, in 1931 proved for the first time that diabetes produced by pancreatectomy can be ameliorated by hypophysectomy. He conclusively showed that it is in the anterior lobe of the pituitary that a diabetogenic hormone is produced.

Houssay & Biasotti (1931); Long & Lukens (1936); Young (1937); and Ingle (1941) and others have shown, in hypophysis and adrenals, the presence of substances with an anti-insulin effect. No doubt, other endocrine organs also, e.g. thyroid, and gonads, are of some consequence (Houssay 1944, 1951).

Young (1937), observed that permanent diabetes developed after injection of anterior pituitary extracts in dogs.

In 1924 Harris suggested that spontaneous hypoglycemia may be caused by over-production of insulin and coined the term "Hyperinsulinism". Wilder, Allen, Power & Robertson (1927), furnished counter proof for insulin through a case of hyperinsulinism caused by carcinoma of the islands of Langerhans. Campbell et al removed the islet-cell tumor for the first time in 1939 in Toronto.

In 1937 Jacobs produced necrosis of the beta cells of the islets of Langerhans by the use of alloxan which is considered to be a diabetogenic chemical substance.
Lazarow in 1945 showed that glutathione protects animals against ill effects of alloxan and in 1949 ventilated the possibility that disturbance in glutathione metabolism may be responsible for the human diabetes.

Murlin was the first to guess that the initial rise in blood sugar seen after insulin injection could be due to a separate substance called glucagon which is a hyperglycaemic, glycogenolytic factor attributed to alpha cells of the islands of Langerhans. Burger later separated glucagon from insulin.

Leubatier's experimental work (1942-1946) on the mechanism of action of hypoglycaemic agent is a landmark in the history of diabetes.

Young (1949) (1951) provided a solid experimental base for the hypothesis that the hypophyseal growth hormone may play a part in the development of essential part of diabetes mellitus in man.

Diabetic patients were found to vary in their response to insulin. Falta (1936) observed that diabetics were of two types - insulin sensitive and insulin-resistant.

Goldner & Clark (1944) found that the diabetes produced by total extirpation of pancreas in man is controllable by insulin doses far smaller than those required in the case of spontaneous diabetes mellitus, mostly 30-50 units per day.

Himmsworth, 1949, Lazarow 1949, Lundbaek 1949, Cahn 1950, claimed that diabetes can no longer be regarded as
a clinical entity, but that it is a syndrome - the only essential criteria of which is a pathological hyperglycaemia, while Wilder (1950) claimed that it ought to be regarded as a clinical entity of pancreatic origin, in which in man the beta cells possess originally and presumably genetically something less than normal endurance.

**DIABETES MELLITUS AND THE KIDNEY**

**HISTORICAL REVIEW**

For eighteen centuries and possibly longer, the condition of diabetes mellitus was recognised by physicians as a primary disease of the kidneys and the urinary tract.

The first accurate account was that of Aretaeus the Cappadocian (1st century A.D.) who thought diabetes might be caused by "something pernicious derived from other diseases which attack the bladder and kidney".

Darwin (1801) wrote at the beginning of the 19th century and believed that diabetes was a disease of the kidneys and was caused by prolonged drinking of alcohol. He recognised a type of diabetes in which the urine could be coagulated by heat, thus confirming the earlier observations of Cotugno (1736-1822) to whom Rayer gave the credit for having first demonstrated the presence of protein in the urine of the diabetics. Darwin associated this type of diabetes with dropsy.
It was Armanni (1875) who described hyaline vacuolisation of the tubular epithelium of the kidneys of patients with diabetes. Eight years later Frerich stated that Ehrlich (1883) working in his laboratory discovered that those vacuoles contained glycogen. This lesion was called "Armanni-Ebslein lesion" and it was regarded as the most valuable evidence of diabetes mellitus post mortem.

Before the insulin era, glycogen infiltration of the epithelium of the proximal convoluted tubule and the loop of Henle, was the only specific histologic lesion identified with diabetes mellitus. Warren in 1938 stated that it was a common lesion in pre-insulin days, but now it has become rare and infrequent.

About the same time Kimmelstiel and Wilson (1936) reported peculiar hyaline masses in the centre of the glomerular lobules in 8 elderly patients, 7 of whom had diabetes. They regarded the masses as representing a broadening of intercapillary connective tissue and called the process intercapillary glomerulosclerosis. Later workers added the prefix "nodular" to distinguish the lesion from other varieties of glomerulo-sclerosis.

In addition to diabetes of long standing, most of their patients had edema, (which they regarded as nephrotic in type) hypertension, albuminuria, and impairment of renal function.

Since Kimmelstiel and Wilson's report and over the next two decades, many papers have been written on the
subject of intercapillary glomerulosclerosis both from a pathological and clinical standpoint. The name has come to mean all things to all men, and considerable interest has centered about location, composition and pathogenesis of glomerular changes in diabetes mellitus.

Since 1936 both clinicians and pathologists have published many reports on Kimmelstiel Wilson syndrome. All of them largely confirmed the observations made by Kimmelstiel and Wilson, and dealt mostly with the histochemical and histopathological characteristics of this lesion and its clinico-pathological correlation.

In younger persons the vascular complications of diabetes may be observed with relative clarity without the confusion created in older individuals in whom atherosclerosis and other degenerative changes, apart from diabetes, may cloud the picture and make interpretations difficult. It is now generally recognised that diabetic nephropathy with its various features occur frequently and in fact characteristically in patients with long term diabetes, which began early in life (Wilson, Root, Marble 1951).

While it is true that any renal disease may occur in patients with diabetes, the lesions commonly found are (Warren and LeCompte 1952):

1. Diabetic glomerulosclerosis
   a) Nodular
   b) Diffuse
   c) Exudative
2. Tubular deposition of glycogen, fat and mucopolysaccharides.
3. Acute and chronic pyelonephritis.
5. Acute tubular necrosis.
6. Toxaemia of pregnancy.

Most diabetic patients dying of chronic renal diseases also have evidence of severe vascular disease elsewhere in the body, including retinopathy, coronary heart disease and peripheral vascular disease.

Therefore, in such patients a substantial part of the disease process leading to death arises from extra-renal sites. Of major importance is coronary artery disease with congestive heart failure which is often intermingled with renal failure as a terminal event.

Although the life expectancy of an average diabetic is longer than in pre-insulin era, the majority sooner or later develop one or more of the so-called degenerative changes in various systems of the human body (Mirsky 1946, Dolger 1947, Lundbaek 1954).

The clinical condition associated with the capillary vascular lesion in diabetes mellitus centres round two main sites – the fundus and the kidney. The vascular lesion in each of these sites is said to be specific for diabetes, and are found in both young and old (Friedenwald 1952, Becker 1952).
INCIDENCE OF DIABETIC NEPHROPATHY

Murkami (1936) made histologic examination of the kidneys from 18 diabetics and found intercapillary glomerulosclerosis in 1 case only (5.6%).

Siegal & Allen (1941) found no case of intercapillary glomerulosclerosis among 100 patients without diabetes and 35 cases among 105 diabetics (33.3%).

Bell in (1942) in a necropsy study noted the intercapillary glomerulosclerosis of various degrees in 20.5 per cent of diabetics.

Horn & Smetna (1942) found frequent intercapillary glomerulosclerosis among non-diabetics with arteriolar nephrosclerosis, glomerulo-nephritis or generalised arteriosclerosis. It is important to note, however, that in every case where glomerulosclerosis was widespread or marked, review of the case record revealed a history of diabetes mellitus. Horn and Smetna (1942) quoted an incidence of diabetic nephropathy of 22.9 per cent in a New York City Hospital. Their own series showed 44.3 per cent of the lesion.

Goodof (1945) found various degrees of intercapillary glomerulosclerosis in 94 (44 %), in 20 of whom considerable, in 25 moderate, and in 49 slight, in an autopsy material of 214 diabetics. In a non-diabetic control material of the same size, in which half the number of patients had
hypertension, 21 cases had intercapillary glomerulosclerosis, but all of minimal degree.

Bell (1946) stated that nodular lesions are almost pathognomonic of diabetes. He observed 1 case only of the nodular type in a patient with primary hypertension without diabetes. But the diffuse form was far more frequent in chronic glomerulonephritis than in diabetes.

Henderson, Sprague and Wagener (1947) found 61 with intercapillary glomerulosclerosis, 31 of whom had early and 30 had advanced lesions. Among 81 cases of glomerulonephritis without diabetes 10 had intercapillary glomerulosclerosis of whom 3 had advanced lesion.

Henderson et al (1947) in a series of 61 histologically proved glomerulosclerosis found only 50% had edema and 4 had massive albuminuria.

White and Waskow (1948) found degenerative changes in 92% cases who survived for 20 years or more in a study of 200 patients in whom diabetes had begun in childhood.

Kimmelstiel & Porter (1948) regarded the nodular type as almost specific for diabetes, while the relation between the diffuse form and diabetes was not clear to them. Kimmelstiel and Porter concluded after reviewing a number of statistics that intercapillary glomerulosclerosis occurred in 17 per cent of all cases of diabetes mellitus.

Bergstrand and Bergstrand (1949) had been unable to find a fundamental difference between the Kimmelstiel-Wilson glomerulosclerosis and the glomerulo-nephritis-
type 2 (Ellis).

Engel (1950) found 1 case only of intercapillary glomerulosclerosis among 24 diabetics coming to autopsy. Martensson (1950) observed signs of intercapillary glomerulosclerosis postmortem in 7 of 30 diabetics with diabetes of over 15 years duration (23.3%). Gilliland (1951) found 11 cases among 43 diabetic autopsies. Iversen & Soberg Ohlsen (1951) observed intercapillary glomerulosclerosis in 7 out of 18 diabetic autopsies (38.8%).

Keiding (1952) in a clinical study of 451 diabetics with onset of diabetes before the age of 30 and duration of more than 10 years found 22 per cent incidence of diabetic nephropathy in a poorly controlled group. The incidence of Nephropathy have been reported by various other authors, which is as follows:

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Bell</td>
<td>1950</td>
<td>24.7%</td>
</tr>
<tr>
<td>Wilson</td>
<td>1951</td>
<td>25.0%</td>
</tr>
<tr>
<td>Hall</td>
<td>1952</td>
<td>37.5%</td>
</tr>
<tr>
<td>Dunlop</td>
<td>1954</td>
<td>19.0%</td>
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<tr>
<td>Bryfogle</td>
<td>1957</td>
<td>10.0%</td>
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<tr>
<td>Ditze</td>
<td>1958</td>
<td>19.0%</td>
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Gellman (1959) studying 53 renal biopsies of diabetics noted an incidence of 75% of diffuse diabetic glomerulosclerosis in renal biopsies and all the 9 autopsies and 48% of nodular diabetic glomerulosclerosis in renal biopsies and 8 out of 9 autopsies. The material was however, a selected group of patients.
Tulloch (1962) reported 15.3 per cent incidence of nephropathy in Jamaica.

Solomon (1963) in an unselected study of 51 renal biopsy concluded that all patients with diabetes have characteristic glomerular alterations, some visible only with the electron microscope, and that diabetic nephropathy may antedate the clinical appearance of hyperglycaemia and glycosuria - a manifestation of pre-mellitus. Levine (1961), Kattine et al (1962), also supported the above observation, for they felt that marked basement membrane thickening could not occur in a few weeks or in a few days.

Among some of the Indian series, Bannerjee, Roy and Mukherjee (1960) noted an incidence of nephropathy of 19.3 per cent. Sinha (1960) found diabetic nephropathy of 10.6 per cent in Indian diabetics in their clinical studies. Mitra and Chhetri (1961) found 14.3 per cent incidence of diabetic nephropathy in clinical series of 280 diabetics. Mathur et al (1960) found 67 per cent incidence of nephropathy after a biopsy study. Pathania and Sachar (1961) noted 5.7 per cent incidence of nephropathy. Mathur et al (1964) in a study of renal biopsies in diabetics found the lesion in 71.9 per cent, 12.4 per cent showed both diffuse and exudative lesion and 61.2 % showed a combination of diffuse, nodular and exudative lesion. Gupta and Chakravarty (1964) by percutaneous renal biopsy noted 50 per cent incidence of nephropathy. In a clinical study Vaishnava et al (1964) noted 5 per cent incidence of diabetic nephropathy.
Thus there are variable reports in the literature regarding the incidence of the renal lesion in diabetes mellitus. They range from 5\% (Vaishnava et al) to 19\% Dunlop (1954), 20\% Robbins & Tucker (1944) to 67\% Mathur et al (1960), 82\% Zins (1949) to 100\% Farquhar, Hopper and Moon (1959).

Luken's & Dohan (1946) found this renal lesion in a dog with experimental metahypophyseal diabetes of 5 years duration. Sprague (1947) reported Kimmelstiel Wilson syndrome in chronic relapsing pancreatitis. Loeb (1947) and Mann & Goddard (1949) observed intercapillary glomerulosclerosis in aloxan-diabetic rats. Lawrence (1951) reported the case of a lipoatrophic patient who after 8 years developed typical initial intercapillary changes in the glomeruli.
AGE

According to most authors the majority of intercapillary glomerulosclerosis cases occur in elderly diabetics. The average age in the extensive series published by Henderson, Sprague & Wagener (1947) was 60 years. Kimmelstiel & Porter (1948) claimed that it was most frequent in the 6th decade of life. Pathania & Sachar (1961), found it highest in the 7th decade.

Diabetic glomerulosclerosis is generally regarded as a complication of mild diabetes in middle aged or elderly diabetics. (Kimmelstiel & Wilson 1938; Allen 1941; Herbut 1941; Henderson et al 1947; Rifkin et al 1948; Gilliland 1951; Rogers et al 1952; Brun et al 1953). Bell (1952), found it more frequent in 3rd and 4th decade about 5 times as frequent as after 40 years.

Juvenile diabetics also have been found to have this complication (Rosenbusch 1945; Mann et al 1949; Root et al 1951; White 1956). Laipply, Eitzen and Dutra (1944), reported diabetic kidney changes at autopsy in a patient aged 16 years.

Goodoff (1945), concluded that 15% of his cases were aged under 40 years. John (1949), found intercapillary glomerulosclerosis in 11 out of 61 patients in whom diabetes started before the age of 20. Bjerkelund (1951), found no case of diabetic renal disease in males under 20 of age, as against in 12% of males between 20 to 30 years,
four out of 56, (7%) females aged under 20 years and 16 out of 95, (17%) females aged between 20 and 30 years had diabetic renal disease. Gellman et al (1959) found it quite frequent in patients under 30, if the duration of diabetes was sufficiently long.

Mathur et al (1960) in their needle biopsy studies found that diabetic nephropathy ranged from 14 to 61 years. It was observed that the incidence of glomerulonephrosis increased with age—(Henderson et al 1947; Zins 1949; Hall 1952; Lambie et al 1955; Taft et al 1954; Reid 1955). Mitra and Chhetri (1961) showed that the highest incidence of diabetic nephropathy was in the 6th decade, and only 3 cases were observed below 30 years in a clinical study of 280 diabetics and maximum incidence of K.W. syndrome was found among those having onset of diabetes between 31 and 40 years of age.

El-Mahallawy and Sabour (1960) observed that age had no significant effect on the development of diabetic nephropathy. Gupta & Chakraverty (1964) observed that age was not an important factor for the appearance of renal histological change and that these changes were more commonly observed in males. However, there is now general agreement that the lesions are more frequent and more severe in patients with the youngest age of onset and with increasing duration of diabetes.
The incidence of nephropathy have been found by many authors, to be more in females (Born & Smetna 1942; Goodoff 1945; Bell 1946; Henderson et al 1947; Hall 1952; Keiding et al 1955; Lambie et al 1955; Taft et al 1954 & Cosnett 1959).

Kimmelstiel & Porter (1948), Alwall, Ekelund and Oras (1950) collected a large number of series and found that the overall incidence of male to female ratio was approximately 1:2.

Laipply, Eitzen & Dutra (1944) & Roger et al (1952) found no difference in the sex ratio. Wilson, Root and Marble (1951) found equal incidence in both sexes especially in juvenile diabetics. Daysog et al (1961) observed renal changes almost equally in males and females.

Gellman et al (1959) noted a higher incidence of both nodular and diffuse varieties in males but it was not found to be statistically significant.

Among Indian series there was male preponderence (Sinha 1960; Pathania 1961; and Gupta et al 1964).

From a review of the literature it seems that the kidney lesion shows no predilection for either sex.
The duration of diabetes seems more important than the age of the patient. Rosenbusch (1946) found renal disease as a late complication among 80 patients with onset of diabetes in childhood.

Alwall, Ekelund & Oras (1950) stated that most patients with intercapillary glomerulosclerosis have had diabetes for at least six years. Bjerkelund (1951) reported renal disease in 3% of the males and in 4.5% of the females with under 5 years of diabetes as against in 32% and 31% respectively of those with a minimum of 15 years duration of diabetes.

Grill (1948) gave the point of time for the occurrence of proteinuria at 11 years in females and 10 years in males after the onset of diabetes. Mann, Gardner and Root (1949) showed the first symptoms of renal disease after an average of 14.8 years.

The time required for the development of intercapillary glomerulosclerosis is not known. Derow & Schlesinger (1949) cited a case of a female of 61 years who died after 8 years of diabetes. Four years before she died she had a nephrectomy for a suspected renal tumor. The kidney removed showed no sign of intercapillary glomerulosclerosis. Two years before death, the patient developed neuropathy, retinopathy and massive proteinuria but no oedema. The patient died of renal insufficiency. The remaining kidney showed severe intercapillary glomerulosclerosis in 47.5% of the glomeruli.
It would therefore seem that she developed the lesion in the course of last 4 years possibly the previous 2 years.

Although duration of diabetes mellitus cannot be stated with any degree of certainty, the duration has been found to have a definite influence on the incidence of nephropathy. Kimmelstiel and Wilson (1936) thought that those with intercapillary glomerulosclerosis had a long standing history of diabetes. Similar observations were made by many other investigators (Hall 1952; Lambie and MacFarlane 1955; Shea, Robin & Mallory 1959).

Bryfogle and Bradley (1957) noted 24% of diabetic nephropathy in those with diabetes for 15 years or more in their series of 394 patients. Bryfogle et al noted an average duration of diabetes of 18.8 years and stated that nephropathy was more characteristic of the younger diabetics. Mitra and Chhetri (1961) observed that 52% of cases with duration of diabetes for more than 16 years had nephropathy. They also showed that the maximum incidence was with a duration of 16 to 20 years (52 per cent). Pathania and Sachar (1961) observed that the duration of diabetes was over 5 years in 77.9 per cent cases, the average being 13.9 years.

Most investigators found that the incidence of nodular glomerulosclerosis also rose with the duration of diabetes. (Henderson et al 1947; Zins 1949; Hall 1952; Lambie 1955; Reid 1955).

In contrast to most authors, John (1949) found no
significantly higher proteinuria frequency among patients with 10-25 years of diabetes than among those with a diabetes duration under 10 years. Laipply et al (1944); Rifkin et al (1948); Wilson et al (1951) and Berkman et al (1952) thought that the duration of diabetes had no effect on the development of nephropathy.

Arnold et al (1958) and Daysog et al (1961) demonstrated early and advanced lesions even in prediabetics, while only minimal lesions were observed in some cases with longer duration of diabetes. Ellenberg (1962) stated that nodular glomerulosclerosis might occur in the absence of manifest aberrations of carbohydrate metabolism. They described one renal biopsy and 2 autopsy records where nodular glomerulosclerosis were found without clinically manifest disturbance of carbohydrate metabolism. They observed that diabetes is a generalised disease process and that its many facets may occur independently of the carbohydrate disorder and that the various manifestations of the disease are concomitants rather than complications.

Gupta & Chakarverty (1964) stated that the duration of diabetes has no significant relationship with the onset of early renal histological changes.

Goetz (1960) found histological changes in two patients with duration of diabetes of 6 and 22 months respectively. Mathur et al (1960) noted the duration of diabetes in his 27 cases of needle biopsy to be 4 months to 12 years. Mathur et al (1964) stated that diffuse type of lesion was
detected after 20 days to 20 years of onset of the symptoms of diabetes. It appeared to them that diffuse type of nephropathy could start even at a young age with diabetes of very short duration (20 days) irrespective of the severity of diabetes while this change could also persist for many years (20 years) without progressing into nodular or exudative forms. The average duration of diabetes showing only the diffuse type of change was only two years while those showing diffuse and nodular was 8.5 years.

Goodoff (1945) observed that intercapillary glomerulosclerosis increased steadily to 100 per cent at a duration of 18 years of diabetes.

Mann et al (1949); Wilson, Root and Marble (1951) emphasized the significance of long duration in the development of renal complications in young diabetes. Hall (1952) found the incidence quite frequent in patients under 30 years if the duration of diabetes was sufficiently long.

Lambie and MacFarlane (1955) stated that average duration of diabetes in patients with diabetic glomerulosclerosis was significantly longer in those under 50 years than in those over 50 years. They also noted that longer the duration of diabetes, the more severe was the glomerular involvement. Clark and Skillern (1955) found maximum cases in the duration group 10-14 years.

Gellman et al (1959) noted that the patients with nodules had diabetes for a longer period than those without nodules. Diffuse lesion was related not only to the duration
of diabetes but also to the age of onset. Patients who developed diffuse lesion had diabetes 14 years earlier on an average than those in whom this lesion did not develop. In Gellman's series the more severe diffuse lesions were seen in those patients who had long duration of diabetes and in whom the diabetes started early in life, with the result that the duration and age of onset, both factors, were operating in causing the severity of diffuse lesion. Diffuse lesion was more frequent in 'Juvenile' diabetics.

Mahallawy (1960) stated that the presence and severity of diabetic nephropathy was definitely related to the duration of diabetic state; in an older patient, even the short duration of diabetes may develop nephropathy.

Hatch et al (1961) suggested that a longer time was required to develop the lesion in the younger age groups.
SEVERITY OF DIABETES

The relationship between severity of diabetes mellitus and nephropathy is unsettled. Many authors believe that the severity of diabetes and renal histological changes are not directly inter-related. (Joske 1956; Rifkin et al 1958; Downie & Martin 1959; Gupta & Chakarvarty 1964).

Anson (1938), Siegel and Allen (1941) and Hall (1952) stated that diabetic glomerulosclerosis occurred in mild diabetes. Porter and Walker (1941) observed that renal changes occurred after the course of an otherwise mild diabetes leading to a serious and progressive malady.


Mann, Gardner and Root (1949) reported that in their series 40 per cent of the younger diabetics with nephropathy required 40 units or more of insulin daily to maintain adequate control of diabetes. Only 7 per cent required less than 20 units of insulin daily. Rifkin, Leiter and Berkman (1952) found that majority of their cases of nephropathy were having mild to moderately severe diabetes, but few needed 30 Units of insulin per day. Lambie and McFarlane (1955) showed that 72.8 per cent of their series had mild diabetes requiring insulin below 40 units daily. They stated that diabetes of any degree of severity might be complicated with glomerulosclerosis.
Platt and Dawson (1950), Mann, Gardner and Root (1949) and Wilson, Root and Marble (1951) stated that glomerulosclerosis was a common complication in younger diabetics with severe diabetes.

Zubroid, Eversole and Dana (1951), Bryfogle and Bradley (1957) and Cosnett (1959) reported a decrease in insulin requirement in those with severe diabetic glomerulosclerosis.

Mathur et al (1960) observed that severity of diabetes had little to do with the development of nephropathy. Pathania (1961) found that the fasting blood sugar values were within normal range or slightly raised in most of their cases.

Bell (1952) stated that over 40 years there was no significant difference in the incidence of this complication between those with mild and those with more severe diabetes.

Solomon (1963) stated that the degree of mild or early diabetic nephropathy in the general diabetic population was not related to the clinical parameters usually considered 'predisposing' to the development of renal complications.

Gupta & Chakraverty (1964) stated that the severity of diabetes and renal changes do not run parallel.
CONTROL OF DIABETES

Of late, much importance has been given to the relationship between the control of diabetes and the development of nephropathy.

Dolger (1947) believed that even the best control would not prevent development of vascular lesion in juvenile diabetes. Similar observations were made by Goodoff (1945) and Ballantyne et al (1943) in adult diabetics.

Henderson et al (1947), Tolstoi (1950) and Bell (1952) found no relationship between control of diabetes and incidence of nephropathy.

Downie & Martin (1959) suggested that the poor control cannot be regarded as an important basis for advanced renal lesions as in many cases of diabetics only inconspicuous altered carbohydrate metabolism was observed.

Solomon (1963) stated that good control had no advantage over "poor" control in the prevention of renal lesions.

Joslin et al (1959), Root et al (1950), Jackson (1950), Daeschner, Deisher and Hartman (1951) believed that excellent control would delay and possibly prevent the development of vascular complications. White, Waskow (1948), Mann, Gardner & Root (1949), Wilson, Root and Marble (1951), Dunlop (1954), Root, Pote and Frehner (1954), Lambie and McFarlane (1955), Johnson (1960), El Mahallawy and Sabour (1960) have also expressed the same opinion. Similarly, Whittaker (1949), Beaser (1951), Hall (1952), Spoon (1951), suggested that
there was an undoubted correlation between the control of diabetes and the incidence of nephropathy.

Wilson, Root & Marble (1951) proved that good diabetes control is greatly important in the prevention of degenerative vascular complications. A series of 27 diabetics, who contracted the disease before the age of 30 years and who had diabetes from 10-34 years duration, gave the following finding: diabetic nephropathy did not develop in 37 patients with good or excellent control even after periods of 20-34 years of diabetes but did appear in 62 of 210 patients with poor or fair control.

Regarding the control Joslin (1959) stated that good diabetic control can be reached only along the thorny path of scrupulous diabetic control and the sin of diabetics who prevent this commandment is sure to find this out in a shorter or longer time.

Root et al (1954) noted in a series of 451 patients at Joslin Clinic, that in 11 patients with excellent control nephropathy did not occur.

Lambie (1955) found that 20 per cent of well controlled diabetics developed nephropathy, while among poorly controlled, 57 per cent developed it.

Keiding and Tuller (1955) and Taft, Finch & Joske (1955) attached great significance to good control of diabetes as a prophylactic measure against the development of renal changes.

Jackson et al (1950) while making a careful comparison of the relative importance of long duration of diabetes and
the influence of control concluded that the incidence of diabetic sequelae, retinitis and nephropathy is more definitely related to the control of diabetes than to the duration of the disease.

El Mahallawy and Sabour (1960) stated that "a shorter duration (5 years) is sufficient for a poorly controlled diabetic to develop the complications, while a longer time (10-15 years) is necessary for a moderately controlled diabetic to develop them, and a patient with excellent degree of control will not develop vascular complications, no matter how long his diabetes remains."

Gupta and Chakravrtty (1964) found the nephropathy to have some relation to the control of diabetes.

Root (1965) has quoted a study of some 661 diabetic patients with onset of diabetes under 20 years of age and studied after 10-40 years of diabetes, in which it was shown that patients under excellent control had no nephropathy, under good control 7% had nephropathy, whereas 30% of 380 patients with poor control had definite nephropathy.

The consensus of opinion at the present moment seems to be that if one uses the frequency of ketosis as a rough guide to the adequacy of control of diabetes, it appears that poorer control may result in proportionately more severe diffuse changes.
HISTOLOGY

A. GLOMERULAR LESIONS

NODULAR DIABETIC GLOMERULOSCLEROSIS

The nodular variety of diabetic glomerulosclerosis was first described by Kimmelstiel and Wilson in 1936 and subsequently Allen (1941), Reid (1955) and others have described the morphology of the lesion. Typically the nodules occurred at the periphery of the glomerulus and there was no connection with the hilus. In hematoxylin and eosin (H&E) stained slides the nodules were eosinophilic, but less than the normal capillary basement membrane. They had a laminated appearance which could be easily demonstrated with the periodic-acid Schiff (P.A.S) and reticulin stain, although it was not apparent on the H & E preparations. When the nodules were small a dilated capillary could often be seen surrounding them, but as they enlarged, the capillary lumen was usually (though not always) obliterated, a few layers of nuclei may remain embedded in the periphery of the nodule. It was unusual to see nuclei in the central parts of the nodule.

Churg et al in 1953 stated that a characteristic feature of the nodular lesion was that the hyaline material was deposited in the capillary wall in relation to the inner aspect of the loop, the outer aspect facing the Bowman's capsule was spared.

Irvine et al (1956) concluded that the first change noticed by them was in the basement membrane which became
Kimmelstiel & Wilson (1936), Fahr (1942) and Bell (1953) suggested that the situation of the nodule was intercapillary, but to Allen (1941, 1951) and to Gellman (1959), it appeared that the location was in the capillary wall.

Gellman (1959) stated that the first deposition of hyaline material occurred within the endothelial cells and that the capillary basement membrane and epithelial cells were affected later. The hyaline mass protruded into the capillary lumen and finally obliterated the capillary loop.

Bergstrand and Bucht reported electron microscopic studies of glomerular lesions in 1959 and observed two distinct processes in the glomerulus:

(A). Thickening of the basement membrane.

(B). Precipitation of hyaline masses in the endothelial cells. These changes correspond respectively to the diffuse and nodular lesions observed under light microscopy, and thus appeared to them predominantly intracapillary rather than intercapillary lesions.

Gellman agreed with the above findings.


Sabour et al (1962) reported thickening of the basement membrane of Bowman's capsule, of the proximal and distal
convoluted tubules, and the glomerular capillaries in four young early diabetic patients on electron microscopy. In two of the four patients these abnormalities were seen five to eight weeks after the onset of clinically manifest diabetes, which go to show that the basement membrane of the entire nephron may become abnormal almost simultaneously with or before the onset of the clinical features of the disease.

It was suggested by them that there was an abnormality of polysaccharide metabolism as the basement membrane consisted essentially of glycoprotein which was responsible for the renal lesions in diabetic patients, although Aldesberg et al (1956) did not find raised polysaccharide levels in only diabetic patients with no clinical evidence of nephropathy or retinopathy. Similar conclusions were drawn by El Mahallawy et al (1960).

On electron microscopy the basement membrane was about 10 times thicker in the glomeruli of the diabetic patients than in normal subjects.

Mathur (1964) stated that nodular type of nephropathy was revealed by those who were elderly patients and had mild form of diabetes for longer duration.

Nodular glomerulosclerosis (the Kimmelstiel-Wilson Nodule) may result from focal thickening in the diffusely thickened basement membrane. This is in accordance with Bell's (1950) original idea that the nodular lesion were derived from the diffuse lesions.
It was suggested by Sabour (1962) that since diabetic glomerulosclerosis developed as a lesion of the basement membrane, it should not be described as inter-capillary or intra-capillary on light microscopy.

As the nephron is involved in the very early stages of the diabetes, it is quite possible and adds considerable weight to the theory that the renal lesions are an integral part of the disease process rather than a complication of it.

**DIFFUSE DIABETIC GLOMERULOSCLEROSIS**

The diffuse variety of diabetic glomerulosclerosis was first described by Fahr in 1942 and later by Laiply Eitzen and Dutra in 1944. They called it "focal fibrosis" and regarded it as an earlier stage of the nodular lesion. Bell (1953) stated that the nodular lesions are always associated with diffuse lesions and that the diffuse lesions are not uncommonly found alone and may progress to complete obliteration of the glomerulus without the formation of definite nodules. He stated that nodular lesions develop from diffuse lesions and that no sharp separations between the two types can be made. Gellman (1959) did not agree with the above view and did not believe that the diffuse lesion was merely an early stage of nodular lesion. He concluded that nodular lesion though of great diagnostic value is of little functional importance and that nephrotic syndrome is caused by diffuse
lesion and by the associated arteriolar and tubular lesion. There was no correlation between the severity of diffuse and nodular lesions.

Extensive studies of the glomeruli of diabetics using light and electron microscopy indicate that the first change in most diabetics, is the development of diffuse glomerulosclerosis, as described by Bell (1960). There is an increase in the number of endothelial cells (or mesangial cells, a point still under debate) with the accumulation of proteinaceous "hyaline" material in these cells. Later similar material appears to be deposited extra-cellularly, either directly or by the death of swollen endothelial cells, containing this material. When the nodules form, these are not thrombosed aneurysmal capillaries, but nodules of extra-cellular protein located in the so called mesangial space. The nodules are predominantly glycoprotein since they are strongly PAS positive.

In diffuse glomerulosclerosis the basement membrane was the first structure to be involved and that the process later spread to include the endothelial cells and epithelial cells. Diffuse diabetic glomerulosclerosis is characterised by the presence of abnormal material in the capillary walls which are thickened. This material is P.A.S positive and probably contains polysaccharides. The capillary wall is completely surrounded and involved so that in cross section it looks like a thickened ring (compare with nodular glomerulosclerosis in which the
part of the capillary wall nearest to Bowman's Capsule remains thin and delicate, until the capillary is completely occluded).

Gellman et al (1959) stated that the diffuse lesions can be distinguished from the somewhat similar lesion which occurs in membranous glomerulonephritis and non-diabetic arteriolar nephrosclerosis, except in the very late stages. The diffuse lesion is local and focal in distribution in the early stages, and even in late stages the degree of thickening varies from place to place. Arteriosclerosis is almost invariably associated with diffuse lesion. The diffuse lesion is usually observed first in the peripheral capillaries of the glomerular tuft. The glomeruli are large and remain large even when completely hyalinized. The diffuse lesion has no fibrillar appearance.

The diffuse lesion does not contain collagen or reticulin although the nodular lesion almost always contained reticulin fibres. In nodular lesion the outer aspect of the capillary loops are not thickened whereas they are involved early in diffuse lesion. The nuclei in the nodular lesion are almost confined to the periphery while in the diffuse lesion nuclei are seen buried uniformly throughout the lesion and it looks as if the abnormal material has spread from the basement membrane to involve the cell cytoplasm. Later the epithelial cell nuclei also seem buried.

For the above foregoing reasons, Gellman (1959) did not believe that the diffuse lesion is merely an early stage of nodular lesion.
Sabour, MacDonald and Robson (1962) reported involvement of the basement membrane of the glomeruli, Bowman's capsule and tubules in all 4 cases when seen by electron microscope, although all of them were without evidence of light microscopic changes of glomerulosclerosis. In one of the above cases known diabetes was present only for five weeks. In some of the glomerular lesions an early "heaping up" of the basement membrane was present, which was considered as the forerunner of the typical nodular glomerulosclerosis of the late stages of the disease. In course of time, depending upon the degree and rate of progress, they become visible under light microscopy.

It has been reported that a pathologic diagnosis of glomerulosclerosis may not always be associated with a clinical diagnosis, as the clinical symptoms may take longer to develop.

The thickening is due to the deposition of P.A.S Positive carbohydrate protein complex in the basement membrane. It is distinguished from arteriolar nephrosclerosis in which the lesions are sclerotic and ischaemic and from glomerulo-nephritis, in which there is cellular proliferation and fibrosis.

Diffuse glomerulosclerosis of mild or moderate degree can be present without any nodular lesions, but nodular glomerulosclerosis is apparently never seen without accompanying
diffuse changes. Arteriolar changes in the afferent and efferent arterioles are always present in severe diffuse glomerulosclerosis, but are not necessarily present when the lesion is predominantly nodular. It is thought that both nodular and diffuse lesions are different expressions of the same basic pathologic process.

THE EXUDATIVE LESION

This is the least common and least specific of the changes seen in the glomerulus in diabetes. It has been given many other names, e.g. fibrinoid crescent (Spuhler & Zollinger 1943); "fibrin cap" and capsular drop (Barrie et al 1953); acellular hyaline lesion (Muirhead & Montgomery 1956) and hyaline fibrinoid lesion (Koss 1952).

Typically, the lesion is found as an intensely crescentic "cap" around part of the periphery of the capillary loops. Frequently, it surrounds a nodule, less often, it is found as small circular "drops" attached to the inner aspect of Bowman's capsule or even may lie free in the capsular space. Koss (1952) stated that these capsular or free lesions were really attached to exudative lesions in or on the capillary tuft.

The lesion looks amorphous and structureless. There are no nuclei or cellular elements. They are vacuolated and vacuoles are filled with fat in frozen sections. These lesions are more strongly eosinophilic than the
nodular or diffuse glomerulosclerotic lesion and stain intense orange red colour with Mallory staining as opposed to blue of the other two diabetic lesions. This lesion is found if severe nodular or diffuse glomerulosclerosis is also present.

Hall (1952) stated that the exudative lesion is a late manifestation of diabetic nephropathy and is always accompanied by severe arteriosclerosis. He further stated that the lesion is due to ischaemia as a result of atherosclerosis of renal artery or its large branches.

Anderson (1954) stated that the exudative lesion showed no attempt at repair and probably meant a terminal event.

Laufer and Stein (1959) noted a correlation between the state of shock and exudative type of lesion. They mentioned that increased vascular permeability of local or systemic origin, was a factor in the pathogenesis of this lesion. Shock is one condition in which increased vascular permeability is known to occur.

Mathur et al (1960) and (1964) stated that exudative lesion did not necessary mean a terminal event.
It is the general impression that at a very early stage of diabetic nephropathy - before any definite evidence of glomerulosclerosis is present the glomeruli are unduly congested and the capillary loops are widely dilated. Armanni (1875) emphasized this finding.

Huckel (1939) described aneurysmal formations on the capillaries that were presumed to precede the hyalinization process in the glomeruli. Gunther (1941) claimed such aneurysmal capillary dilatations secondary to congestion, due to the efferent branch of the capillary loop being compressed by the hyaline masses before the afferent one. Fahr (1942) never saw such aneurysms in his large material.

Dana & Zubroid (1954) and Anderson (1954) emphasized that with the development of the diffuse variety of glomerulosclerosis, most of the capillaries became narrowed out, an occasional one remained dilated or became an aneurysm.

Typically, they surround the nodular lesions and are rarely seen in specimens which contain no nodular lesion.

Mackenzie and Nettleship first described the capillary microaneurysms in the retina in 1879 and were rediscovered by Ballantyne and Loewenstein in 1943. Friedenwald (1948) stated that the walls of the retinal
Aneurysms stain strongly with P.A.S. stain and caps of laminated PAS positive material surround them.

Ashton (1949) & Friedenwald (1950) believed the inter capillary glomerulosclerosis and retinopathy diabetica to be manifestations of the same pathologic process modified by different anatomical structures of the parts. Friedenwald ventured the possibility that the aneurysmal capillary dilatations in glomeruli might be analogous to the retinal microaneurysms. Ashton (1950, 1957) and Ballantyne & Lowenstein (1943) emphasized the many points of similarity between retinal and glomerular capillary aneurysms and nodules and the close clinical associations between them.

Ashton (1957) found 67.4% retinal microaneurysm and 30.9% nodular glomerulosclerosis in a post-mortem study of 203 diabetic patients. Every patient with nodular glomerulosclerosis had clinical or histological evidence of retinopathy.

Eston (1960) believed that comparison between the renal and the retinal lesion was not entirely convincing.

Mathur et al. (1964) could not find any correlation between microaneurysms of the diabetic nephropathy and retinopathy.
They are large vacuolated cells and contain fat. Hartercoft (1955) stated that they represent circulating cells which have become impacted in the glomerular capillaries. There is another view which states that these are local endothelial cells which have taken up lipids from the blood. Similar cells are found in nephrotic syndrome due to diseases other than diabetes mellitus, in which nodules and diffuse lesions are not found.

The role of lipophages in the pathogenesis of nodular and diffuse lesion is questionable (Gellman et al 1959).

PERICAPSULAR FIBROSIS

It is the layers of fibrous tissue which is frequently seen surrounding the Bowman's capsule. It is roughly proportional to the severity of glomerulosclerosis. Glomeruli which become almost completely ischaemic or hyalinized are frequently surrounded by thick concentric fibrous bands. Periglomerular fibrosis in diabetes is said to be associated with ischaemia rather than inflammatory process (Gellman et al 1959).
ISCHAEMIA & COMPLETE HYALINISATION

The glomeruli become increasingly ischaemic and become completely hyalinized as the nodular and diffuse lesion increases in severity. In end stage kidney, it is often impossible to identify the underlying pathology although it may still be possible to recognise some nodule or diffuse lesion.

As the lesion becomes "older" the glomeruli take less strongly the PAS stain, as if the polysaccharide material is replaced by the fibrous tissue, which suggests some change in the composition of the abnormal material (Gellman et al. 1959).

B. TUBULAR LESIONS

ARMANNI-EBSTEIN LESION: DEGENERATION

This striking pathologic change is found only in those diabetic patients who die of prolonged uncontrolled diabetes, particularly in diabetic acidosis and coma.

HISTOLOGY: The tubular epithelial cells become swollen and granular with vacuolated cytoplasm which contain large amounts of glycogen. This change was frequently observed before insulin therapy when many patients died in diabetic coma.

Ritchie & Waugh (1957) stated that they have not noted the Armanni-Ebstein lesion in renal biopsy specimens and is no longer seen frequently at autopsy. This was also corroborated by Gellman et al (1959). This lesion is said to be now a medical or pathologic curiosity without clinical significance.
ATROPHY & DILATATIONS

It is a sequale of glomerular damage. Gellman (1959) noted some degree of tubular atrophy in 75% of 53 cases and in all the 9 autopsy series. Tubular dilatation was seen less often. Dilated tubules did not contain colloid casts.

PERTITUBULAR HYALINE CUFFS

Fahr (1942) was the first to describe this lesion. Special stains (specially PAS) showed that the material lay outside, but on, the tubular basement membrane which gave it a smudged appearance. The strong PAS staining suggested a high polysaccharide content.

Koss (1952) suggested that it is a form of hyaline fibrinoid similar to the material seen in exudative lesion in diabetic nephropathy and in the acinar ducts in the breasts of diabetic patients.

The overall appearance of this material gave an impression of amyloid disease, but neither the nodules nor the peritubular "Cuffs" take the Congo-Red or Crystal Violet Stain. Gellman (1959) noted peritubular hyaline Cuffs in 42 biopsies (67%) and in all the autopsies. Some of the tubules were surrounded by cuffs of eosinophilic material.
Almost all authors agree that some degree of renal arterio-and/or arteriolo-sclerosis, as a rule is found together with intercapillary glomerulosclerosis. By many authors the arteriosclerosis is considered a condition, sine qua non and the intercapillary glomerulosclerosis is regarded by some as a special form of nephrosclerosis.

Fahr (1942) distinguished two forms of independent primary hyalinisation leading to glomerulosclerosis:

(A) One running parallel with arterio-sclerosis and with a similar genesis (capillary glomerulo-sclerosis), and

(B) A form, independent of arteriosclerosis namely the extra capillary glomerulosclerosis - the Kimmelstiel Wilson lesion.

Bell (1946) showed that the inter-capillary lesions are closely related to arteriosclerosis. The arteriolar disease in some way brings out the inter-capillary lesion, but a severe arterio-sclerosis did not produce a glomerular lesion of any kind in one third of his cases. Bell (1946) studied the occurrence and the degree of such changes in an autopsy material of 606 diabetics at the University of Minniesota (1910-1940). He found that in those aged under 40 years, the small renal arteries were either normal or showed a grade I intimal thickening; after the age of 50 years renal arterio-sclerosis was found somewhat more
pronounced than in a control material. Renal arteriosclerosis was not a frequent finding of Juvenile diabetics, while it occurred in 77.6% of diabetics over 50 years of age. This was 5 times as often as in the control material, and the arteriolar changes were far more pronounced than in the non-diabetics, particularly so among the females. He declared that a thick homogenous hyaline deposit in the arterioles is strong presumptive evidence of diabetes. He concluded that renal arteriosclerosis is an age-change which develops independent of hypertension.

Henderson, Sprague and Wagener (1947) showed a patchy thickening of the arteriolar walls with considerable hyalinisation. In cases with hypertension the arteriolar changes often were identical to those in malignant hypertension. Henderson, Sprague and Wagener (1947) in 78 cases of intercapillary glomerulosclerosis found some degree of arteriosclerosis in all kidneys, in many cases it was minimal. They concluded that arteriosclerosis cannot be thought the only etiological factor.

Kimmel-stiel & Porter (1948) declared that the possibility of arteriosclerosis being a contributory cause cannot be excluded, but it cannot be considered the only cause of intercapillary glomerulosclerosis.

Hall (1952) as well as Gellman (1959) noted atherosclerotic plaques and lipophages in the walls of parenchymal branches of the renal artery. They have not seen these in any condition other than diabetes and consider them pathogno-
Gellman (1959) found vascular lesion almost universally present and noted hyalinisation of arterioles in 83% of the biopsies and all 9 autopsy specimens. Abnormal amounts of fat were frequently found in the vessel walls when tissue was stained with special fat stains. Gellman noted greater degree of hyalinisation of glomerular arterioles in diabetics than in any other condition, and felt that the material seen in the vessel walls is not in fact the kind of hyaline seen in arteriolar-sclerosis, but is the same polysaccharide rich material which is deposited in the glomeruli, around the tubules, vasa nervosa (Fagerberg 1957) mammary tissue (Merriam 1957). The arterolar damage increased pari passu with the glomerular lesions, in contrast to primary arteriolar nephrosclerosis, wherein the glomerular lesion follows the development of vascular lesion.

Some degree of benign nephrosclerosis is commonly found in older diabetic patients with or without any other associated renal disease. It does not seem to be much more severe in diabetic patients than in non-diabetics and probably reflects the ageing process. (Lee 1963).
The fundamental cause of the specific glomerulosclerosis is not known.

The presence in some diabetics of a so-called nephrotic syndrome with massive proteinuria and edema had been known for a long time. Naunyn (1910), Kramer (1928), Labbe, Nepveux & Saligman (1927) described the nephro-pancreatic syndrome of diabetes with albuminuria and edema. Fahr (1924) observed glomerular changes characterized by well defined roundish homogenous formations giving a typical amyloid reaction. Bell & Clawson (1928) observed similar renal changes in diabetic patients. Volhard (1931) regarded such cases as nephro-sclerosis with secondary parenchymal degeneration. Meyer (1932) described cases of prolonged diabetes complicated by arteriosclerosis and arteriolar-sclerotic contracted kidney distinguishable by a combination of nephrotic syndrome and polyneuritis. Bachman (1936) found glomerulosclerosis in diabetes kidney. Kimmelstiel Wilson (1936) gave a detailed description of the histologic picture of the condition later termed intercapillary glomerulosclerosis. They regarded these intercapillary lesions as part of a clinical syndrome, consisting of diabetes, severe and extensive edemas of nephrotic type and massive proteinuria. Hypertension was frequent and
renal insufficiency occurred in many cases. The characteristic histologic changes consisted of pronounced hyaline thickening of the intercapillary connective tissue (mesoangium) in the centre of the glomeruli, where homogenous hyaline masses were found.

Allen (1941) claimed the process to originate within the capillary wall. (mural glomerulosclerosis). Fahr (1942) preferred the term of extra capillary glomerulosclerosis. Spuhler & Zolinger (1943) believed the process to be a mesoangium-hyalinose spreading to the vascular wall. However, no sharp distinction was demonstrated between mesoangium and the basement membrane. Laippy, Eitzen and Dutra (1944) described a focal fibrosis in the glomeruli, which in their interpretation represented an early stage of the intercapillary glomerulosclerosis. Bell (1946) stated that the hyaline masses were derived from the inner basement membrane of the capillaries. Kimmelstiel (1948) preferred the original term "intercapillary" because it appeared to be the most descriptive one and most authors agree that the fully developed lesion creates an impression that it is situated between the capillaries.

Henderson, Sprague & Wagener (1947) classified intercapillary glomerulosclerosis as follows:

(a) Early stage - Small deeply staining club shaped masses situated in the midst of a diffuse thickening along the axis of the lobule.
(b) Advanced Stage:- Hyaline like globular, deeply staining lesions like those situated in the midst of a diffuse thickening along the axis of the lobule.

Fahr (1942) thought the hyaline formations to be due to a local conditioned plasma or albumin precipitation. Spuhler & Zollinger (1943) reported that the homogenous substance possesses sudanophil qualities because of fatty deposition. The fatty deposits in the glomeruli in intercapillary glomerulosclerosis were mentioned by a number of authors (Kimmelstiel & Wilson 1936; Anson 1938; Newburger & Peters 1939; Simon 1940; Allen 1941; Porter & Walker 1941; Laipply, Eitzen & Dutra 1944). Braehetto-Brain, Repetto, Farrari & Benzerry (1946) stated that the essential part of the process is a glomerulus filtration of large proportion of proteins and scarce lipids.

Jacobs (1949) showed that considerably larger amounts of mucopolysaccharide in the form of glycosamine were found in the blood of diabetics than in those of non-diabetics. The highest glycosamine values were found in uncontrolled diabetes regardless of the patient's age. The relation between the glycosamine and the blood sugar remained remarkably constant, even when insulin was given.

Friedenwald (1950) found that the hyaline material lying in the renal glomeruli is of mucopolysaccharide nature and thus a common pathophysiological basis was established for the diabetic retinopathy (with microaneurysm)
and intercapillary glomerulosclerosis.

Wilens, Elster & Baker (1951), found statistically significant higher fatty content in the glomeruli in intercapillary glomerulosclerosis than in any other renal disease. They thought that deposition of fat in the glomeruli is of primary importance in the development of the lesion of intercapillary glomerulosclerosis.

Colwell (1957); Duncan (1958) and Kark & Gellman (1960), discussed the possibilities regarding the pathogenesis of diabetic glomerulosclerosis but no definite conclusions have been drawn.

Goth et al (1957), incriminated fluctuation of blood sugar levels, Rich et al (1950) and Bloodworth & Hamwi (1956), thought it was caused by abnormalities of steroid metabolism, while Hartcort (1955) wondered whether the fat laden cells from liver impacted the glomerular capillaries.

Many investigators have questioned whether these lesions are inevitable concomitants of diabetes mellitus (Dolger 1947; Taft et al 1954; Downie & Martin 1959), or whether these lesions are complications which could be avoided by careful correction of the metabolic defect (Spoont et al 1951; Dunlop 1954; Hardin et al 1956).

McManus (1949), however thought that the immediate cause of the lesion seems to be the deposition of one of the abnormal products of metabolism in the vascular system of the kidney. Fagerberg (1957), reported similar material in vasa nervorum and Merriam (1957) found
periductal hyaline substances in the mammary glands of the diabetic women. Warren and LeCompte (1952) observed that practically all the pathological features of diabetes mellitus can be explained by the deposit of the mucopolysaccharide. In this connection, Berkman, Rifkin and Ross (1952); Gilliland Hanno & Strudwick (1954); Keiding-Tuller (1955); Bastenie et al (1958); Interozzi, Bernasconi, and Buscarini (1958), have reported increased levels of glycoproteins in the blood of diabetic patients with vascular lesions.

Barkeroff (1955) regarded the characteristic renal lesion due to lipid thrombi from a locally concentrated lipaemic plasma. Raphael & Lynch (1958) thought that the nodules developed as local thrombi in glomerular capillaries rendered weak by toxic anoxic effects and later, homogenized by lysis of RBC and concentrated by plasma lipids. Rose, Becker & Maengwyn-Davis (1954) and Wilens & Strumpf (1955) suggested that lipids in the cortisone preparations or the effects of cortisone on the level of circulating lipids might be responsible for the glomerular lesion in rabbits. Such observations and the presence of lipids in the glomerular nodules of human diabetes and the characteristic intense periodic acid Schiff reaction led many workers to correlate serum lipid and the mucopolysaccharide levels with the presence or absence of diabetic nephropathy and retinopathy. (Lynch & Raphael 1957; Muirhead et al 1956; Raphael & Lynch 1958; Wilens et al 1951).
Gellman et al (1959) regarded the glomerular change in artereolar nephrosclerosis as ischaemic and atrophic, the glomeruli being usually small, while diffuse glomerulosclerosis was not considered to be a sclerotic process at all and was due to the deposition of some substance, probably a mucopolysaccharide, first in the basement membrane and later in the endothelial cells and in contrast, the glomeruli were larger than normal.

Goldenberg et al (1959), Blumenthal et al (1960, 1961), however pointed out that similar elevations of these serum components occurred in a variety of diseases not linked with diabetes nor with the occurrence of the characteristic retinopathy or nephropathy.

Hyman, Hurwitz, Robbins, McDonald and Freinkal (1958) suggested that the nodular lesion did not occur as frequently prior to 1936 as it does now, because they found that in their study of the kidney sections of 42 diabetic patients, performed at the Mallory Institute of Pathology prior to 1923, (the year in which insulin was introduced in the general population), there was no kidney lesion, thereby suggesting the incrimination of exogenous insulin.

Gellman et al (1959) felt that there was a possibility that the nodules were caused by insulin. Schiller and Dorfman (1957) conceived that the prolonged usage of insulin (a foreign protein) might result in the formation of antibodies, and subsequent vascular damage. Freedman (1957) reported two patients with Kimmelstiel-Wilson nodules in whom diabetes was not suspected and did not receive any
insulin during life, but it was argued by Gellman (1959) that it does not mean that the body can not produce antibodies against endogenous insulin as it does against its own thyro-globulin.

Mathur et al (1964) felt that the nodular and diffuse type of lesions were the manifestations of the same metabolic change which occurred in the basement membrane. The diffuse changes occur first and the nodular changes are superseded later on with the passage of time.

Blumenthal et al (1959) (1960) (1961) stressed the importance of non-atheromatous proliferative lesion of the small arteries in a number of organs of diabetic subjects (e.g. peripheral vessels, coronary artery and retina). Some authors have shown that such lesions are similar to vascular changes produced by a variety of immunological mechanisms like erythroblastosis foetalis, metabolic diseases in pregnancy and in a variety of non-diabetic states, which suggests that in diabetes, insulin might be the antigenic agent. It has thus been suggested by Blumenthal et al that diabetic glomerulosclerosis might represent an immunological reaction and that proliferative lesions in diabetes may involve the small vessels of many organs. Proliferative vascular lesions were encountered about twice as often among diabetics as among non-diabetics.

Proliferative vascular lesions were characterised primarily by endothelial proliferation and the deposition of a PAS positive colloidal iron negative material, consistent
with the histochemical reaction of glycoprotein. These lesions were found in 48% of large vessels and 53% of small vessels in the kidneys in an autopsy series of 130 cases (Blumenthal 1962). This process could progress to complete hyalinization of the wall with a resulting lesion which would be indistinguishable from arteriosclerosis.

Freedman et al (1960) utilising fluorescence microscopy, showed that the nodular lesions of diabetic glomerulosclerosis bind anti-human globulin, thus indicating the presence of a globulin which may represent antibody. Berns et al (1962) demonstrated, by means of fluorescence microscopy, the presence of a substance in various structures of the kidney in diabetic glomerulosclerosis which appeared specifically to bind insulin. Other observations presented in that study suggested that the vascular complications of diabetes may be the result of a hypersensitivity reaction to this hormone.

Berns et al (1962) discussed three likely possibilities as to the nature of this substance in the renal lesions of diabetic glomerulosclerosis which possess this insulin binding capacity:

(1) It may be a mucopolysaccharide or lipoprotein.

(2) It may represent tissue deposits of the insulin binding antagonists in the serum which have the electrophoretic mobility of albumin or alfa-globulin.

(3) It may consist of an antibody, against insulin.
There are a number of studies on the above possibilities like those of Bornstein & Hyde, Freedman et al, Taft et al & Dixon et al. It is possible that insulin preparations contaminated by species protein may be antigenic but this appears unlikely since most preparations are of high purity and have been tested to ensure removal of such impurities.

Sanger (1960) showed that while insulins from a number of species like pig, rabbit, human, cattle, sheep, horse, and whale are identical in their biological activity, there are species variations in respect to three amino acids contained within the disulfide ring of the A chain, and judging from the high incidence of antibody formation in humans receiving insulin, such differences appear significant, to act as antigens.

Gordan (1958) and Blumental et al (1961) suggested the possibility of an auto-immune mechanism based on a report by LeCompte (1958) on the occurrence of insulitis of pancreatic islets in the early juvenile diabetics, before exogenous insulin therapy could be given. This auto-immune phenomena may be similar to that present in patients with lymphocytic thyroiditis.

Lonergan and Robbins (1959) reported absence of inter-capillary glomerulosclerosis in 62 diabetic patients with hemochromatosis, while Becker & Miller (1960) found 22 instances of this renal lesion in 52 patients. It is thus clear that this renal complication occurs with less frequency in diabetes with haemochromatosis than in diabetes.
Blumenthal et al (1962), suggested that the various components of the diabetic glomerulosclerotic lesion contains an insulin anti-insulin complex and there is a possibility that this renal complication may be immunologic with insulin as the definitive antigen.

Marble (1963), stated that it is often forgotten that the failure to recognise changes in kidneys by earlier observers was due, in considerable part to the fact, that prior to the introduction of insulin and the chemotherapeutic agents and antibiotics, the diabetic patient died before conspicuous renal changes could develop.
SPECIFICITY OF THE GLOMERULAR LESION


Intercapillary glomerulosclerosis has been reported in non-diabetic arteriosclerotic kidneys from 0.8 to 12 per cent (Laippeley, Eitzen and Dutra 1944 and Goodoff 1945).

Horn & Smetna (1942), Goodoff (1945), Laippeley, Eitzen & Dutra (1944), Raphael & Lynch (1958), included diffuse and exudative lesion in their studies.

Grant (1954) stated that absence of glycosuria is not adequate evidence of absence of diabetes as the renal threshold rises with renal failure in diabetes mellitus. Even a normal fasting blood sugar does not rule out diabetic state and Freedman in 1957 pointed out that in none of such cases was there good evidence that they did not have diabetes.

Kimmelstiel & Porter (1948); Gilliland (1951); Robbins et al (1952); Rogers et al (1952) and LeCompte (1958), pointed that much of the confusion regarding specificity of the glomerular lesion was due to lack of precision and definition.

Gellman et al (1959) in their study of more than 600 renal biopsy specimens and numerous autopsies never saw nodular
glomerulosclerosis in any disease other than diabetes mellitus. Superficially similar lesions were seen in amyloidosis and lobular glomerulonephritis, but they have not met the test of strict diagnostic criteria laid down by them for diabetic glomerulosclerosis.

In addition to nodular lesions in diabetes mellitus, Fahr (1942), Horn (1942), Laippley (1944), Goodoff (1945), and Bell (1950) described diffuse type of glomerular changes. Although nearly similar changes may be found in chronic glomerulonephritis, pyelonephritis and nephrosclerosis, it was affirmed by Laippley, Eitzen and Dutra (1944) and Gellman (1959) that it was possible to distinguish histologically, the diffuse diabetic hyalinization of other etiology.

Fahr (1942), Bell (1950) and Gellman & Pirani (1959) have expressed the view that diffuse lesions are much more frequent than the nodular lesion.

Gellman (1959) stated that there was no regular relationship between nodular glomerulosclerosis (Kimmelstiel-Wilson lesion) and proteinuria, hypertension, renal failure and nephrotic edema (Kimmelstiel Wilson syndrome) and that the changes in renal function were caused by the diffuse diabetic glomerulosclerosis and by the associated arterolar and tubular changes.
Gellman (1959) stated that mild and moderately severe diffuse glomerulosclerosis was often seen in specimens in which no nodules could be found but nodular lesions were never found in the absence of diffuse lesion. There was no relationship between the severity of nodular lesion and the severity of the accompanying diffuse lesion.

Neither lesion was seen unless arteriolarsclerosis was also present. Severe degrees of arteriolarsclerosis were invariably accompanied by severe degrees of diffuse glomerulosclerosis, but not necessarily by severe nodular lesion.

Exudative lesions were found in the more severely damaged kidneys. They were never found except in the presence of moderately severe arteriolarsclerosis.

The severe grades of tubular damage were invariably found in association with severe degrees of glomerular damage, and were probably secondary to them. There was no correlation between degree of peritubular cuffing and nodular glomerulosclerosis, but there was a correlation with diffuse glomerulosclerosis. Severe degrees of 'cuffing' were only found in specimens containing other severely damaged tubules. It seemed that the tubules which continued to function were more liable to develop pertibular deposits of this polysaccharide rich material.

The severity of diffuse diabetic glomerulosclerosis correlated with the severity of vascular and tubular lesion, but the severity of nodular diabetic glomerulosclerosis could
The presence of nodular lesion was associated with abnormal findings in the height of diastolic B.P., ketosis, diabetic retinopathy, edema, proteinuria, the levels of serum urea nitrogen, serum creatinine, serum albumin and the creatinine clearance, but there was no tendency for the test to become more abnormal as nodular lesion became more severe. In contrast, increasing severity of diffuse lesion was closely correlated with the increasing diastolic pressure, proteinuria, serum urea nitrogen, serum creatinine levels, creatinine clearance, ketosis, retinopathy, edema, and the nephrotic syndrome.

Mathur et al (1964) concluded that no definite correlation could be demonstrated between diffuse type of nephropathy with age, sex, duration, severity of diabetes or with the clinical picture. This type of lesion appeared to be the earliest change seen in the kidneys of diabetic patients, and the nodular type of lesion further developed in course of time.

The exudative lesion was manifested mainly by those who went into the stage of shock, which was not uncommon in uncontrolled diabetics.
The renal involvement in diabetes mellitus is almost invariably of the mixed etiology including both degenerative and infectious elements, which contribute significantly to the total disease process (diabetic nephropathy, pyelonephritis and nephrosclerosis).

The term infectious elements is usually employed to signify pyelonephritis, the pathological process resulting from the immediate or late effects of bacterial infection in the renal substance and pelvocalyeal system. Chronic pyelonephritis has been defined as the end result of bacterial inflammation in the kidney (Haaschou 1948; Kleeman et al 1960).

INCIDENCE

It is generally admitted that diabetic patients are more prone to urinary tract infection. However, there is no agreement on just how common the infections are. Surveys of various groups of diabetic patients both living and dead have yielded divergent results. The variation depends upon the criteria used for diagnosis of pyelonephritis.

Sharkey & Root (1935) found that almost one in every five diabetic patients coming to autopsy at the New England Deaconess Hospital since 1919 showed some infectious process in the urinary tract. They found purulent infections in some part of the urinary tract in 18 or 30 per cent in a
series of 196 autopsies on diabetic patients, and also reported an incidence of only 6% in their clinical series. Baldwin & Root (1940) found that serious renal infections occur five times as frequently in the diabetic as in the general group at autopsy.

Bowen & Kutzman (1942) made complete urological examinations of 82 unselected diabetic females aged between 36 and 79 years and found that leucocytes and microbes were present in the renal pelvis on one or both sides in 34 (41.5%) and 14 (17%) had leucocytes and microbes in the vesical urine. Harrison & Bailey (1942) found asymptomatic bacilluria in 27 (54%) and pyuria in 10 (20%) of 50 unselected diabetics. In a non-diabetic control material the corresponding number were 4 (8%) and 2 (4%) respectively. They claimed bacteriuria with pyuria to be indicative of an already existing focus of infection in the renal tissue, and initial destruction of the tissues. They said that if bacteriuria is found on repeated examinations they should be considered as indicating an active stage of infection, even in the absence of pyuria in patients with diabetes mellitus. They also reported an incidence of 54 per cent of urinary tract infection among diabetics in their autopsy series.

Bechgaard (1946) found 135 cases of renal disease among 1000 hypertensive cases. Of these 22, 16% were diabetics mostly females. They offered the same clinical picture namely that of nephrosclerosis, in many cases complicated by infection of the urinary tract. Eleven (50%) had pyelonephritis.
Robbins et al (1949) found acute pyelonephritis in 19.5 per cent of 307 postmortems/diabetic persons. Rohrer (1948) found incidence of pyuria about twice as often as in the control material, on examination of 2674 diabetics during a 25 year period at the Mason Clinic, Seattle. Mann, Gardner & Root (1949) stated that of 83 diabetics with proven urinary tract disease 12.1% had cystitis and 25.2% had pyelitis and pyelonephritis.

Ternoe (1951) examined 127 diabetics with a view to infection of the urinary tract. 89 patients had sterile urine and 28 (22%) had pyuria. Bernard et al (1953) found 30% suffered significant infection of the urinary tract in a series of 100 necropsies on diabetics dying in the hospital.

Kass (1956) reported that the incidence of significant bacteriuria was three times as high in diabetic women out-patients as in non-diabetic women in the general medical clinic of the same hospital, while Huvas and Rocha (1959) found an equal incidence of asymptomatic bacteriuria in hospitalized diabetic and non-diabetic patients. Jenson at Pennsylvania Hospital (as quoted by Lee 1963) reviewed the autopsy evidence of renal infection in diabetic and non-diabetic patients and found that each group had a 22% incidence of disease. He concluded that there was no greater frequency of pyelonephritis in diabetic patients at the time of death. Young and Clancy in 1955 found that 30% had positive urine cultures as opposed to 10% of non-diabetic women from the general medical clinic.
Havas & Rocha (1959) found a higher incidence of infection in diabetics than in non-diabetics. Gellman et al (1959) reported that according to the classical criteria of Weiss & Parker (1939), in none of the biopsies or autopsy specimens could a definite diagnosis of acute or chronic pyelonephritis be made. In six biopsies out of 53 renal biopsies, (10%) chronic pyelonephritis was strongly suspected because of the degree of interstitial fibrosis and cellular infiltration. Chronic pyelonephritis was suspected in five out of 9 autopsies, 55%. White in Joslin (1959) reported an incidence of 40.8 per cent of significant urinary infections for adult and juvenile diabetics from 1950 - 1957 in their autopsy studies at New England Deaconess Hospital. White also reported incidence of clinical pyelonephritis of 2 per cent for males and 12 per cent for females in their clinical study of youth onset diabetics who survived their disease for at least 20 years.

Kass (1960) stated that true bacteriuria was present at autopsy in 40 per cent of unselected diabetic cases and that 15-20 per cent of persons examined post mortem had active pyelonephritis. He also reported an incidence of 40 per cent in those pregnant women who were untreated for bacteriuria and none in whose urine cultures had been made sterile by treatment. Rengarts (1960) found a much higher incidence of urinary infection in patients confined to bed than among ambulatory diabetics. The incidence of infection
among ambulatory diabetics was 14% of 43 patients. Kark and Gellman (1960) reported an incidence of 20 per cent infected urine in a random series of 55 male diabetic outpatients in a county hospital clinic. None of these patients had symptoms suggestive of urinary tract infection.

Among some of the Indian series Sathe (1960) reported an incidence 32 per cent in their predominantly male series of mostly uncontrolled 50 diabetics. Mitra et al (1960) noted 2 cases of infective elements among 6 cases of nephropathy with duration of diabetes within 5 years.

O'Sullivan et al (1961) found prevalence of urinary infection in 2 out of 59 diabetic males (3%) and 18 out of 91 females (19%) in diabetic out patient population. He did not find significant incidence of infection of the urinary tract between diabetic and control group of patients. Daysog et al (1961) reported incidence of 50 per cent pyelonephritis in 62 cases of renal biopsies conducted on prediabetic and diabetic cases. Solomon (1963) found very little histological evidence of renal infection in 51 unselected diabetic renal biopsies although it was carefully searched for. Hansen (1964) found prevalence of urinary infection in 5 out of 67 males (7%) and in 15 out of 81 females (18 %). Mathur et al (1964) illustrated that the presence of pus cells in the urine of a male diabetic should not be regarded lightly and on account of intermittent nature of bacteriuria, pyelonephritis may not be diagnosed even by culture. Parrish (1965) found prevalence
of urinary infection in men to be 2% and in women 14% attending an out patient diabetic clinic and 84% of the women with infection had a history of previous catheterisation, which in many had been done on more than one occasion.

The incidence of acute and chronic pyelonephritis both in general population and in persons with diabetes mellitus varies widely from report to report. In studies at autopsy and on living individuals in the general population, the frequency has been found to range from 10-20 per cent (Strauss 1963). Variation in incidence as reported in the literature is due not only to differing types of autopsy material but also to the varying criteria for diagnosis of pyelonephritis. Regardless of the diagnostic criteria used, there is general agreement that acute and chronic pyelonephritis as well as urinary tract infection in general, are more common in diabetic than non-diabetic individuals. Many a time the infection is present without any constitutional symptom or symptoms referable to the urinary tract so that it is very likely that many cases of urinary tract infection may go undetected as patients may never complain about it.

According to autopsy studies Sharkey and Root (1935), Baldwin & Root (1940), Bernard et al (1953), diabetes mellitus predisposed to infections of the urinary tract and these were more common in diabetics than in the general population. Kass (1960) reported an incidence of bacteriuria of 4 per cent in males and 6 per cent in females in the general population and 5 per cent in males and 18 per cent
in females in the diabetics, in medical O.P.D at Boston City Hospital, Joslin clinic and Joslin Research Laboratory (1962-63) reported an incidence of asymptomatic bacteriuria 1.6 - 2 per cent among diabetic girls screened at a summer camp, (Younger, 1965). Other workers have reported an incidence of bacteriuria of 0.6 to 1.0 per cent in non-diabetic girls in the general population, (Kunin 1964).
Joslin clinic reported 7 per cent (18 out of 253) prevalence of bacteriuria in pregnant diabetics, (Unpublished data as quoted by Younger 1965). Kass (1960) reported 4-7 per cent of bacteriuria in pregnant women. Kaitz and Hodder (1961) reported an incidence of 4.4 per cent significant bacteriuria in 616 patients at a prenatal clinic. It is not clear whether there is a significant difference in the incidence of bacteriuria for diabetic and non-diabetic women.

Whatever is the absolute incidence of pyelonephritis, the disease may be more common in diabetics. The great frequency of infections of the urinary tract in diabetes makes pyelonephritis a very frequent complications in diabetics. According to Weiss & Parker (1939) there is no isolated pyelitis. The kidney is always simultaneously affected and therefore the condition is always a pyelonephritis. Although this view is as extreme one (Baldwin & Root 1940), it will undoubtedly be best to take into account that there is always a renal lesion (Raaschou 1948).
"Ascending infection of the urinary tract with uremia, like a Damocles Sword overhangs the diabetic with vesical paresis, wherein the occurrence of necrotising pyelonephritis is impending."

Harrison & Bailey (1942).

This a special complication of local renal infection and is seen more commonly in diabetic than in non-diabetic patients. (Joslin 1959). A consequence of pyelonephritis in diabetics, nearly always fatal, is necrosis of the renal papillae. The condition was first described by Friedreich (1877) and Gunther (1937) first called attention to the frequent occurrence of this condition in diabetes mellitus.

INCIDENCE:

Edmondson, Martin & Evans (1947) gave an excellent review of this important condition. Of 859 diabetics, 107 died of pyelonephritis 29 of whom (3.4% of all diabetics) had papillary necrosis. Among 1021 non-diabetics 33 had pyelonephritis, 21 of whom (2.05 % of all non-diabetics) had papillary necrosis.

Gaustad & Hertzberg (1950) described 6 cases of papillary-necrosis, five were diabetics. Arteriosclerosis of the renal artery was found in 5, arteriolosclerosis renis in 3 and
intercapillary glomerulosclerosis in 2. Muirhead, Vanetta & Grollman (1950) while experimenting on dogs arrived at the result that the pyelonephritis in papillary necrosis is secondary to obstructive uropathy, while in diabetics the infection with interstitial inflammation is primary. Whitehouse & Root (1956) found renal papillary necrosis in 4% of the diabetic patients in an autopsy series.

CLINICAL FINDINGS:

Necrotising renal papillitis is usually associated with a triad of findings:

(a) renal infection,
(b) vascular disease of the kidney,
(c) some degree of urinary tract obstruction.

In non-diabetic patients it is associated with uraemia, angiitis involving the kidneys and renal vein thrombosis, when it is associated with pyelonephritis.

PATHOGENESIS:

The pathologic appearance is that of infarction and necrosis of the pyramids associated with pyelonephritis and sloughing of some medullary tissue into the urine.

Edmondson, Martin & Evans (1947) claimed that the diabetic state, the renal vascular disease (including Kimmelstiel Wilson's syndrome) and the poor blood supply to the papilla are contributing factors in the pathogenesis of papillary necrosis. Arterio- and arteriolo-sclerosis are practically always found in the kidneys.

Robbins and Angrist (1949) pointed out that papillary
necrosis in diabetics is found in connection with acute pyelonephritis, in non-diabetics it is associated with mechanical obstruction of the urinary tract. They also ventilated the possibility of the papillary necrosis being analogous to the renal cortical necrosis produced by altered hemodynamics, with spasm of the medullary vessels rather than that of the cortical vasculature, as the significant factor in the mechanism.

Beeswick (1960) produced the lesion in animals by occlusion of the renal vein. This causes medullary infarcts. When the renal artery is occluded, it produces cortical and medullary necrosis.

**DIAGNOSIS:**

The lesion should be suspected in any diabetic patient who has pyelonephritis and progressive renal failure.

Ellis (1942) declared that chronic pyelonephritis is difficult to recognise clinically, for only rarely is there a history of symptoms suggesting pyelitis and in the late stages, when these patients first come under observations, pus is often absent from the urine and bacteria of which E.coli is the most common, may or may not be present.

Whitehouse and Root (1956) believed that there were two distinct types of onset of necrotising renal papillitis:—

(A) Acute type, which was associated with fulminating renal sepsis, prostration, fever rapidly progressive renal failure, and uraemia leading to death.

(B) Chronic smouldering pyelonephritis with acute exacerbation.
I.V.P. & retrograde pyelography may show characteristic changes in the kidney due to the sloughing of a papilla.

Necrotising renal papillitis may not be diagnosed until autopsy.

**AUTOPSY FINDINGS:**

Whitehouse & Root (1956) reported unilateral lesion in 8 out of 11 cases, and it was associated with diabetic nephropathy in more than half the time. Papillary necrosis thus is far more frequent among diabetics than among non-diabetics.

**PREVENTION:**

Prevention of this condition is by vigorous, prompt and prolonged treatment of pyelonephritis in a diabetic patient.

Minor evidences of pyelonephritis should not be ignored. Overtreatment is better than undertreatment. (Aarseth 1953).
**CLINICAL CONSIDERATIONS**

The clinical feature of intercapillary glomerulonephritis are known from a large number of reports and systematic investigations. A few significant studies are enumerated here:

1. Kimmelstein & Wilson (1936)
2. Anson (1938)
3. Newburger & Peters (1939)
4. Simon (1940)
5. Siegal (1940)
6. Siegal & Allen (1941)
7. Clarke (1941)
8. Porter & Walker (1941)
9. Herbut (1941)
10. Mauser, Rowe & Michael (1942)
11. Horn & Smetna (1942)
12. Morales & Rivera (1942)
13. Spuhler & Zollinger (1943)
14. Laipply, Eitzen & Dutra (1944)
15. Newman (1944)
16. Hilden (1945)
17. Goodoff (1945)
18. Henderson, Sprague & Wagener (1947)
20. Rifkin Parker, Polin, Berkman & Spiro (1948)
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<tr>
<td>21.</td>
<td>White &amp; Waskow</td>
<td>(1948)</td>
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<td>22.</td>
<td>Mann, Gardner &amp; Root</td>
<td>(1949)</td>
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<td>23.</td>
<td>Martensson</td>
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<td>24.</td>
<td>Bell</td>
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<td>25.</td>
<td>Alwall, Ekelund &amp; Oras</td>
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<td>26.</td>
<td>Gilliland</td>
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<td>Recht</td>
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<td>29.</td>
<td>Azerad et al</td>
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<td>30.</td>
<td>Iversen &amp; Ohlsen</td>
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<td>31.</td>
<td>Keiding et al</td>
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<td>32.</td>
<td>Hall</td>
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<td>33.</td>
<td>Rifkin et al</td>
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<td>34.</td>
<td>Aarseth</td>
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<td>35.</td>
<td>Taft et al</td>
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<td>36.</td>
<td>Dunlop</td>
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<td>37.</td>
<td>Dietzel et al</td>
<td>(1958)</td>
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<td>38.</td>
<td>Gellman et al</td>
<td>(1959)</td>
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<td>39.</td>
<td>Cosnett</td>
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<td>40.</td>
<td>Bannerjee et al</td>
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<td>41.</td>
<td>Sinha</td>
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<td>42.</td>
<td>Mitra &amp; Chhetri</td>
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<td>44.</td>
<td>Pathania &amp; Sachhar</td>
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<td>47.</td>
<td>Tandon et al</td>
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Most cases described represent the fully developed pathologic anatomical picture of intercapillary glomerulosclerosis with severe clinical symptoms.

Weiss (1941) and Moore et al (1948), pointed out that the kidney lesion may be a chance finding without clinical importance. Horn & Smetna (1942) found that the clinical features which have been regarded as specific for the kidney lesion are lacking in a large number of cases; Spuhler & Zollinger (1943) pronounced that in juvenile diabetics it is the nephrotic syndrome which is of dominant clinical importance while in the elderly, the nephrosclerotic symptoms become prominent. Lefeber & Decherd (1946) concluded that a clinical diagnosis of intercapillary glomerulosclerosis can be proven only in a small number of diabetic cases who present with a nephrotic type of edema. Out of 11 diabetics with edema of the nephrotic type only 2 had intercapillary glomerulosclerosis.

During life, the diagnosis of intercapillary glomerulosclerosis, cannot be established with complete certainty, but the condition can be strongly suspected in diabetes of long duration with albuminuria, hypertension and diabetic retinopathy (Henderson, Sprague & Wagener 1947). Neither Henderson, Sprague & Wagener (1947), Gauld et al (1948) nor Alwall et al (1950) found clinical correlation with the
Rifkin, Parker, Polin, Berkman & Spiro (1948) stressed the importance of the presence of doubly refractile fatty cells or casts in the urine sediment in the diagnosis of intercapillary glomerulosclerosis.

Mann, Gardner & Root (1949) stated that the clinical features of diabetes are more closely correlated with the diffuse lesion than with the nodular lesion.

Gilliland (1951) stressed the following syndrome in arriving at a diagnosis of Kimmelstiel-Wilson syndrome, hypertension with heart failure, peripheral neuropathy, edema at least of the dependant parts and retinitis or cataract obscuring the retina.

According to Bell (1952), there are no definite clinical features to establish the changes of intercapillary glomerulosclerosis.

The clinical features associated with the K.W. syndrome are:

- Edema
- Hypertension
- Retinopathy
- Albuminuria
- Hypoalbuminemia
- Renal failure — (Clark & Skillern 1955)
Kimmelstiel-Wilson Syndrome

Kimmelstiel and Wilson (1936), first described the nodular type of glomerulosclerosis and associated it with edema in seven out of 8 patients which they regarded as nephrotic in type.

Derow et al (1939); Siegal (1940) and Simon (1940); reported clinical and biochemical features of nephrotic syndrome in nodular nephrosclerosis, but there was some degree of heart failure in all these cases.

According to many investigators, edema in diabetes mellitus was more common due to heart failure than due to nephrotic syndrome, (Lefeber, Decherd 1946; Henderson, Sprague and Wagener 1947; Rifkin, Parker, Polin and Berkman 1948; Rogers, Robbins and Feghers 1952; Bell 1953); whereas many other workers noticed nephrotic syndrome on renal biopsy or autopsy study with diffuse glomerulosclerosis but no nodular lesion. (Adams 1947; Rogers & Robbins 1952; Bell 1953; Runyan, Hurwitz and Robbins 1955; Lambie, Macfarlane 1955).

Zins (1949), found that hypertension, proteinuria, nephrotic syndrome and renal failure were not related to the involvement of the kidney (by intercapillary glomerulosclerosis) except in those in which the lesion was far advanced. Rogers, Robbins, Feghers (1952), reported that out of 229 diabetics studied clinically, 26 had the triad of albuminuria,
hypertension and edema (probable nodular glomerulosclerosis), of these, only 20 had the nodular lesion at autopsy. Of 15 patients with hypertension and albuminuria but no edema (possible nodular glomerulosclerosis) only 8 had the anatomical lesion. The autopsy studies showed that 66 out of 229 patients had the nodular lesion but it could be suspected clinically in only 28.

Reubi (1957) reported that it was the diffuse lesion and not the nodular lesion which was accompanied by massive proteinuria with edema. It had been conclusively demonstrated by various authors that the clinical picture of nephrotic syndrome in diabetes need not be accompanied by the nodular pathologic lesion and vice versa (Robbins et al 1952; Bell 1953; Lambie et al 1955; Reubi 1957; Gellman et al 1959).

Gellman (1959) stated there was no significant difference in the duration of diabetes between the group who had and the group who did not have the nephrotic syndrome. He, however, suggested that the patients who developed diabetes early in life were especially liable to develop the nephrotic syndrome. Nephrotic syndrome was associated with severe degrees of diffuse glomerulosclerosis but not with the severity of nodular glomerulosclerosis. He also noted 26% incidence of nephrotic syndrome in his series. This high incidence undoubtedly reflected their known interest and being a selective study, to most clinicians, nephrotic edema in diabetics is the Kimmelstil Wilson syndrome and suggested to them that nodular lesion was present, which was not borne true. These patients with
nephrotic syndrome had serum albumin of 3.5 Gm. per 100 ml. or less and serum cholesterol of 300 mgm per 100 ml. or more.

Lowy and Barach (1957) found the cholesterol and other lipid factors normal in diabetic men and slightly raised in diabetic women in 901 diabetes without complications. Interrozi, Bernasconi and Buscarini (1958) found increased cholesterol and total lipid levels in uncomplicated diabetics.

Gellman (1959) postulated that serum albumin might be low in diabetics as a result of malnutrition and liver disease and that nephrotic syndrome may be a chance variation of these four common features proteinuria, edema, hypoalbuminemia and hypercholesterolemia, but his data on the above factors with and without the nephrotic syndrome showed difference which was highly significant. He also demonstrated that the severity of hypertension, proteinuria and renal failure and the incidence of edema and the nephrotic syndrome could be correlated mathematically with the severity of diffuse diabetic glomerulosclerosis.

Kark, Pirani, Pollak and Muehrcke (1958) postulated that the widespread involvement of capillary basement membranes by diffuse glomerulosclerosis is sufficient to account for the proteinuria and the loss of protein in the urine if sufficiently great and sufficiently prolonged, will lead to the other features of nephrotic syndrome.

Brun, Germsen, Hilden, Iversen and Haaschow (1953); Taft, Finch and Joske (1954); Howe (1955) and Gellman (1959) are some of the only foreign studies which were based on
kidney tissue obtained from living patients by renal biopsy. They did not correlate the severity of lesion with the functional data as was done in Gellman series, but they concluded as did Gellman that there was no regular association between nodular glomerulosclerosis (Kimmelsteil-Wilson lesion) and proteinuria, hypertension, renal failure and nephrotic edema (the so called Kimmelsteil-Wilson syndrome). Gellman came to the conclusion that the nodules do not cause the functional abnormalities and that the changes in renal functions were caused by the diffuse diabetic glomerulosclerosis and by the associated arteriolar and tubular damage and further pleaded that the term Kimmelsteil-Wilson syndrome should be abandoned and the name reserved for the histologic lesion which the Kimmelsteil & Wilson described in 1936.

The terms Kimmelsteil-Wilson disease and Kimmelsteil-Wilson syndrome, have been and still are widely used to describe the pathologic lesion and the clinical entity respectively. The term "Glomerulosclerosis", either nodular or diffuse is gradually replacing the older terms, because Gellman and Pirani in 1959 have shown that the nodular thickening of the glomerular tufts originally described by Kimmelsteil-Wilson in 1936, is a functionally less important lesion, although it is striking in appearance on histological examination, than the diffuse thickening of the glomerular capillary basement membrane described by Gellman & Pirani.

The original Kimmelsteil-Wilson cases had the 'Classic' clinical features of edema, hypertension and proteinuria, but
it is now known that either nodular or diffuse glomerulosclerosis can occur with none, or one, or all of these clinical findings. Thus it is better to speak of the kidney disorder as diabetic glomerulosclerosis and to define it in terms of the clinical picture seen in the individual case.

APPARENT REMISSION OF DIABETES ON DEVELOPING K.W. LESION

It is a point of interest that the glycosuria may vanish with the appearance of proteinuria. Auroi (1943) and Spuhler (1944) stated that this was due to the elevation of the renal glucose threshold with consequent dissimilation of the diabetes, unless tests were made for blood sugar, while Hilden (1945) explained the high sugar threshold due to a dissociation between the glomerulus and the tubular function.

Hatlehol (1926) and Barlow (1939) described that in rare cases the renal disease was capable of lowering the renal glucose threshold, while Zubrod, Eversole & Dana in 1951 showed that some cases showed a real improvement in the diabetic state with a reduction of insulin need by the patient with the development of intercapillary glomerulosclerosis. There was also a tendency to hypoglycaemia with progression of their renal condition irrespective of the change in the renal threshold.

Many workers in this field have brought forth evidence that there was amelioration of diabetes with the onset of severe glomerulosclerosis. (Manus 1949; Wilder 1949; Zubrod,
Similar lessening of the diabetic state was also noticed by Runyan, Hurwitz and Robbins (1955) and Kalant, Clamen & Hoffman (1958) in cases of nephrotic syndrome. Hatch & Parrish (1961) noted apparent remission of diabetes on developing Kimmelstiel-Wilson syndrome as renal failure progressed. In one case the insulin requirement fell from 100 units daily to zero and the diabetes seemed to go into complete remission. No entirely satisfactory explanation was available. Several factors were said to be involved:

1. Lowered glomerular filtration may raise the renal threshold for glucose, so that glycosuria was reduced and blood sugar was raised.

2. Decrease in food intake may be due to inactivity, anorexia, and nausea of renal failure.

3. Hypoalbuminemia may lead to less albumin bound insulin and greater amount of free active insulin.

4. Immune mechanism may be interfered with by the renal failure, so that less insulin antibodies were produced and there was less insulin resistance, so that greater amount of insulin was available for metabolic activity.

The consensus of opinion however is that a decrease in glycosuria does not necessarily indicate any real change in the severity of diabetes or reduction in insulin requirement.
PROTEINURIA
(ALBUMINURIA)

INCIDENCE

Naunyn (1910) examined 139 cases of uncomplicated diabetes in persons aged under 50 years and found 34 (25%) with proteinuria, transitory in 20 and permanent in 14. In a material from 1900 v. Noorden found 140 (21.5%) cases of proteinuria among 650 diabetics (v. Noorden & Isaac 1927). Hatlehol (1926) found proteinuria in 27 (54%) of diabetic as a rule slight or transitory. Bachman (1936) registered 53 cases of proteinuria (10%) among 531 diabetics.

Persistent albuminuria was usually considered to be the earliest clue to the presence of intercapillary glomerulosclerosis.

Kimmelstiel and Wilson (1936); Anson (1938); and Newburger & Peters (1939); reported persistent albuminuria in all their cases of Kimmelstiel-Wilson syndrome, while Clarke (1941), reviewing the first 76 published cases of nodular glomerulosclerosis found that 25% did not have albuminuria.

Bell (1946) reported no albuminuria in 4 per cent, faint trace in 25 per cent and one plus to 4 plus in 71 per cent of his 76 cases of intercapillary glomerulosclerosis.

Henderson et al (1947) reported albuminuria in 95 per cent of patients with nodular glomerulosclerosis. Kimmelstiel and Porter (1948) reported albuminuria in
approximately two thirds of cases. Mann, Gardner and Root (1949), found that proteinuria was an early finding and was accompanied by hyaline casts in the urine in their diabetic patients. Martensson (1949), reported proteinuria in 69 (33.3 %) of 207 patients with diabetes duration over 15 years.

Ytrehus (1950), found proteinuria in 50 (12%) of 422 diabetics from 1944. Bartels & Poulsen (1950) gave proteinuria in 299 (22%) of 1335 diabetics treated in the State Hospital in Oslo in course of the period (1930-1950). Thernoe (1951), found proteinuria in 220 (30.1%) of 733 diabetics in a Danish material from the years 1938-49, 84 (11.5%) of whom had permanent proteinuria. Joslin (1951) found proteinuria in 10 (25%) of 40 patients who had contracted diabetes before the age of 15 years and with diabetes of over 30 years duration, and 32 (18%) of 181 patients with diabetes of 25-30 years duration. Hecht (1951) showed proteinuria in 12 out of 24 juvenile diabetics after minimum of 10 years observation.

Rifkin et al (1952), observed that finding of doubly refractile fat in urine pointed to a diagnosis of diabetic intercapillary glomerulosclerosis. All their diabetic patients had 4 'plus' proteinuria. Dana and Zubroid (1954), reported an incidence of 64.4 per cent with more than 2 plus albumin in cases of diabetic glomerulosclerosis. Clark and Skillern (1955), reported albuminuria in 96 per cent and stated that urinary casts when present were of hyaline nature.
Gellman et al (1959) found that 75 per cent had proteinuria, 64 per cent had 2 plus or more. Those with severe (3 or 4 plus) diffuse glomerulosclerosis passed more than 2G of protein in urine in 24 hours. No comparable relationship existed with the nodular lesion and many patients who had no nodules, were found to have heavy proteinuria.

Gellman et al (1959), stated that formal concentration tests were not made. The specific gravities were recorded on the early morning specimens. There was no correlation between specific gravity and severity of either glomerular or or tubular damage, because the specific gravity were affected by the differing amounts of glycosuria and/or proteinuria.

Gellman et al (1959), noted that increasing abnormalities of urinary sediment (w.b.o., r.b.o., & casts) occurred with severe degrees of total glomerular and tubular damage, with diffuse glomerulosclerosis and tubular atrophy but not with nodular lesion or tubular dilatation.

Hatch et al (1961), found that proteinuria was the most common abnormality and the earliest positive finding. It was found in 87.5 per cent of diffuse lesion. Severity of proteinuria correlated poorly, with the extent of nodular change, but showed a significant relationship to the severity of diffuse lesion. Among some of the Indian Series, Pathania and Sachar (1961), reported albuminuria in all the 20 cases of their clinically diagnosed diabetic nephropathy, and Mitra et al (1961) reported albuminuria in all 40 cases of diabetic nephropathy.
RENAL FUNCTION

It is stated that laboratory findings in renal involvement in diabetes mellitus are generally predictable. Some degree of tubular damage and disruption is associated with severe degree of diffuse glomerulosclerosis. The renal function tests and blood biochemical abnormalities reflect the combined glomerular and tubular dysfunction and thus indicate the degree of total renal damage. (Strauss 1963). Renal failure may be present and associated with predominantly nodular glomerulosclerosis, but one is also likely to find nephrosclerosis and proliferative vascular change or chronic pyelonephritis as well. (Lee 1963).

Numerous investigations have been published on the renal function in diabetes.

Hatlehol (1926) examined the renal function in 50 diabetics. The great majority of patients with proteinuria had normal NPN and only a few showed permanent or considerable delay of phenol-sulfon-phthalein excretion. In several patients examined at years intervals, during which time their diabetes had been progressive, no tendency to reduction of the renal function was demonstrable.

Bachman (1936) studied the occurrence of azotemia in an extensive diabetes material of 344 simple diabetics. 208 (62%) had blood urea under 40 mgm per 100 ml. 94 (27%) had blood urea between 40 and 50 mgm per 100 ml. and 39 (11%) had pathologic increase of urea over 50 mgm per 100 ml.
Bell (1942) stated that some extreme forms of intercapillary glomerulosclerosis are associated with reduced renal function and in cases of marked changes in all the glomeruli, the patient will have urea retention.

Hilden (1945) made clearance examination in a typical case of intercapillary glomerulosclerosis and found urea clearance more reduced than diodrast clearance.

Henderson, Sprague and Wagener (1947) determined blood urea in 55 diabetics with and 91 without intercapillary glomerulosclerosis. Elevation of blood urea (over 40 mgm per 100 ml) was found in 64% of the former and 53% of the latter group. They concluded that impairment of renal function was not a universal accompaniment of intercapillary glomerulosclerosis.

Hogeman (1948) showed reduced insulin and diodrast clearance and reduced filtration fraction in most.

 Rifkin, Parker, Polin, Berkman & Spiro (1948) reported uraemic death for 9 out of 22 patients with clinically diagnosed diabetic nephropathy. They also examined 45 patients with clinical Kimmelstiel-Wilson syndrome and found urea clearance under 40% in 20.

Kimmelstiel & Porter (1948) reported uraemia in approximately 20 per cent of cases with intercapillary glomerulosclerosis.

Hilden (1949) found in 7 patients with clinical Kimmelstiel-Wilson syndrome, reduction of the glomerular and tubular function, but the renal blood circulation was not reduced to
the same degree which resulted in low filtration fraction. This functional pattern resembles that seen in the nephrotic stage of chronic nephritis (type 2 nephritis of Ellis). Corcoran, Taylor and Page (1948), had arrived at the same conclusions on a study of 6 patients with Kimmelstiel-Wilson syndrome.

Lundbaek and Peterson (1949), found that in patients with diabetes of over 15 years duration without proteinuria and hypertension, they had a normal or slightly reduced filtration rate, the glucose Tm, however, in many cases showed a more pronounced depression.

Mann, Gardner and Root (1949), was impressed by the number of patients with clinical syndrome of intercapillary glomerulosclerosis, who exhibited loss of pheno-sulphon-phthalein clearance and showed hyposthenuria at a late stage of the disease.

Alwall, Ekelund and Oras (1950), found the specific gravity of urine in 40% of patients with intercapillary glomerulosclerosis at over 1020 while 60% had specific gravity under 1020.

Martensson (1950), examined urea clearance in 45 patients who had diabetes for a minimum of 15 years. A patient with massive proteinuria and hypertension had urea clearance of 85%. Autopsy revealed typical intercapillary glomerulosclerosis. Two others with identical autopsy findings only, had slightly reduced urea clearance. Of 11 patients with urea clearance less than 40%, 10 had symptoms of severe nephropathy.
Robertson, Gray and Baynes (1951) examined 9 patients with clinical Kimmelstiel-Wilson syndrome by insulin clearance, para-amino-hippurate clearance, maximal tubular reabsorptive capacity and maximum para-amino-hippurate tubular excretory capacity. Like the other mentioned investigators they found a functional pattern identical to that of chronic nephritis. They concluded that the Kimmelstiel-Wilson lesion remains a condition which on clinical findings and laboratory investigations may be diagnosed during life with only a limited degree of certainty, the final diagnosis must depend on the autopsy observations. (Note:—Percutaneous Renal Biopsy was introduced in 1951 by Iverson and Brun).

Gellman (1959) estimated blood urea nitrogen on 55 occasions. He noted close correlation with the severity of diffuse lesion. Similar relationship was found with total glomerular damage and total tubular damage. There was no concurrent increase of severity of nodular lesion, although the average level in patients without nodules (15.1 mgm/100 ml) was less than the average level (34.9/100 ml) with nodules. He also found close correlation with severity of diffuse lesion, total glomerular, total tubular damage and the blood urea nitrogen. He did not notice progressive increase with increasing severity of nodular lesion. He also found serum creatinine, urea clearance and creatinine clearance, to have significant correlation with diffuse lesion, but not with nodular lesion.
Hatch et al (1961) observed that 60 per cent with diffuse lesion had azotemia at the time of renal biopsy, but blood urea nitrogen was not more than 45 mgm per 100 ml. All patients with mixed lesions had azotemia and showed considerably higher blood urea nitrogen. They also found a good correlation between the elevation of blood urea nitrogen and the severity of diffuse lesion. No such correlation existed with the severity of nodular lesion. It is the degree of diffuse glomerulosclerosis which seems to determine the degree of azotemia.

Among some of the Indian Series, Sinha (1960) reported high blood urea in all his 8 cases of Kimmelstiel-Wilson Syndrome ranging from 50 to 150 mgm. Pathania and Sachar (1961) observed raised blood urea above 50 mgm per cent in 50 per cent of cases with clinically diagnosed diabetic nephropathy. Mitra (1961) observed high blood urea in 15 out of 40 cases of diabetic nephropathy (37.5 %), the highest reading being 74 mgm. Renal function tests showed impairment in 12 out of 40 (30%). Gupta & Chakraverty (1964) stated that in the presence of definitely high blood urea renal changes are those commonly observed but cases with normal blood urea could also have early renal changes.
### Laboratory Findings in Diabetic Glomerulosclerosis

*LEE 1983*

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Type of Pathologic Change</th>
<th>Predominantly Diffuse</th>
<th>Predominantly Nodular</th>
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<tbody>
<tr>
<td><strong>Urine</strong></td>
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</tr>
<tr>
<td>1. Proteinuria</td>
<td>Positive Correlation</td>
<td></td>
<td>± Correlation</td>
</tr>
<tr>
<td>2. Sediment (WBC, RBC, Casts)</td>
<td>Positive Correlation</td>
<td></td>
<td>± Correlation</td>
</tr>
<tr>
<td><strong>Blood Chemistry</strong></td>
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<td></td>
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<tr>
<td>1. BUN</td>
<td>Positive Correlation</td>
<td></td>
<td>No Correlation</td>
</tr>
<tr>
<td>2. Creatinine</td>
<td>Positive Correlation</td>
<td></td>
<td>No Correlation</td>
</tr>
<tr>
<td>3. Serum Albumin</td>
<td>Positive Correlation</td>
<td></td>
<td>No Correlation</td>
</tr>
<tr>
<td>4. Serum Cholesterol</td>
<td>No Correlation</td>
<td></td>
<td>No Correlation</td>
</tr>
<tr>
<td><strong>Renal Function</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1. Urea Clearance</td>
<td>Positive Correlation</td>
<td></td>
<td>No Correlation</td>
</tr>
<tr>
<td>2. Creatinine</td>
<td>Positive Correlation</td>
<td></td>
<td>No Correlation</td>
</tr>
</tbody>
</table>

**Positive Correlation**: A greater degree of abnormality of the laboratory finding is usually associated with an increasingly severe pathologic change.

**No Correlation**: No predictable relationship between the laboratory abnormality and the extent of the pathologic change.
During the last 15 years, the needle biopsy of the kidney has become established as an important investigation in renal diseases. With modern technique it is reasonably safe procedure and is regularly used in most centres where renal disease is seriously studied (Brewer 1964).

In 1943 Castleman and Smithwick published the first systematic study using renal biopsy, when kidney tissue was taken during the course of splanchnic sympathectomy for hypertension and the degree of hypertension assessed in a series of 100 patients.

Before 1943, there were only a small number of reports of histological studies of the kidney during the life of the patient, and these were usually done incidentally during open surgical operations. In 1916, Gwyn performed an open renal biopsy on 2 patients, one being a case of nephrotic syndrome (renal amyloidosis). Similarly Dorothy Russel (1939) in her classic monograph on Bright's disease included 8 cases in whom biopsy of the kidney had been performed during decapsulation.

Ball (1934) was the first to use percutaneous aspiration biopsy to diagnose intra-abdominal masses and he described a case of hypernephroma diagnosed by renal biopsy.

The first systematic attempt at needle biopsy of the
kidney appears to be that of Alwall. The biopsies were performed in 1944 but not reported until 1952. Biopsy was attempted in 13 cases and sufficient kidney tissue was obtained in 10. Alwall abandoned the technique, as unfortunately one patient suffering from oliguria and uraemia died, following biopsy. Iversen and Brun resumed the method and published their results in 1951 and showed that in the right hands and with proper technique percutaneous needle biopsy is a safe clinical method, which stimulated the widespread adoption of this method and has led to the present interest in the renal biopsy as a clinical research tool.

Iversen and his colleagues believed that biopsies could be done in the uraemic patients without hazard. They have done approximately 200 biopsies in patients ill with acute renal failure and although many of these patients had rising N.P.N, no untoward events occurred. Kark et al (1954) have done renal biopsies on patients with very high N.P.N levels in the blood, as high as 259 mgm/100 ml.

With regard to hypertension, it is proper to mention that patients with severe hypertension developed complications more frequently than with normal blood pressure. In patients ill with malignant hypertension the biopsy should be done with great care and only when indications clearly warrant the procedure.
ADEQUACY OF MATERIAL

Even with the most careful technique it is not possible to obtain satisfactory piece of renal tissue each time one attempts a renal biopsy. The inherent difficulty with renal biopsy is in finding the lower pole of the kidney with the biopsy needle.

Renal tissue was considered adequate for pathological evaluation, when 5 or more glomeruli were seen in the section. There are times, of course, when one can make a clear cut diagnosis with less than 5 glomeruli per section, (Kark et al 1958).

Many workers have commented that renal function tests per se do not permit the diagnosis of diabetic nephropathy and have emphasized the importance of kidney biopsy technique as a tool in the diagnosis of renal diseases. (Irvine et al 1956; Brun 1953; Kark et al 1954, 1958; Bergstrand & Bucht 1957; Gellman et al 1959; Daysog et al 1961; Sabour et al 1962 and Solomon 1963).
Two types of vascular changes have been noted in diabetes mellitus. One is the microangiopathy, i.e. the involvement of the medium sized vessels, affected by atheromatous and arteriosclerotic disease with common clinical sequela such as myocardial infarction, cerebral thrombosis, arteriolar nephrosclerosis and ischaemic lesions in legs and feet. Many believe that this is same as is found in non-diabetics, but occurs much earlier in diabetics. The other type is the microangiopathy, i.e. a distinctive small blood vessel disease, seldom seen in non-diabetics, which appears to cause retinopathy, glomerulosclerosis and possibly neuropathy (Goldenberg, Alex, Joshi, Blumenthal 1959; Yamashito & Becker 1961; Bloodworth 1962).

The small arterioles, capillaries and venules are characteristically involved. The changes differ morphologically and histochemically from the changes of atheromatous lesion, chiefly in the endothelial proliferation, basement membrane thickening and accumulation in the capillary wall of a hyaline PAS positive mucopolysaccharide substance similar to that which forms the nodules of diabetic glomerulosclerosis in contrast with the lipid, fibrotic and calcific lesions of the atherosclerosis (Colwell 1965).

Although the ultimate cause of diabetes mellitus is shrouded in mystery, no doubt exists at present in the minds of many medical men that the garden variety of diabetes is
a genetically determined abnormality.

The exact pattern in which the diabetic gene or group of genes is transmitted is not understood. It is said that 20% of the population are carriers of the diabetic gene and 5% of the population are susceptible. Matings of diabetes carrier and susceptible would yield offsprings who are susceptible as follows: 25% of the offsprings of the two carriers, 50% of the offsprings of one carrier and one susceptible and 100% of the offsprings of two susceptibles, would be diabetes susceptibles. Something abnormal occurs at conception but the exact nature of this abnormality is unknown. (Root 1965).

According to Steinberg (1961) the probability that a person is genetically liable to diabetes is approximately 100% for subjects with both parents diabetic, 50-80% in individuals with one diabetic parent and a diabetic sibling and 30-40% in the individuals, when the diabetic relatives are two grand parents (not spouses).

The family tendency to diabetes has been recognised for centuries. It was noted in India as early as the seventh century. Most authors agree today that diabetes mellitus is a simple autosomal recessive trait (White 1965). Although it is generally accepted that the tendency to diabetes is inherited, there is disagreement as to whether the diabetic person inherits a single trait that of metabolic defect, which if uncorrected favours vascular disease or whether he inherits two separate and basically independent traits, one for the metabolic defect and one for vascular disease,
which run concurrent and relatively independent courses. May be both the metabolic defect and vascular disease stem from a common inherited abnormality of unknown nature. (Marble 1965).

Some investigators feel that vascular lesions (thickening of the renal glomerular basement membrane and perhaps the basement membrane of other capillaries (e.g. retina, vasa nervorum), in diabetes mellitus are a part of the hereditary syndrome without demonstrable abnormalities in the carbohydrate metabolism, in other words, there is an inherent abnormality in the vessel structure which precedes altered carbohydrate metabolism (Camerini Davolos, 1964); whereas some other workers favour the abnormality in carbohydrate metabolism as playing the principle role in the causation of the diabetic lesion, wherein due to insulin deficiency there is disturbed carbohydrate metabolism and unchecked liberation of free fatty acids from adipose tissue into the circulation, much more than can be burnt by peripheral tissues or removed by the liver or incorporated into complex metabolic compounds, with the result that there is deposition as lipid in the vascular intima or as mucopoly-saccharide component of the Kimmelsteil-Wilson lesion in the kidney.

Thus there are two views one states that the vascular lesion may be an independent expression of the genetic abnormality and not secondary to the carbohydrate metabolism and conversely the vascular lesions are a direct result of
carbohydrate abnormality. Concrete proof of either is said to be lacking (Cahill 1965).

White (1965) stated that because of the genetic origin of diabetes the diagnosis of premellitus or prediabetes, (the period from conception to the positive glucose tolerance curve - see Review Diagram - Natural history of diabetes mellitus on page 5) can be made in the child when both parent, four grand parents or an identical twin give a family history of diabetes. The index of suspicion is high if all other siblings have diabetes.

Conn (1964) suggested a new terminology for the pre-diabetic period as familial dysinsulinism and microangiopathy and stated that a genetically determined insulin antagonist, perhaps through an enzymatic defect in the biosynthesis, produces an abnormal insulin like polypeptide, to which he traced the production of diabetic retinopathy, high serum insulin like activity, diabetic neuropathy with gross evidence of vascular disease both in the large vessels "macroangiopathy" (atherosclerosis) and in the smaller vessels "microangiopathy" of the kidneys (diabetic nephropathy) and eyes (diabetic retinopathy).

Rees et al (1963) stated that in the development of microangiopathy initial events include widening and tortuosity of the venules, reduction in linear velocity of blood flow, aggregation of formed elements and perivascular edema, which were noticed in the studies of bulbar conjunctiva in the early stages of diabetes. These reversible changes may be seen in the retina also.
Marble 1965, following the same line, stated that the first visible structural abnormalities are capillary microaneurysms on examination of fundus by conventional means. Although the pathogenesis of these is not clear, it appears that there is microcirculatory stasis, accumulation of basement membrane substance in the walls of the capillaries and focal weaknesses in the vessel walls. Cogan & Kuwabara (1963) postulated that this last named change is due to a loss of "mural cells", which he thought normally maintains the tone of the capillary wall. The further development of progressive diabetic retinopathy is characterised by large and small bloty hemorrhages, "hard" white exudates, preretinal and vitreous haemorrhages and haemorrhagic glaucoma, although the appearance and extent of these changes vary from patient to patient. Linear or flame-shaped hemorrhages and "soft" or "cotton wool" exudates may be seen when hypertension and renal disease complicate the situation. In many patients proliferation of new blood vessels (neo-vascularisation) develops with or without accompanying strands of fibrous connective tissue (Marble 1965).

Although diabetic nephropathy includes the changes of arterio- and arteriole-sclerosis (with hyalinization of arterioles leading to and from the glomerulus) and acute and chronic pyelonephritis, it is the component of intercapillary glomerulosclerosis, first described by Kimmelsteil and Wilson in 1936, which is of particular interest. The pathogenesis of this lesion is still controversial in certain
aspects, but it would appear that an early abnormality is that of thickening of the capillary basement membrane, at first focal and later diffuse. In addition, accumulation and branching of basement membrane substance occurs gradually in the intercapillary (mesoangial) cell region. This basement membrane material stains positively with the periodic acid-Schiff (PAS) reagent and is therefore assumed to be composed of glycoprotein. The infoldings of the tortuous basement membrane of the capillary loops become elongated and widened to form finger like projections or branches continuous with the intercapillary substance of the mesoangium. Marble (1965) postulated that as these branches increase in size, they gradually coalesce into large masses of PAS positive material which ultimately comprise the nodules noted by Kimmelsteil and Wilson in 1936.

Spira (1959) explained the increased amounts of glycoprotein, which are deposited within and about the basement membrane of small blood vessels in the development of glomerulosclerosis and called attention to the observations of many workers as follows:—

"that the liver has two enzymes capable of phosphorylating glucose "glucokinase", which takes part in glycogen synthesis and is decreased in insulin deficiency and a general "hexokinase" which acts independantly of insulin. It is possible that in diabetes, in which there is both insulin deficiency and excess glucose, there may take place a re-routing of glucose from insulin dependent pathways into
those, which might result in the formation of excess glyco- 
proteins.

Glomerular capillary basement membrane is believed to 
consist of glycoprotein (MacDonald 1964). Glucose is essential 
for the bio-synthesis of glycoprotein. The presence of excess 
glycoprotein in diabetic glomeruli has been shown by Patrick, 
Marini and Lazarow (1964), who have compared glycoprotein 
content of diabetic and normal human glomeruli. Colwell 
(1965), observed that the thickening of capillary and other 
basement membrane was a consistent early finding in diabetes. 
He has reasons to believe that a retarded basement turnover 
rate of glycoprotein, may be the reason for the abnormal 
accumulation of mucopolysaccharide in the walls and lumens 
of arterioles and capillaries with organ damage, and suggested 
that diabetic angiopathy may be associated with antigen- 
antibody reaction, with insulin as the responsible antigen.

White (1965) reported that chronic diabetes (defined 
as the stage of diabetes characterised by vascular lesions) 
is uncommon under age 20, unknown under age 10. She examined 
1072 juvenile onset diabetics who had survived more than 20 
years and found no lesions under age 10. From age 10 to 
20, they were as follows:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcified arteries</td>
<td>6.5</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>4.8</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>4.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Under 5 year's duration, they were negligible, from 5 to 9.9 years and from 10 to 14.9 years duration they were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Percentage in 5 to 9.9 years</th>
<th>Percentage in 10 to 14.9 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcified arteries</td>
<td>1.7</td>
<td>14</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>2.5</td>
<td>19</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>1.5</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.2</td>
<td>4.5</td>
</tr>
</tbody>
</table>

If typical retinopathy and glomerulosclerosis were found in non-hereditary diabetes, either in man or animals, this would support the concept that vascular disease develops as a consequence of insulin lack. Bloodworth (1965) and Engerman & Bloodworth (1965) have shown that after one to over five years of diabetes, during which poor control was maintained, all 10 animals (dogs) were found to have diffuse glomerulosclerosis and 7 had characteristic nodular lesion, retinopathy comparable to that seen in human diabetic patients was present in 3 out of 10. Characteristic changes have been noted in the eyes and/or kidneys by many investigators in human subjects in whom diabetes has followed removal or damage to the pancreas (Sprague 1947 Burton et al 1957, Duncan et al 1958).

Antoniades and his co-workers (1962) showed that insulin circulates in the blood of diabetic patients as an inactive complex and in them the rate at which insulin could
be set free as biologically active free insulin was slower than in non-diabetics. Brolin et al (1964) demonstrated the occurrence of insulin antibodies (i.e., binding of insulin by protein) during acidosis, during infections and during long duration of diabetes and stated that the prevention of diabetic complications (microangiopathy plus infections) will depend in the future upon a new knowledge regarding the synthesis, storage, transportation and intracellular effectiveness of insulin itself.

Colwell (1964) in a review article has cited the names of those who have questioned whether the microangiopathic complications of diabetes are related to the degree of control (Dolger 1947; Taft et al 1954; Downie & Martin 1959; Collyer & Hazlett 1961); whereas he has quoted other investigators who have favoured the opposite view that the incidence and severity of retinopathy and nephropathy bear a significant relationship to the degree of control of diabetes. (Speont et al 1951; Keiding et al 1952; Dunlop 1954; Lamble & MacFarlane 1955; Hardin et al 1956; El Mahalawy & Sabour 1960; Johnson 1960).

In a retrospective survey carried out at the Joslin clinic, Keiding et al (1952), found that with increasing duration of diabetes there were increasing extent and severity of vascular complications. However, at all durations, the incidence of angiopathy was less in patients whose control of diabetes had been excellent or good, 22% of the 451 patients had diabetic nephropathy recognizable
clinically, none of the 11 with excellent and only 1 of the 50 with good control had this complication. On the other hand 17% of 92 patients with fair control and 28% of 298 with poor control had nephropathy.

Similarly, Johnson (1960) compared results in two groups of young patients. Those in Series I were treated from 1922 to 1935 on a strictly regulated diet and those in Series II from 1936 to 1945 on a "free diet" program. Nephropathy and severe retinopathy were significantly more common in Series II although the average duration of diabetes was 10 years less than in Series I.

It seems logical to suppose; if we wish to explain the etiopathogenesis of early diabetic abnormalities; that a decrease in the metabolic effectiveness of insulin may antedate some of these changes. It may be due to modification in the chemical structure of insulin or to an altered protein carrier, or to anti-insulin factors (synalbumin etc.) or to some unknown factors (tissue?), one does not know at the present moment (Camerini-Davalos 1964).

If diabetes and its complications have to be prevented it seems entirely reasonable to have a working knowledge of the natural history of diabetes mellitus, not the end story, not just the history of the terminal days, but the true and entire history front to back. (Camerini-Davalos 1964).

It therefore seems sensible that an accurate knowledge of the various biochemical abnormalities during this usually slow and prolonged period of pre-diabetes; wherein there is
minimal hyperglycaemia with high insulin like activity (ILA)
and elevated immune-reactive insulin due to increased
production of insulin by the beta cells of the islets of
Langerhans, and wherein there is incomplete utilisation of
the insulin complexes (increased bound and free insulin ratio);
should be utilised for the prevention of diabetes and its
complications (Colwell 1965 - Camerini-Davalos - 1964).

Excessive synalbumin antagonism may be regarded as
a biochemical mark to ascertain whether or not a given individual
is predisposed to diabetes mellitus (Vallance-Owen 1963).

It is possible that the long sought unifying concept
clarifying the numerous and diverse diabetic lesions may be
the primary capillary angiopathy.

The problem of glycoprotein (Sialic Acid in Serum),
structure of the capillary basement membrane, its relation
to glucose and the influence of insulin are some of the urgent
challenges in this field at the present time. Butterfield
(1964) stated, that if you have the misfortune to inherit a
really poor Beta cell apparatus you age quicker as far as your
blood sugar is concerned and diabetes appears while you are
still growing. If you are born with a good Beta cell apparatus,
you may be able to get right up into the 70's and your gluco-
homeostatic apparatus still functions adequately.
A CONCEPT OF DIABETES
(KINCH, 1961)