DISCUSSION
DIABETIC NEPHROPATHY

There is considerable variation in the incidence of characteristic histological changes in diabetes, depending upon the source of the material, autopsy or renal biopsy and whether the material is selected or unselected. (Kimmelstiel & Porter 1948; Gellman et al 1959; Mathur et al 1960, 1964). Solomon 1963 in an unselected study of 51 renal biopsies concluded that all the patients with diabetes mellitus have characteristic glomerular alterations, some visible only with the electron microscope.

In the present study diabetic nephropathy was found in 37.5% who had intercapillary glomerulosclerosis on kidney biopsy, seen under light microscopy. Diffuse glomerulosclerosis was seen exclusively in 31.4 per cent, diffuse cum nodular lesion was seen in 4.1 per cent, diffuse cum exudative lesion was seen in 2.1% of diabetics. In addition, there was a case of K.W. syndrome with edema, albuminuria, hypertension, hypo-proteinemia in whom a kidney biopsy was not done due to raised blood urea above 100 mgm %, thus giving an overall incidence of diabetic nephropathy of 39.6%, among these 48 diabetics.

Western observers (Kimmelstiel & Porter 1948; Dunlop 1954; Bryfogle et al 1957), have found lower percentages of incidence as compared to Indian workers, (Mathur et al 1960, 1964; Gupta & Chakravarty 1964), the reason is probably to be found in the nature of the material, the diabetes being better controlled than their counter parts in India where diabetes is invariably poorly treated and inadequately controlled.
## INCIDENCE OF DIABETIC NEPHROPATHY IN DIABETES MELLITUS

### AUTOPSY SERIES

<table>
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<tr>
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<td>1941</td>
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<td>3.</td>
<td>Horn &amp; Smetna</td>
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<td>Bell</td>
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### CLINICAL STUDY

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<td>75.0 - Diffuse &amp; Nodular</td>
<td>48.0 - Nodular</td>
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<td>Present study</td>
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Vaishnava et al (1964) in a clinical study noted 5.0% incidence while Mathur et al (1964) in a biopsy study noted
71.9% incidence. The results of the present study in an unselected group lie midway between the highest and the lowest incidence among Indian series.

**AGE**

Most workers are agreed that diabetic glomerulosclerosis occurs mainly in middle-aged or elderly diabetics. (Kimmelstiel-Wilson 1936; Allen 1941; Henderson et al 1947; Gilliland 1951; Brun et al 1953); whereas some other workers (Hall 1952; Bell 1952), thought it to be rare under 30 years. In our present study youngest patient was 17 years and oldest patient was 70 years who had diabetic glomerulosclerosis and 7 out of 23 cases, 30.4% percent occurred below 30 years and 11 out of 21 cases, 52.4% occurred above 30 years of age. However, when incidence of nephropathy was compared in the age groups below and above age 30, there was no statistical significance (See table No.4).

Rosenbusch (1945); Mann et al (1949); Root et al (1951); and White (1956), have reported a high incidence of renal lesion among juvenile diabetics. Gellman et al (1959), stated that they found the complication quite frequent in patients below 30 years, if the duration of diabetes was sufficiently long. Mahallawy & Sabour (1960), and Gupta & Chakarvarty (1964), observed that age had no significant effect on the development of diabetic nephropathy. Mitra and Chhetri (1961), showed that the highest incidence of diabetic nephropathy was in the 6th decade. Our study showed the maximum incidence in the 7th decade.
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. In our study, we had 4 out of 13 (31%) under age 20 and 3 out of 10 (30%) under 21 to 30 years, who showed diabetic glomerulosclerosis.

In most series, the sex incidence was more in females, (Henderson et al 1947; Hall 1952; Lambie et al 1955); and in the collective statistics of Kimmelstiel & Porter (1948); Alwall et al (1950); the male to female sex ratio was 1:2; whereas Laippley et al 1944; Roger et al 1952; found no difference in the two sexes. Gellman et al (1959), found higher incidence of both nodular and diffuse varieties in males in his selected study and even there the sex ratio was not found statistically significant.

In the Indian series, there is male preponderance in the diabetic population. (Sinha 1960; Pathania & Sachar 1961; Vaishnava et al 1964). Gupta et al (1964), found male predominance in the diabetic nephropathy cases. In the present study, the male to female ratio was 3.9:4.5 and on statistical analysis it was noted that the male to female ratio could be a chance variation. (Table No.5).

**DURATION OF DIABETES**

It is believed that the duration of diabetes has got a definite influence on the incidence of nephropathy.
The relationship of longer duration of diabetes with changes of glomerulosclerosis has been emphasized by many investigators. (Kimmelstiel & Wilson 1936; Rosenbush 1945; Bjerkelund 1951; Hall 1952; Lambie & Macfarlane 1955; Bryfogle and Bradley 1957; Gellman et al 1959; Mahallawy et al 1960). In a few other studies the duration of diabetes was not found to have a very significant role in the production of diabetic nephropathic changes. (Laippley et al 1944; Rifkin et al 1949; Wilson et al 1951; Berkman et al 1952; Methur et al 1964; Gupta & Chakarverty 1964).

In the group with less than 5 years duration of diabetes, the incidence was 41.7% and in the group with more than 5 years duration, surprisingly enough it was 37.5%. However, this difference did not reach statistically significant levels (Table No.6).

In the present study the duration of diabetes in patients in whom intercapillary glomerulosclerosis was seen varied from 6 months to 23 years. The incidence of nephropathy in this series was found to be 50% in those patients with less than a year's duration of diabetes, 40% in the group 1 to 5 years duration and 28.6% in the group 6 to 10 years duration. There was one patient with more than 21 years duration of diabetes who showed diabetic nephropathy. It is needless to emphasize that in an Indian diabetic the onset of diabetes is difficult to pinpoint because of unreliable history and also many patients with a subacute onset seek medical advice only when some complication arises. These factors might
have operated in the patients reported by Indian workers who have also reported a high incidence in diabetics with a short duration. The other reason may be that the kidney changes may be concomitants rather than complications and could occur in the absence of manifest aberrations of carbohydrate metabolism (Ellenberg 1962).

Goodoff (1945), observed that intercapillary glomerulosclerosis increased steadily to 100% at a duration of 18 years of diabetes. Clark and Skillern (1955) found the maximum incidence in 10–14 year's duration and Mitra & Chhetri (1961) found it in 16 to 20 years duration of diabetes.

Gellman et al (1959) observed that the more severe diffuse lesions were seen in those patients who had long duration of diabetes and in whom diabetes started early in life with the result that the duration and age of onset both factors were operating in causing the severity and incidence of diffuse lesion. They found diffuse lesions more frequent in juvenile diabetics.

From the review of literature and the present study two features emerge. Firstly if a patient lives long enough it is highly likely that he will develop nephropathy, secondly that even patients with a very short history of diabetes may have an early diffuse lesion, which can be demonstrated by kidney biopsy.

**SEVERITY OF DIABETES**

The relationship between the diabetes mellitus and nephropathy is believed to be unsettled.
There is a group of workers who believe that nephropathy develops in mild diabetes. (Anson 1938; Siegal and Allen 1941; Porter and Walker 1941; Hall 1952; Pathania & Sachar 1961); whereas others have stated that severity of diabetes has little to do with the development of nephropathy. (Jeske 1956; Rifkin et al 1958; Mathur et al 1960; Gupta & Chakraverty 1964). In the present study maximum incidence of 50% was seen in grade III, i.e. those who needed more than 20 but less than 50 units of Insulin daily for adequate control of diabetes. The incidence dropped to 38% and 33% in grade IV and grade II respectively. For statistical comparison, the two groups, one needing less than 50 units of Insulin and the other needing more than 50 units of Insulin were analysed, and showed no significance (Table No.7).

The results of the present study are in agreement with the observations made by certain workers (cited above) who have stated that the severity of diabetes has little to do with the development of nephropathy.

CONTROL OF DIABETES

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

There is a group of workers who believe that there is no relationship between the control of diabetes and the incidence of nephropathy, (Goodoff 1945; Dolger 1947; Henderson et al 1947; Bell 1952; Downie & Martin 1959; Solomon 1963); whereas others strongly believe that excellent control would delay

In the present study all the patients were inadequately and poorly controlled prior to hospital admission and this may be one of the reasons for greater incidence of diabetic nephropathy. Joslin (1952), stated that good diabetic control can be reached along the thorny path of scrupulous diabetic control and the sin of diabetics who do not follow this commandment is sure to be found out in a shorter or longer time, and in this connection it is worthwhile considering the view expressed by El Mahallawy et al (1960), that a shorter duration of 5 years, is sufficient for a poorly controlled diabetic to develop the complications, while a longer time of 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.

The consensus of opinion at the present moment is that poorer control results in proportionately greater incidence of diabetic nephropathy.
HISTO-PATHOLOGY

The histological lesion in diabetes has been studied by various workers since the time Arnanni (1875) described hyaline vacuolation of the tubular epithelium in the kidneys of patients with diabetes mellitus (Ritchie & Waugh, 1957). The tubular cells become swollen with vacuolated cytoplasm which contained large amounts of glycogen. It was a common lesion in pre-insulin days (Warren 1938), but it has now become rare and infrequent.

The characteristic lesion of diabetic nephropathy (intercapillary glomerulosclerosis) was described by Kimmelstiel Wilson (1936), as peculiar hyaline masses in the centre of the glomerular lobule, called nodular by later workers to distinguish the lesion from other varieties of glomerulosclerosis. Since then, many studies have been reported emphasizing the nature and specificity of the glomerular lesion. (Allen 1941; Fahr 1942; Bell 1953; Reid 1955; Gellman et al 1959; Bergstrand and Bucht 1959; Farquhar et al 1959; Goetz et al 1960; Daysog et al 1961; Sabour et al 1962; Solomon 1963).

It is said that any renal disease may occur in patients with diabetes but the lesions most commonly found are (Warren and LeCompte's Classification 1952):

(1) Intercapillary glomerulosclerosis:
   (a) Nodular lesion
   (b) Diffuse lesion
   (c) Exudative lesion
Figure No. 1

Showing: Normal renal architecture.
(2) Tubular deposition of glycogen, fat and mucopolysaccharide.

(3) Acute and chronic pyelonephritis.

(4) Nephrosclerosis.

It is now generally recognised that diabetic nephropathy with its various features frequently and characteristically occurs in patients with long term diabetes which began early in life (Wilson et al, 1951).

**PATHOLOGY**

The main changes of diabetic glomerulosclerosis occur in the intercapillary space of the glomerulus. Glomerular capillaries are supported by the branching connective tissue stalk which arises at the hilus and extends to the periphery. The branches of the stalk are surrounded by capillaries and the stalk is said to occupy the intercapillary space, and is named mesangium by Zimmerman (1929). The mesangium consists of cells and fibres. The cells have the properties of connective tissue cells and also resemble histiocytes and even smooth muscle cells. The fibres have the properties characteristic of basement membrane, and appear to arise from it, or at least seem to be attached to it. These fibres are often called basement membrane branches or basement membrane-like material.

Normally this intercapillary tissue or mesangium occupies a very small part of the glomerulus, but under the stimulus of disease, it can expand tremendously. (Figure No.1)
Figure No. 2

Showing: Nodular glomerulosclerosis
This was first described by Kimmelstiel & Wilson in 1936 and subsequently, Allen (1941); Held (1955); Gellman et al (1959); and others have described the morphology of the lesion.

Kimmelstiel & Wilson (1936); Fahr (1942) and Bell (1953); suggested that the situation of the nodule was inter-capillary, but to Allen (1941), (1951) and to Gellman et al (1959); it appeared that the location was in the capillary wall. Bergstrand and Bucht reported electron-microscopic studies of glomerular lesion 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 appeared to them intracapillary rather than intercapillary lesions. It was suggested by Sabour et al (1962), that since diabetic glomerulosclerosis developed as a lesion of the basement membrane it should not be described as inter or intracapillary on light microscopy. In this series there were two patients who showed some degree of nodular glomerulosclerosis and in these the nodule occurred at the periphery of the glomerulus and there was no connection with the hilus. The nodules were more eosinophilic than the normal
Figure No. 3

Showing: nodular glomerulosclerosis
capillary basement membrane on H.E. stained slides and had a laminated appearance which was easily demonstrated with periodic acid Schiff (P.A.S). It has been described that, when the nodules are small, a dilated capillary can be seen surrounding them but as the nodules enlarge, the capillary lumen is obliterated, and a few layers of nuclei remain embedded in the periphery of the nodule, making it unusual to see nuclei in the central parts of the nodule. (Figure No2 & 3).

Bell (1950), stated that nodular glomerulosclerosis results from "focal fibrosis" in the diffusely thickened basement membrane and further stated (1953) that the nodular lesions are always associated with diffuse lesions and that diffuse lesions may occur alone and progress to complete obliteration of the glomerulus without the formation of definite nodules and that no sharp separation between the two types can be made. In the present series both the patients with nodular glomerulosclerosis had also diffuse lesion. Gellman et al (1959) found that the first deposition of hyaline material occurred within the endothelial cells and the capillary basement membrane and epithelial cells were affected later. Gellman et al did not believe that the diffuse lesion is merely an early stage of the nodular lesion with which we also agree, because the two cases of nodular glomerulosclerosis in this series had mild to moderate diffuse glomerulosclerosis.

Extensive studies of the glomeruli of diabetics using
FIGURE NO. 4

Showing: Early diffuse glomerulosclerosis
Light and electron microscopy indicate that the first change in most diabetics is the development of diffuse glomerulosclerosis. There is an increase in the number of endothelial cells (or mesangial cells, a point still under debate), and there is accumulation of proteinaceous "hyaline" material in these cells. Later similar material is deposited extracellularly, either directly or by the death of swollen endothelial cells. When the nodules form they are not thrombosed aneurysmal capillaries but they are nodules of extracellular proteinaceous material located in the mesangial space. These nodules are predominantly glycoprotein since they are strongly PAS positive. (Figure No. 3).

DIFFUSE DIABETIC GLOMERULOSCLEROSIS

The diffuse variety of diabetic glomerulosclerosis was described by Fahr in 1942 and by Laiply et al. in 1944 and subsequently Bell (1953), Gellman et al. (1959) and others have described the morphology of the lesion. In diffuse glomerulosclerosis the basement membrane is the first structure to be involved and that the process later spreads to include the endothelial cells and epithelial cells. Diffuse glomerulosclerosis is characterised by the presence of abnormal material in the capillary walls which are thickened, involved and completely surrounded so that in cross section it looks like a thickened ring as compared to nodular glomerulosclerosis in which the capillary wall nearest to Bowman's capsule remains thin and delicate, until the capillary is completely occluded. (Figure No. 4 & 5).
Figure No. 5

Showing: Late diffuse glomerulosclerosis
**NODULAR LESION**

- It occurs at the periphery of the glomerulus, and there is no connection with the hilus.
- Glomeruli are generally not enlarged.
- Has fibrillar appearance.
- Contains collagen.
- Contains reticulin.
- Nuclei are confined to periphery, unusual to see nuclei in the nodule. (Figure No.5 & 6).
- Capillary wall nearest to the Bowman capsule remains thin and delicate.

**DIFFUSE LESION**

- The diffuse lesion is local and focal in the early stages – in late stages the degree of thickening varies from place to place.
- Glomeruli are large and remain large even when completely hyalinized.
- No fibrillar appearance.
- No collagen.
- No reticulin.
- Nuclei are buried uniformly throughout the lesion. (Figure No.5 & 6).
- Seen first in the peripheral capillaries of the glomerular tuft.

In the present series there were 18 cases of diffuse glomerulosclerosis only. The histological appearances were similar to the lesions described above.
Figure No. 6

Showing: Nodular lamination and diffuse glomerulosclerosis.
Figure No. 7

Showing: Nodular laminations (high power)
Figure No. 8

Showing: Capsular dropp. (PAS stain)
EXUDATIVE LESION

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

Typically the lesion is found as an intensely crescentic "cap" round part of the periphery of the capillary loops. Often it surrounds a nodule and less often, it is found as small circular 'drops' attached to the inner aspect of Bowman's capsule or may even lie free in the capsular space. Koss (1952) stated that these capsular or free lesions were really attached to the exudative lesions in or on the capillary tuft. The exudative lesion looks amorphous and structureless. There are no nuclei or cellular elements. There are vacuoles which are filled with fat. The exudative lesion is more eosinophilic than nodular or diffuse glomerulosclerosis. It is found if severe nodular or diffuse glomerulosclerosis is also present. It is a late manifestation of diabetic nephropathy and is always accompanied by severe arteriosclerosis. Hall (1952) and Koss (1952) considered the lesion to be due to ischaemia as a result of atherosclerosis of the renal artery or its branches. Anderson (1954) found that these exudative lesions showed no attempt at repair and
Figure No. 9

Showing: Periglomerular fibrosis
probably meant a terminal event. Mathur et al (1960), (1964), did not agree with the above view and stated that exudative lesion did not necessarily mean a terminal event. In the present series this was seen in only one case (Figure No. 8) and also arteriosclerotic changes were seen in the same patient. (Figure No. 11). But he was not all in the terminal stage.

**PERICAPSULAR FIBROSIS**

This is the layer of fibrous tissue which is frequently seen surrounding the Bowman's capsule. It is roughly proportional to the severity of glomerulosclerosis. Periglomerular fibrosis is said to be associated with ischaemia rather than the inflammatory process, Gellman et al (1959). (Figure No. 9).

**PERITUBULAR HYALINE CUFFS**

It was first described by Fahr (1942). The hyaline material lies outside but on the tubular basement membrane. Koss (1952) suggested that it is a form of hyaline fibrinoid material as seen in exudative lesion in diabetic nephropathy. It gives a smudged appearance and is strongly PAS positive which suggests that it also has a high polysaccharide content. The overall appearance of this material gives an impression of amyloid disease but neither the nodules nor the peritubular "cuffs" take the Congo red stain for amyloid disease. In the present series this was seen in 6 cases. (Figure No. 10).
Figure No. 10

Showing: Peritubular hyaline cuffs (PAS Stain)
ARMANNI-EBSTEIN LESION

This was first described by Armanni in 1875. This striking pathological change is found in those diabetic patients who die of prolonged uncontrolled diabetes, particularly in diabetic acidosis and coma. (Hitchie & Waugh, 1957). This change was seen in pre-insulin era and is said to be now a medical or pathological curiosity without clinical significance. In this series none of the biopsies showed Armanni-Ebstein lesion.

In the present study 2 renal biopsies showed nodular glomerulosclerosis out of a total of 44 (4.6%) and 18 showed mild to moderate diffuse glomerulosclerosis (40.8%). All with nodular glomerulosclerosis had also diffuse lesions. 95% of the positive kidney biopsy showed grade I to II (mild) and 5% showed grade III (moderate) diffuse glomerulosclerosis.

ARTERIOSCLEROTIC CHANGES (NEPHROSCLEROSIS)

Many workers believe that intercapillary lesions are closely related to arteriosclerosis (Bell 1946; Henderson et al 1947; Kimmelstiel & Porter 1948; Hall 1952; Gellman et al 1959); while Fahr (1942), distinguished two forms of independent hyalinization leading to glomerulosclerosis:

(a) One running parallel with arteriosclerosis which he called capillary glomerulosclerosis and,

(b) a form independent of arteriosclerosis namely the extra-capillary glomerulosclerosis, the Kimmelstiel-Wilson lesion.
Figure No. 11

Showing: Arterio-sclerotic changes in kidneys
Bell (1946) studied the occurrence and the degree of arteriosclerosis in an autopsy material of 606 diabetics at the University of Minnesota (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 arteriosclerosis was found in 77.6% of diabetics which was 5 times as often as in the control material. He also concluded that renal arteriosclerosis was not a frequent finding of juvenile diabetics, and that arteriolar disease in some way brings out the intercapillary lesion, but a severe arteriosclerosis did not produce a glomerular lesion of any kind in one third of his cases. Almost all authors are agreed that 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 patient than in non-diabetic and probably reflects the ageing process (Lee 1963).

In the present study arteriosclerotic changes in the afferent and efferent arterioles to the glomerulus and other blood vessels were seen in 7 biopsies, and all the patients were above the age of 40 (figure No. 11).
PATHOGENESIS

The fundamental cause of the specific glomerulonephritis is not known.

Fahr (1942) thought the hyaline formations to be due to a local conditioned plasma or albumin precipitation, while other workers reported that the homogenous substance possesses sudanophil qualities because of fatty deposition. (Kimmelstiel & Wilson 1936; Anson 1938; Newburger & Peters 1939; Simon 1940; Allen 1941; Porter & Walker 1941; Laipply et al 1944 and Wilens & et al 1951). Hartcourt (1955) regarded the characteristic renal lesion due to concentrated lipaemic plasma. The presence of lipids in the glomerular nodules and the characteristic intense periodic acid Schiff reaction led many workers to correlate serum lipids and mucopolysaccharide levels with the presence or absence of diabetic nephropathy and retinopathy (Jacobs 1949; Wilens et al 1951; Muirhead et al 1956; Lynch et al 1957; Raphael et al 1958). Warren & LeCompte (1952) observed that practically all the pathological features of diabetes mellitus can be explained by the deposit of mucopolysaccharides and in this connection many workers have reported increased levels of glycoproteins in the blood of diabetic patients with vascular lesions. (Berkman et al 1952; Gilliland et al 1954; Keiding-Tuller 1955; Intereszzi et al 1958).

Jacobs (1949), showed that considerably larger amounts
liver impacted the glomerular capillaries while Goth et al (1957) incriminated fluctuations of blood sugar levels.

Dolger (1947), questioned whether the lesions were inevitable concomitants of diabetes, while Wilson et al (1951), Joslin et al (1952) and Dunlop (1954), felt certain that these lesions were complications which could be avoided by excellent control of the metabolic defect.

Gellman et al (1959) and others felt that there was a possibility that the nodules were caused by insulin, and they conceived that the prolonged use of insulin (a foreign protein) might result in the formation of antibodies and subsequent vascular damage (Schiler and Dorfman 1957) or that the body may produce antibodies against endogenous insulin as it does against its own thyroglobulin. Freedman (1957), reported two patients with Kimmelstiel-Wilson nodule who did not receive any insulin during life. In the present series 4 patients with positive renal biopsies had not received insulin prior to hospitalisation.

Blumenthal et al (1960, 1961) stressed the importance of non-atheromatous proliferative lesions of small arteries in a number of organs of diabetic subjects e.g. peripheral vessels, retina, coronary artery, suggesting that insulin might be the antigenic agent. They thought that diabetic glomerulosclerosis represents an immunological reaction and that the proliferative lesions in small vessels of many organs in diabetes are similar to vascular changes produced by a variety of immunologic mechanisms like erythroblastosis foetalis, metabolic diseases in pregnancy.
Proliferative vascular lesions are characterised primarily by endothelial proliferation and deposition of a P.A.S. positive colloidal iron negative material consistent with the histochemical reaction of glycoprotein.

Bern et al (1962), demonstrated by means of fluorescent microscopy the presence of a substance in various structures of the kidney in diabetic glomerulosclerosis which appeared specifically to bind insulin. They felt that:—

1. It may be a mucopolysaccharide or lipo-protein,
2. it may represent tissue deposits of insulin binding antagonist, or
3. it may consist of an antibody against insulin.

Gordon (1958) and Blumenthal et al (1961), suggested the possibility of an anti-immune mechanism based on a report by LeCompte (1959), on the occurrence of insulitis of pancreatic islets in early juvenile diabetics before exogenous insulin therapy could be given. This autoimmune phenomena may be similar to that present in patients with lymphocytic thyroiditis.

Blumenthal et al (1962), suggested that the various components of the diabetic glomerulosclerosis lesion contain an insulin anti-insulin complex and there is a possibility that this renal complication may be immunologic with insulin as the definitive antigen.
Kimmelstiel & Wilson (1930), who first described the nodular type of glomerulosclerosis associated with edema, which they described as nephrotic in type. As further work was done to study the morphology, location and relationship of the lesion with the clinical features, some workers agreed with the findings of Kimmelstiel & Wilson, but stated there was some degree of heart failure in all these cases (Derow et al 1939; Siegel (1940) and Simon (1941); whereas other workers felt that edema in diabetes mellitus was more common due to heart failure than due to nephrotic syndrome. (Lefèbvre et al 1946; Henderson et al 1947; Rifkin et al 1949; Rogers et al 1952; Bell 1953); while lately some workers have noticed nephrotic syndrome with diffuse glomerulosclerosis and no nodular lesion. (Adams 1947; Bell 1953; Runyan et al 1955; Lumbie et al 1955; Gelman et al 1959). Mathur et al (1964), concluded that no definite correlation could be demonstrated between diffuse type of nephropathy with age, sex, duration or severity of diabetes or with the clinical picture. This type of lesion appeared to be the earliest change seen in the kidney of diabetics and the nodular type of lesion further developed in subsequent time. The exudative lesion was manifested mainly by those who go into the stage of shock, which was not uncommon in uncontrolled diabetics.

The clinical features associated with K.W. syndrome are
edema, hypertension, diabetic retinopathy, albuminuria, and renal failure (Clark & Skillern 1955).

Gellman et al (1959), noted 26% incidence of nephrotic syndrome in their selected series. This high incidence reflects their known interest. To most of the clinicians nephrotic edema in diabetes is the K.W. syndrome and suggests that nodular lesion is present, which is not borne true by the present study. They also concluded that the patients who developed diabetes early in life were especially liable to develop the nephrotic syndrome and that the duration of diabetes was not significant between the group with and without nephrotic syndrome. They demonstrated that the severity of hypertension, proteinuria, renal failure, incidence of edema and nephrotic syndrome, could be correlated with the severity of diffuse diabetic glomerulosclerosis. The 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. Interozzi et al (1958) also found increased cholesterol and total lipids in uncontrolled diabetics while Lowy et al (1957) found the cholesterol and other lipid factors normal in diabetic males and slightly raised in diabetic females in 901 diabetes without complications.

Gellman et al (1959), postulated that serum albumin might be low in diabetics as a result of malnutrition and liver disease and that nephrotic syndrome might 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 differences which were highly significant.

Many workers have postulated that the widespread involvement of the capillary basement membrane by diffuse glomerulosclerosis is enough to account for the proteinuria and if this loss is sufficiently high and prolonged, it will lead to the other features of nephrotic syndrome (Brun et al. 1953; Taft et al. 1954; Howe, 1955; Kark et al., 1958). Gellman et al., 1959, concluded that there is no regular association between nodular glomerulosclerosis (the Kimmelstiel-Wilson lesion) and proteinuria, hypertension, renal failure and nephrotic edema (the so-called Kimmelstiel-Wilson syndrome). Among the above studies it was only Gellman et al. study which correlated the severity of lesion with the functional data. They were further of the view that the changes in renal function were caused by the diffuse diabetic glomerulosclerosis and by the associated arteriolar and tubular damage and not by the nodules. They therefore pleaded that the term Kimmelstiel-Wilson syndrome should be abandoned, and the name reserved for the histological lesion which Kimmelstiel and Wilson described in 1936.

In the present study nephrotic syndrome or K.W. syndrome was clinically diagnosed in 2 out of 19 patients of diabetic nephropathy among 48 diabetics. None was a juvenile diabetic. It was seen in elderly patients above age 50, both were males, the duration varied from 2½ to 7
years and severity of diabetes varied from grade II to grade III. One patient showed nodular glomerulosclerosis and in the other, kidney biopsy was not done due to hypertension and high blood urea. The E.C.G was normal in both, although peripheral vascular calcification was seen in either. Serum cholesterol was less than 250 mgm % and serum albumin was less than 3.5 Gm % in both.

**ALBUMINURIA**

It is believed that in early stages, proteinuria is slight or transitory and later on, it becomes severe and permanent. Persistent albuminuria is usually considered to be the earliest clue to the presence of intercapillary glomerulosclerosis (Kimmelstiel-Wilson 1936; Anson 1938; Newburger & Peter 1939; Mann et al 1949; Rifkin et al 1952; Hatch et al 1961). A number of workers reported that urinary casts when present, were of hyaline in nature (Mann et al 1949; Clark & Skillern, 1955). Proteinuria is believed to have positive correlation with diffuse glomerulosclerosis but no definite relationship exists between nodular glomerulosclerosis and proteinuria (Clarke 1941; Gellman et al 1959).

The incidence of albuminuria in diabetes has varied in the different series from 10% to 55% (Bachman 1936; Martensson 1949; Ytrehus 1950; Joslin 1951; Aarseth 1953; Gupta & Chakravarty 1964); whereas it is present in more than 75% of cases of diabetic glomerulosclerosis (Bell 1946; Henderson et al 1947; Gellman et al 1959; Hatch et al 1961;
In the present series proteinuria was found only in 6 out of 18 (33.3%) patients with diabetic glomerulosclerosis and in 10 patients out of 26 (38.5%) patients without this lesion on kidney biopsy. The reason for this low incidence is that most of the cases had mild diffuse glomerulosclerosis.

Clarke (1941), reviewing the first 76 published cases of nodular glomerulosclerosis found that 25% did not have albuminuria, while in Gellman's series (1959), 8 out of 13 (61%) grade I cases of diffuse glomerulosclerosis on K.B, did not have proteinuria.

In the present study 12 out of 18 (66.6%) cases of diffuse glomerulosclerosis did not have proteinuria, while both the cases of nodular glomerulosclerosis had proteinuria, in one of them granular casts were also seen. Proteinuria in all our cases was of mild degree.
## INCIDENCE OF ALBUMINURIA

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naunyn</td>
<td>1910</td>
<td>25.0</td>
</tr>
<tr>
<td>Hatlehol</td>
<td>1926</td>
<td>54.0</td>
</tr>
<tr>
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<td>1927</td>
<td>21.5</td>
</tr>
<tr>
<td>Bachmann</td>
<td>1936</td>
<td>10.0</td>
</tr>
<tr>
<td>Kimmelstiel &amp; Wilson</td>
<td>1936</td>
<td>100.0</td>
</tr>
<tr>
<td>Bell</td>
<td>1946</td>
<td>96.0</td>
</tr>
<tr>
<td>Henderson et al</td>
<td>1947</td>
<td>95.0</td>
</tr>
<tr>
<td>Kimmelstiel &amp; Porter</td>
<td>1948</td>
<td>66.0</td>
</tr>
<tr>
<td>Martensson</td>
<td>1949</td>
<td>33.0</td>
</tr>
<tr>
<td>Ytrehus</td>
<td>1950</td>
<td>12.0</td>
</tr>
<tr>
<td>Bjerkelund</td>
<td>1951</td>
<td>22.0</td>
</tr>
<tr>
<td>Joslin et al</td>
<td>1952</td>
<td>43.0</td>
</tr>
<tr>
<td>Aarseth</td>
<td>1953</td>
<td></td>
</tr>
<tr>
<td>Dana &amp; Zubrod</td>
<td>1954</td>
<td>64.4</td>
</tr>
<tr>
<td>Gellman et al</td>
<td>1959</td>
<td>75.0</td>
</tr>
<tr>
<td>Hatch et al</td>
<td>1961</td>
<td>87.5</td>
</tr>
<tr>
<td>Pathania &amp; Sachar</td>
<td>1961</td>
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<td>Mitra &amp; Chhetri</td>
<td>1961</td>
<td>100.0</td>
</tr>
<tr>
<td>Gupta &amp; Chakarverty</td>
<td>1964</td>
<td>55.0</td>
</tr>
<tr>
<td>Present study</td>
<td></td>
<td>33.3</td>
</tr>
</tbody>
</table>
It is believed that laboratory findings in renal involvement in diabetes mellitus are generally predictable, and that some degree of tubular damage is associated with severe degrees of diffuse glomerulosclerosis. The renal function tests and blood biochemical abnormalities reflect the combined glomerular and tubular dysfunction. Renal failure may occur with predominantly nodular glomerulosclerosis wherein, one is also likely to find associated with it, chronic pyelonephritis, nephrosclerosis and proliferative vascular changes. (Lee 1963), Stauss (1963).

There is a group of workers who believe that renal function tests do not reflect the true incidence of diabetic nephropathy and that the great majority of patients have normal NPN, (Hatlehol 1926; Bell 1942; Gupta & Chakraverty 1964); whereas, there are other workers who are impressed by the number of patients with diabetic nephropathy, who exhibit loss of renal function (Henderson et al 1947; Hogeman 1948; Mann et al 1949; Alwall et al 1950; Gellman et al 1959; Sinha 1960; Hatch et al 1961).

Alwall et al (1950) found the specific gravity of urine under 1030 in 60% of the patients with intercapillary glomerulosclerosis while 40% had specific gravity over 1020.

Gellman et al (1959) has stressed the close correlation of raised blood urea with the severity of diffuse lesion, but not with the severity of nodular lesion. He also noted
similar positive correlation with serum creatinine, urea clearance and creatinine clearance.

In the present series blood urea above 40 mgm per 100 ml was found in 10 out of 18 cases of diabetic glomerulosclerosis, (55.5 %) and in 10 out of 26 cases without diabetic glomerulosclerosis (38.5 %).

Abnormal P.S.P. excretion was found in 77.7 % with and 30.8 % without, concentration of urine (after pitressin tennate in oil I.M) below 1020 was found in 77.7 % with and 88.5 % without, dilution of urine above 1003 was found in 77.7 % with and 80.8 % without diabetic glomerulosclerosis.

It is apparent from the results quoted above that the concentration and dilution tests showed almost equal incidence with and without diabetic glomerulosclerosis and as such were not helpful in the early diagnosis of the K.W. lesion. It is questionable as to how much one can rely on the concentration and dilution tests in uncontrolled diabetics because of the profuse solute diuresis. Similarly albuminuria was not significant as it was detected in about equal percentage with and without K.W. lesion. As far as blood urea and serum creatinine were concerned, there was a slightly better correlation with and without nephropathy and it showed a positive trend towards relationship, but it was not statistically significant.

As far as P.S.P excretion test is concerned, it showed a ratio of about 8 to 3 of abnormal excretion with and without nephropathy. P.S.P test thus tells of kidney
impairment in much more remarkable manner than other kidney function test, apart from glomerular filtration rate. It is useless and fallacious to do creatinine clearance in uncontrolled diabetics when there is marked solute diuresis (Gellman et al 1959). Hence one would feel that P.S.P. excretion test is a good indicator of kidney function provided the limitations of the test are kept in mind, e.g. under conditions of shock wherein there is diminution of renal plasma flow, or in diabetic acidosis and coma when it will give false positive results.

### INCIDENCE OF ABNORMAL BLOOD UREA

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Percentage with Nephropathy</th>
<th>Percentage without Nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henderson et al</td>
<td>1947</td>
<td>64.0</td>
<td>53.0</td>
</tr>
<tr>
<td>Rifkin et al</td>
<td>1948</td>
<td>40.9</td>
<td></td>
</tr>
<tr>
<td>Kimmelstiel &amp; Porter</td>
<td>1948</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>Sinha</td>
<td>1960</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Pathania &amp; Sacher</td>
<td>1961</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td>Mitra &amp; Chhetri</td>
<td>1961</td>
<td>37.5</td>
<td></td>
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<tr>
<td><strong>Present study</strong></td>
<td></td>
<td>33.3</td>
<td>38.5</td>
</tr>
</tbody>
</table>
In contrast to the numerous studies centered around diabetic nephropathy, where there is a certain degree of uniformity of opinion, the literature regarding the infective element is scanty and varied. Most of the autopsy series point to the fact that pyelonephritis and urinary tract infection are more common in diabetes. (Sharkey & Root 1935; Baldwin & Root 1940; Harrison & Bailey 1942; Robbins et al 1946; Kass 1956; Gellman et al 1959; Huvas & Rocha 1959; White 1959; Kass 1960.)

In clinical series the incidence of infectious element has varied from 2% to 50% (Sharkey Root 1935; Bowen & Kutzman 1942; Mann et al 1949; Gellman et al 1959; White 1959; Sathe 1960; Kass 1960; O'Sullivan et al 1961; Mathur et al 1964). While other workers were not impressed by the difference when comparison was made with non-diabetics (White 1959; O'Sullivan et al 1961).

Jenson (quoted by Lee, 1963), stated after reviewing the autopsy evidence of renal infection in diabetic and non-diabetic patients, 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.

Solomon (1963) found very little histological evidence of renal infection in 51 unselected diabetic renal biopsies although it was carefully searched for and it is surprising
that Daysog et al (1961) reported an incidence of 50% of pyelonephritis in 62 renal biopsies. In the general population, in autopsy studies and in clinical series the frequency has been found to range 10-20 per cent (Strauss 1963). Variation in incidence as reported in the literature is due not only to differing type of material, autopsy or clinical, 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. According to Weiss & Parker (1939), there is no isolated pyelitis. The kidney is always simultaneously affected and therefore pyelonephritis is always present. Although this view is an extreme one (Baldwin & Root 1940), it will undoubtedly be wise to postulate that there is always a renal lesion (Raaschou 1948). The great frequency of infections of the urinary tract in diabetes makes pyelonephritis a very frequent complication in diabetics. Many a time the infection (asymptomatic bacteriuria) is present without any constitutional symptoms or symptoms referable to the urinary tract so that it is very likely that many cases of urinary tract infection or pyelonephritis may go undetected as patients never complain about it. With a view to establishing the presence of renal or urinary tract infection a detailed study of these 48 diabetics and 16 non-diabetic controls was undertaken.
In the present study chronic pyelonephritis was noted in 14 out of 48 diabetics 29.2% while urinary tract infection was detected apart from the above in another 5 cases (10.4%) making a total of 39.6% out of which 25% were males and 14.6% were female. The marked incidence in males is because of the predominantly male series, among the diabetic population.
### Incidence of Pyelonephritis or Urinary Tract Infection

<table>
<thead>
<tr>
<th>Author</th>
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<tr>
<td>Sharkey &amp; Root</td>
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<td>30.0</td>
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</tr>
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</tr>
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<td></td>
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</tr>
<tr>
<td>Robbins et al</td>
<td>1946</td>
<td>19.5</td>
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<tr>
<td>Mann et al</td>
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<td>37.3</td>
</tr>
<tr>
<td>Bernard et al</td>
<td>1953</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>Gellman et al</td>
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<td>55.0</td>
<td>10.0</td>
</tr>
<tr>
<td>White</td>
<td>1959</td>
<td>40.8</td>
<td>14.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2 % males)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(12% females)</td>
</tr>
<tr>
<td>Kass</td>
<td>1960</td>
<td>20.0</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>22.0</td>
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<td></td>
<td></td>
<td>(3 % males)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(9 % females)</td>
</tr>
<tr>
<td>Daysog et al</td>
<td>1961</td>
<td></td>
<td>50.0</td>
</tr>
<tr>
<td>Hansen</td>
<td>1964</td>
<td></td>
<td>25.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(7 % males)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(18% females)</td>
</tr>
<tr>
<td>Parrish</td>
<td>1965</td>
<td></td>
<td>16.0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(2 % males)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(14% females)</td>
</tr>
<tr>
<td>Present study</td>
<td></td>
<td>39.6</td>
<td>(25% males)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(14.6 % females)</td>
</tr>
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</table>
The small contracted kidney of chronic pyelonephritis remains one of the enigmas of medicine. Chronic pyelo-
nephritis was reviewed in a classical paper by Weiss and 
Parker in 1939 and since then it has become an increasingly 
popular diagnosis. (Rosenheim 1963). He further states 
that as a pathological process its progress is often slow 
and insidious, and it frequently presents clinically as 
a recurrent or refractory urinary tract infection, patients 
are often first seen because of hypertension or proteinuria 
or because of many manifestations of renal failure. It is 
now recognised as the commonest cause of the syndrome of 
renal failure with hypertension.

Chronic pyelonephritis has been defined as the end 
result of bacterial inflammation in the kidney (Kleeman et 
al 1960), inflammation usually associated with the gram-
negative coliform bacilli. Until recently it has been 
essentially a pathological diagnosis, the pathologist still 
has the final word, but modern radiology has provided a 
means of establishing the diagnosis during life. (Rosenheim, 
1963).

The pathological changes of chronic pyelonephritis 
are nearly always focal. The condition may affect one 
or both kidneys often leading to a marked disparity in 
size. The individual kidney is irregularly scared as 
though by multiple infarcts, and these scared fibrotic
areas adjoin areas of relatively normal renal tissue. (De Navasqez 1950, 1956; Rocha et al 1958; Freedman & Beeson 1958), suggested the importance of medullary scarring and tubular obstruction in the causation of localised pyelonephritis. Interstitial changes of chronic inflammation and fibrosis are seen in these scarred areas. Many of the glomeruli are hyalinized or markedly distorted, others show characteristic periglomerular fibrosis, and often appear crowded together. The tubules may be dilated and contain pink staining colloid material that produces a thyroid-like appearance; elsewhere areas of atrophic and ischaemic tubules are found. Rosenheim (1960), stated that it would be fair to say that while the majority of cases of chronic pyelonephritis are due to bacterial invasion of the kidney, by haematogenous or ascending routes, it is possible that other forms of damage may occasionally produce similar pathological changes.

The clinical diagnosis of chronic pyelonephritis is difficult to establish, and in recent years, new methods of diagnosis have become available and include renal biopsy, radiological examinations like intravenous pyelogram and micturating cystogram; urinary colony count, provocative urinary white cell excretion rate and other renal function studies. (Leather 1963).

**RENAI BIOPSY**

de Wardener (1960), stated that it is probably true that a renal biopsy is the most certain method of making
the diagnosis of chronic pyelonephritis, but the focal nature of the disease makes even this technique uncertain. Renal biopsy has not been much used in cases diagnosed clinically as pyelitis. Hutt and de Wardener (1961) reported that in 4 out of 10 such cases there were foci of acute inflammation in the renal cortex, demonstrating that many clinical cases of pyelitis are really cases of pyelonephritis. Allen (1962) described such changes occurring in the kidney as hypersensitivity reaction to sulphonamides. The value of renal biopsy in chronic pyelonephritis is limited because the histological changes seen are irregularly distributed within the kidney and even when changes are found they are difficult to interpret and distinguish particularly from changes due to hypertension or ischaemia (Brewer 1964).

The criteria of pyelonephritis as laid down by Weiss & Parker (1939), have been recently considered critically by Kimmelstiel et al (1961), and they came to the conclusion that interstitial infiltration with lymphocytes only, is of no significance but that an active pleomorphic inflammatory infiltrate particularly accumulation of polymorphonuclear leukocytes is the safest criterion for the diagnosis of chronic pyelonephritis. In chronic pyelonephritis inflammatory cells particularly polymorphonuclear leukocytes may be absent. They then regarded the presence of areas of thyroid-like tubular atrophy to be most helpful, and the glomerular changes to be of limited value, and found hyalinized glomeruli to be irregularly placed and separated.
Showing: Dilated tubules filled with colloid cast and diffuse interstitial infiltration by round cells, characteristic of chronic pyelonephritis.
Leather (1963), found conclusive histological changes in 4 out of 15 renal biopsies among 30 cases of chronic pyelonephritis. He stated that the histological changes of pyelonephritis are not straightforward and many of its histological features are still in dispute and that nephrosclerosis and hypertension may mimic some of the changes attributed to pyelonephritis.

Brun and Rasschou (1961), concluded that nearly all cases of chronic pyelonephritis with impaired renal function show definite histological changes. The reason for this finding by these workers is probably due to their method of kidney biopsy in which a large piece of tissue is obtained and in some cases even a piece of papilla is available for examination.

In the present study there were only 3 biopsies which fulfilled the criteria of Weiss & Parker (1939), even though 14 cases were regarded to have chronic pyelonephritis on other grounds to be described below. (Figure No. 12).

**INTRAVENOUS PYELOGRAM**

According to Rosenheim (1963), radiology offers the best means of establishing the diagnosis of chronic pyelonephritis in life and the criteria laid down by Hodson (1959, 1961, 1962) in England and Dejdar (1959) in Czechoslovakia are now widely accepted. Hodson (1959), stated that in the great majority of cases chronic
Figure No. 13

Showing: Normal kidneys with smooth outline.
Figure No. 14

Showing: Normal I.V. Pyelogram with normal cupping of Calyces.
Showing: Minimal calycectasis and irregularity of the kidney surface, suggestive of chronic pyelonephritis.
pyelonephritis is a well circumscribed focal disease of the kidney and only in advanced stages is there a widespread involvement. The essential feature of these focal lesions is shrinkage or coarse scarring of the renal tissue which shows up radiologically as a decrease in thickness of the renal substance, and if a pyramid is involved, as an absence of the pyramid, i.e. as clubbing of a calyx. The majority of kidneys, with pyelonephritis are smaller than average. The radiological findings are, therefore, small kidneys, in which there is focal decrease in the thickness of the renal substance associated with clubbing of the adjacent calyx. Leather (1963), stated that excretory urography is useful and simple, but other conditions such as nephrosclerosis and renal infarction may occasionally mimic the appearance of chronic pyelonephritis and this must be taken into consideration in assessing the radiological findings.

Recognition of these changes in early cases thus calls for careful assessment of the outline and caliceal pattern of both kidneys. In more advanced cases the kidney is usually smaller still with multiple scarred areas, a grossly irregular renal outline and with generalised irregular distortion of the pelvicaliceal system.

In the present series there were 5 patients who had intravenous pyelograms suggestive of chronic pyelonephritis. There was irregular margin and clubbing of the calyx. (Figure No. 13, 14. & 15 ). In 3 other patients there was spasticity
of the uretero-caliceal system which is only suggestive of pyelonephritis. But in these patients I.V. Decadron provocative cell excretion rates and colony count of the midstream urine were strongly positive.

**VESICO-URETERIC REFLUX**

Cabot and Crabtree (1916), subdivided pyelonephritis into primary and secondary. In the former, infection occurred in a kidney with no preceding lesion of the urinary tract, while in the latter there was present some antecedent lesion, such as a stone in the renal pelvis or ureter or damage dependent upon some obstruction to the ureter or bladder. This subdivision into obstructive and non-obstructive pyelonephritis was maintained for a long time. Brod et al (1960), reported that while in two-thirds of cases of chronic pyelonephritis coming to post-mortem, partial or complete obstruction to the free flow of urine could be found, in about one third of the cases there was no obvious abnormality in the urinary tract.

With ascending infection in mind, the competence of the vesico-ureteric reflux came under discussion. Charles Bell (1812), described the anatomy of the intramural portion of the ureter. Young (1898), was the first to discuss the possible occurrence of ureteric reflux in man and Sampson (1903), recognised reflux as a possible cause of renal infection. The recognition of the association of vesico-ureteric reflux with atrophic non-obstructive chronic
pyelonephritis raises many questions of interest among diabetic patients. Rosenheim (1963), stated that from a study of published papers there is now general agreement that reflux, rarely if ever, occurs in normal healthy urinary tract (Turner-Warwick 1962), and that it is associated with the presence of urinary infection and that reflux disappears when urinary infection clears up. Hanley (1963) and Edwards (1961), showed that damage to the ureteric orifices may be followed by a trophic pyelonephritis. Stephens and Lenaghan (1962) and Hutch (1962), considered that the basic defect in most patient with pyelonephritis is a damaged vesico-ureteric function, and Garrett et al (1961), have stated that regurgitation may precede, promote and perpetuate pyelonephritis. The relief of known bladder neck obstruction in obstructive pyelonephritis may cure reflux. Three main factors thus play a part in the production of reflux:

(a) obstruction in the lower urinary tract,
(b) infection, and
(c) some anomaly of the intravesical ureter.

Hodson (1959), in a study of 1000 normal I.V.Ps showed that there is a remarkable symmetry in shape, size and thickness of renal substance between the two kidneys and that unilateral or bilateral decrease in the size of the renal outline is frequently seen in cases of reflux. This reduction in size is associated with dilatation and deformity of the calyces. Vesico-ureteric reflux has been demonstrated
Figure No. 16

Showing: Normal micturating cystogram.
in 32 out of 41 patients with radiological evidence of chronic pyelonephritis. He believed that reflux once established produces progressive destruction of renal tissue and considered that cysto-urethrography should be a routine investigation in all patients with clinical or radiological evidence of chronic pyelonephritis.

In the present series there were 14 cases of chronic pyelonephritis and 5 urinary tract infection. It is surprising that there was no vesico-ureteric reflux in any one of these patients. One is tempted to conclude that in diabetic men and women with no history of previous catheterisation, like the patients in the present series, the infection to the kidney must have been purely through a haematogenous route. Most of the cases of pyelonephritis with a positive vesico-ureteric reflux have been women with the previous history of catheterisation and lower urinary tract infection.

**COLONY COUNT**

Kass (1957, 1960) in Boston has drawn a clear distinction between bacterial contamination and true urinary infection and believes that symptomless infection of the urinary tract is not uncommon. He has shown that it is not necessary to use catheter specimens of urine in women for the diagnosis of infection, but that mid-stream clear specimens will do as well, provided that cultures are set up early, before contaminant organisms have had time to multiply. Kass found
that counts of over 100,000 ($10^5$) organism per ml indicate a true infection while counts of under 10,000 ($10^4$) indicate contamination. He found considerable number of women to have symptomless infection without pyuria and believes that such women are especially prone to develop pyelonephritis.

Beeson and his colleagues (Rocha et al 1958), have shown that renal medullary tissue is particularly susceptible to infection.

Freedman and Beeson (1958) reported that an injection of less than 10 organisms into the medulla provoked infection there while some 100,000 were usually necessary to infect the cortex. If the ureter was obstructed very few organisms in the ureter led to rapid renal infection, but large numbers of bacilli in the urine failed to cause such infection in the absence of obstruction, and this close association of infection and obstruction emphasizes the possible importance of vesicoureteric reflux as a factor predisposing to infection of the kidney, whether the organism reach the renal medulla from the urine or the blood stream. (Rosenheim 1963).

**URINARY WHITE CELL EXCRETION**

It appears, therefore, that if chronic pyelonephritis can be present with no localised signs or symptoms, a sterile urine and a normal pyelogram, and if the renal functional changes are unspecific, the only way to make the diagnosis is by renal biopsy or to wait until the pyelographic changes finally appear, which is clearly undesirable (de Wardener 1960).
In England there is an increasing interest in the provocative urinary white cell excretion as an aid to the diagnosis of pyelonephritis (Houghton & Pears 1957) while in America the focus of attention is almost entirely on the number of organisms (Kass 1957).

Intrarenal infection can be notoriously silent (Kleeman 1960). In recent years new methods of diagnosis have become available. Besides renal biopsy, radiology and colony count, "Pyrogen" (Pears & Houghton 1958), or steroid test (Katz and Moore, 1960; Katz et al, 1962; Little & deWardener, 1962), are in vogue for estimation of urinary W.B.C count (Houghton & Pears, 1957). The test consists of estimating the rate of urinary white cell excretion, particularly after the injection of pyrogen. Pears & Houghton (1958, 1959) found that in cases of undoubted chronic pyelonephritis there is a prompt rise in the rate of white cell excretion. The mechanism underlying the phenomena is not understood (deWardener 1960). He said that the test has certain disadvantages but nevertheless it is an advance. This response was further studied by Hutt, Chambers, MacDonald and deWardener (1961), and Pinkerton et al (1961), who particularly stressed its value in revealing the presence of active urinary tract infection when the results of other tests are equivocal. The side effects of pyrogen test are a disadvantage and Katz and Moore (1960), claimed that in dogs with pyelonephritis, adrenal steroids have an effect on the white
cell excretion rate similar to that of pyrogen. Katz et al (1962), also found that prednisolone also increased the white cell excretion in some control patients without pyelonephritis but to a lesser extent.

Montgomery et al (1963), found the rate of excretion of white cells in the urine doubled by pyrogen in only 13 of 21 patients with chronic pyelonephritis. They did not find the test specific for chronic pyelonephritis as it was found positive in 3 out 4 cases of chronic glomerulonephritis and in 1 healthy subject. They have thrown some doubt on the reliability of the test especially in picking out all cases of chronic pyelonephritis. In none of our 16 controls did the provocative cell excretion reach a level above 400,000 per hour which we have taken as the demarcation line.

The normal urinary white cell excretion rate is almost always below 200,000 per hour to 400,000 per hour. deWardener have chosen 400,000 per hour as a safe upper limit of normal but considers counts between 200,000 and 400,000 per hour as suspicious. Their findings (1960), confirmed that with a few exceptions patients with chronic pyelonephritis will respond to an injection of a pyrogen by increasing their rate of white cell excretion by 100 per cent or more to a rate greater than 400,000 per hour whether or not the urine is infected or the initial white cell excretion rate is within normal limits. In patients with chronic pyelonephritis the administration
of antibiotics may lower the probability of obtaining a positive response, although it remains positive in some patients. In addition it shows that not only treatment is often ineffective in controlling the inflammation, but also that, in most instances, measuring the urinary excretion of white cells is a more effective means of detecting this than culturing the urine (deWardener 1960). Some patients with a positive kidney biopsy have a normal pyrogen test, while the test is positive in latent non-gonococcal urethritis (false positive). deWardener (1960), concluded that a positive pyrogen test is an indication of a renal inflammatory process secondary to an infective agent but a negative response does not rule out the possibility of chronic pyelonephritis. According to deWardener (1960), the test was not positive in chronic glomerulonephritis without nephrotic syndrome. Little & deWardener (1962), found that the white cell excretion rate after I.V. steroid did not change significantly in normal subjects, in patients with glomerular nephritis or in patients with acute pyelonephritis undergoing treatment. In chronic pyelonephritis there was significant change and the response was better with I.V. steroid over bacterial pyrogen, and the side effects of I.V. steroid were negligible.

Little (1962), found that the urinary white cell excretion in women using a midstream sample is similar to those obtained when the urine is collected with a catheter
and found that in a substantial proportions of the urines, the number of white cells seen per high power field gives a poor index of white cell excretion rate. In 42 out of 155 urines in which only 1-5 cells were seen per high power field they noticed abnormally high white cell excretion counts. Leather (1963), stated that pyrogen or steroid test is the most single useful diagnostic test employed and was positive in over half of his 30 cases. He however pointed out that it is not pathognomonic for pyelonephritis, as positive results have been recorded in glomerulonephritis. (Hutt et al 1961; Montgomery et al 1963; Leather et al 1963). It should not be regarded as evidence of pyelonephritis in the absence of other features. The substitution of steroid for pyrogen has materially reduced the discomfort to the patient entailed by this test. (Katz et al 1962; Little & deWardener 1962).

Leather (1963), concluded that the most useful diagnostic aid in the diagnosis of pyelonephritis was the pyrogen or steroid test; excretory urography and renal biopsy are also of value but an absolute count of urinary excretion of white blood cells was more reliable than a single examination of the urinary deposit. However, in most cases, the clinical features and a combination of diagnostic measures are necessary to establish the diagnosis of chronic pyelonephritis.

The diagnosis of chronic pyelonephritis is difficult and in many ways it is probably true that a renal biopsy is
the most certain method of making the diagnosis but the focal nature of the disease makes even this technique uncertain (de Wardener 1960). Radiological changes of chronic pyelonephritis have been described by Hodson (1959), but the radiological changes are late in appearance. Hence the focus of attention in recent years has been:

(a) on the urinary cell excretion rate with provocation by pyrogens or corticosteroids (Houghton & Pears 1957; Katz 1962);

(b) on the number of micro-organisms or abnormal colony count (Kass 1957); and

(c) the micturating cystogram (Edwards 1960).

As the vesico-ureteric reflux is non-specific, concentrated attention has been focussed on the first two tests mentioned above.

In the present study 16 controls were subjected to the above tests and in none of them were any of the tests positive. Among 48 diabetic patients 14 cases (29.2%) were considered to have chronic pyelonephritis as per criteria of diagnosis for chronic pyelonephritis as given on page 120. Out of which 2 patients (4.1%) showed positive pyelonephritic changes of interstitial fibrosis and inflammatory exudate on kidney biopsy, 5 patients (10.4%) showed definite changes of chronic pyelonephritis on I.V. pyelogram such as irregular margin, clubbing of calyces and in 3 pyelograms (6.2%) there was spasticity only. Provocative urinary cell excretion was positive (increase in the rate
of white cell excretion after I.V. Decadron by 100% or more to a level greater than 400,000 per hour), in 13 out of 48 (27.1%) diabetics. In two patients who had unequivocal histological and radiological signs of pyelonephritis, the test was negative. Both these patients had previously been treated intensively by antibiotics. A similar result was obtained in treated cases by deWardener (1960). Urinary colony count was abnormal (more than 100,000 colonies per ml) in 21 patients (43.7%). Surprisingly, in none of the patients could a vesico-ureteric reflux be demonstrated. The possible explanation is that in diabetes the kidneys get affected through the hematogenous route, which has already been discussed.
correlation between the diffuse lesion was not due to age, as in his series there was no tendency for the diastolic pressure to be higher in older patients. He thought that hypertension might have been due to narrowing of the afferent arterioles and small renal artery due to deposition of the hyaline material.

In the present study hypertension was present in 4 out of 48 cases (8.3%). In 3 cases it was moderately raised; only in 1 case it rose to 210/110.

75% of cases were above age 50; sex ratio was nearly 1:1. Duration, severity and control of diabetes did not seem to be related to the incidence of hypertension.

Coronary arteriosclerosis was associated in 1, diabetic retinopathy in 1, cataract in 1, vascular calcification of limb vessels in 2, diabetic nephropathy in 2 (50%), K.W. syndrome in 2 (50%), urinary tract infection in 1, chronic pyelonephritis in none.

Hypertension was present in 2 out of 18 cases of nephropathy (11.1%) and in 2 out of 26 cases without nephropathy (7.7%).

It would thus seem that hypertension was not an essential feature of K.W. lesion, that is there was roughly 1:10 chance of finding hypertension among cases of diabetic glomerulosclerosis, but once hypertension was detected, B.P being above 150/90, there was 50% chance of finding either K.W. lesion or K.W. syndrome.
## INCIDENCE OF HYPERTENSION AMONG DIABETIC GLOMERULOSCLEROSIS

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<th>Percentage without Nephropathy</th>
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