CLINICAL SYNDROME ASSOCIATED WITH KIMMELSTIEL-WILSON LESION OF THE KIDNEY

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[WITH SPECIAL PLATE]

The liability of the diabetic patient to develop kidney disease is due in part to the more frequent occurrence and severe nature of infections, ranging from pyelitis to necrotizing renal papillitis, and in part to degenerative disease of the renal arteries and arterioles. The clinical criteria for recognizing these complications have been established. But diabetics are also subject to a renal disease called "intercapillary glomerulosclerosis" by Kimmelstiel and Wilson (1936), which is probably peculiar to diabetics, and for the recognition of which during life there are as yet no accepted clinical criteria.

Several clinical and pathological studies of intercapillary glomerulosclerosis have appeared since the original observations, many tending to confirm that the typical lesions are associated with a recognizable syndrome, but others describing cases in which no syndrome was discerned. More recently, Kimmelstiel and Porter (1948) have done much to clarify this position by suggesting that two distinct and possibly different lesions have been recognized in the literature as intercapillary glomerulosclerosis—a diffuse form in which there was only a widespread basement membrane thickening and a nodular form in which there are distinct well-defined islands of hyaline material in the glomeruli. They observe that the evidence of the literature shows that the "nodular" type is a lesion found only in diabetics, and that these diabetics had usually shown a definite syndrome. Further, as the original paper of Kimmelstiel and Wilson refers clearly to cases showing the "nodular" form, only such a lesion should be described as "intercapillary glomerulosclerosis" or the Kimmelstiel-Wilson lesion. This procedure has been adopted in this paper.

A comparison between the clinical syndrome recorded in association with different types of renal disease in diabetics should show whether there was a syndrome associated with the lesion, at least in its advanced stages. We decided to make such a comparison after analysing the clinical records and post-mortem material of all diabetics coming to necropsy in Hammersmith Hospital from July, 1936, to August, 1948. The cases were classified according to their renal condition into one of the five groups shown below, and a comparison made between the clinical features of these five groups provides the results presented.

Pathological Grouping

There were 46 cases. Three were discarded, as adequate pathological material was not available. There were no cases of nephritis. The remaining 43 were placed in the following groups:

Group 1: the Kimmelstiel-Wilson Group (11 cases; 8 with lesions in nearly every glomerulus, 3 in only occasional glomeruli).—All cases showing nodular intercapillary

glomerulosclerosis as described by Kimmelstiel and Wilson were placed in this group, irrespective of other disease conditions—that is, all cases showed the following features: (a) Discrete hyaline islands in the glomeruli (Plate, Fig. 1). The capillaries around them appeared to remain patent and even, in places, dilated (Fig. 2). (b) A pronounced degree of arteriosclerosis (Fig. 1). This may be seen to affect both afferent and efferent arterioles (Fig. 3). (c) A hyaline "cap" on a thickened Bowman's membrane (Fig. 1). In some cases special stains were employed which showed the protein nature of the hyaline material (Fig. 3), the fatty changes in it and in the adjacent tubules (Fig. 4), and the argentophil staining of the hyaline balls (Fig. 5).

Group 2: the Arteriolosclerotic Group (three cases).—This consisted of those cases in which arteriolosclerosis was present without the typical Kimmelstiel-Wilson lesions (Fig. 6).

Group 3: the Arteriosclerotic Group (4 cases).—This was composed of those cases which showed arteriosclerosis, both macroscopically and microscopically, but no Kimmelstiel-Wilson lesions.

Group 4: the Pyelonephritic Group (four cases).—This consisted of those cases in which pyelonephritis was the dominant lesion and no Kimmelstiel-Wilson lesions were noted.

Group 5: the "Other Diabetic" Group (21 cases).—This group included all the remaining cases which showed no more permanent renal change than "cloudy swelling," "fatty degeneration," or "toxic change."

Results

Comparison of the recorded clinical features of these five groups with different renal pathological conditions showed that the groups also differed in their clinical features. The tables show the number of records giving adequate information on each point examined. Though the groups were small, several of the differences appeared significant, and attention is drawn below to those which seem to help to delineate the syndrome associated with Kimmelstiel-Wilson lesions.

Age and Sex.—The distribution (Table I) confirmed the usual finding that intercapillary glomerulosclerosis involves the elderly female especially.

TABLE I.—Age and Sex Incidence

	Renal Pathology Group				
	1 (11 Cases)	2 (3 Cases)	3 (4 Cases)	4 (4 Cases)	5 (21 Cases)
Mean age at death ..	69.1	52	69	48.2	51.2
Range of ages ..	52-81	41-73	60-75	18-80	12-81
No. of females ..	10	3	2	1	11

Diabetes.—An attempt was made to classify the diabetes according to its severity and controllability so far as the available records permitted. Cases which had been satisfactorily controlled for long periods without insulin were classed as mild; those which always required more than 20 units of insulin daily were classed as severe. Patients whose symptoms disappeared and who gained and maintained weight without incident were assessed as "easily controlled"; and those whose symptoms recurred or who needed more than an initial hospital admission for stabilization or coma were assessed as difficult to control. No clear difference could be distinguished between these small pathological groups in these respects. In view of previous observations it is worth noting that the Kimmelstiel-Wilson group showed instances of both severe and mild cases, some easily controlled and

I. GILLILAND: KIMMELSTIEL-WILSON LESION

FIG. 1. — Kimmelstiel-Wilson lesion, Group 1. General picture. (H. & E. $\times 60$.)

FIG. 2. — One large and several small islands. (H. & E. $\times 173$.)

FIG. 3. — Both afferent and efferent arterioles are affected. (Periodic acid of Schiff. $\times 205$.)

FIG. 4. — Fatty changes. (Sudan IV. $\times 205$.)

FIG. 5. — Argentophil nodules. (Gordon and Sweet's modification of Wilder. $\times 205$.)

FIG. 6. — Arteriosclerotic kidney, Group 2. (H. & E. $\times 205$.)

J. LI. TEMPLE: BENIGN CALCIFIED EPITHELIOMA

FIG. 1. — Mummification with "ghost" nuclei. ($\times 1,000$.)

FIG. 2. — Areas of viable epithelium. ($\times 400$.)

FIG. 3. — Bone formation. ($\times 400$.)

others not. There were no severe diabetics in the arteriosclerotic group, and all the pyelonephritic group were difficult to control.

Urinary Finding and Renal Function (Table II).—Proteinuria characterized all groups of permanent renal disease, and was found in the "other diabetic" group

TABLE II.—*Renal Tests*

	Renal Pathology Group				
	1 (10 Cases)	2 (3 Cases)	3 (3 Cases)	4 (4 Cases)	5 (21 Cases)
Proteinuria +++	7	2	—	3	1
" +	10	3	3	4	6
Urinary-tract infection	6	2	2	4	4

only in tests made during the course of a terminal coma. A heavy and persistent proteinuria seemed to characterize the Kimmelstiel-Wilson group and the pyelonephritic group. Urinary infection was judged to be present when a catheter specimen of urine had shown pus cells and given a positive culture, or when clear post-mortem evidence of renal pelvic inflammation was found. Infection was a frequent feature of all groups with permanent renal trouble. There were insufficient observations to compare the incidence of renal failure and anaemia.

Hypertension and Heart Failure (Table III).—The one Kimmelstiel-Wilson case which was not recorded to have hypertension, on the standard of 150/90 as the

TABLE III.—*Hypertension and Heart Failure*

	Renal Pathology Groups				
	1 (10 Cases)	2 (3 Cases)	3 (3 Cases)	4 (4 Cases)	5 (21 Cases)
Mean B/P	182/96	144/82	187/102	132/77	148/76
No. recorded to be in failure	8	1	1	—	1
No. with raised J.V.P.	6	1	—	—	1
No. with paroxysmal nocturnal dyspnoea	3	1	—	—	—

upper limit of systolic and diastolic pressure respectively, was admitted in heart failure from which she did not recover. At necropsy her heart weighed 410 g. and had two myocardial infarcts, so it seems reasonable to assume that she had previously been hypertensive.

Oedema.—All the cases of the Kimmelstiel-Wilson group had oedema, at least of the dependent parts, while in four cases it extended beyond the legs and sacrum, which was not shown in the other groups. Two arteriosclerotics revealed oedema of the ankles, as did three of the "other diabetic" group.

Peripheral Neuropathy.—Symptoms suggesting peripheral neuropathy are often found in the diabetic without easily demonstrable physical signs. Records noting complaints of darting or lancing pains, or paraesthesiae, such as burning, numbness, or tingling in the limbs, were classed as relevant subjective symptoms. Where note was made of muscle tenderness, sensory loss, or absent tendon jerks, these were classed as objective signs. Such peripheral neuropathy was recorded as more frequent and more obvious among diabetics found to have Kimmelstiel-Wilson lesions than among other groups. Ankle tendon jerks were absent in all but one of the Kimmelstiel-Wilson group, the remaining one showing subjective symptoms.

Eye Changes.—Eye changes were a feature of all Kimmelstiel-Wilson cases, retinopathy being present in all cases in which the fundus was not obscured by cataract. In three cases it was severe enough to make the patient "virtually blind," in contrast to the infrequent and relatively symptomless eye changes in the other groups.

Summary of Results (Table IV)

Thus, while proteinuria and urinary-tract infection were features of all the groups with renal disease, other clinical features were almost universally present in the cases with Kimmelstiel-Wilson lesions, and not found together in any other group.

TABLE IV.—*Clinical Features of the Kimmelstiel-Wilson Syndrome Among Renal Pathology Groups*

	Renal Pathology Groups				
	1 (10 Cases)	2 (3 Cases)	3 (3 Cases)	4 (4 Cases)	5 (21 Cases)
Suggestive:					
Proteinuria	10	3	3	4	6
Urinary infection	6	2	2	4	4
Hypertension—over 150/90	9	1	3	1	4
Probable:					
Heart failure	8	1	1	—	1
Oedema of ankles or more	10	2	—	—	3
Retinopathy or obscured by cataract	10	1	—	1	6
Peripheral neuropathy	9	2	2	—	5
No. showing all the above probable symptoms	8	—	—	—	—

These non-renal clinical features which seem to distinguish diabetes with Kimmelstiel-Wilson lesions from diabetes with other pathological conditions of the kidney were: Hypertension with heart failure; peripheral neuropathy; oedema at least of the dependent parts; and retinopathy or obscuring cataracts. These features were rare in the other groups studied, and in none were all four features present in the same patient.

Discussion

Attention has recently been drawn to the fact that the kidneys of the diabetic are peculiarly liable to disease of more than one sort. Of the 43 fatal diabetic cases reviewed in this paper 51% had irreversible kidney conditions, 25% showing intercapillary glomerulosclerosis, often in addition to evidence of arterial disease, while 44% of all cases showed evidence of urinary infection. Millard and Root (1948) found that 52% of 110 diabetics examined post mortem showed well-marked kidney disease, and in 23.5% there were two or more forms of kidney disease present. Bell (1946) showed arteriosclerosis to be five times as frequent in the diabetic over 50 as in a control group of a similar age, while Baldwin and Root (1940) found renal infection five times more often in diabetics compared with others examined post mortem. Indeed, urinary infection has been found to be an important cause of death in the diabetic (Robbins and Tucker, 1944). The incidence of the Kimmelstiel-Wilson lesion was found to be 17% in the summary of the literature by Kimmelstiel and Porter.

Many authorities (Bell, 1946; Kimmelstiel and Porter, 1948) agree that the lesions are almost pathognomonic of diabetes. Some authors, considering diffuse glomerular hyalinization without island formation

as a lower grade of the lesion, have found it also in non-diabetics (Horn and Smetana, 1942), but concede that the "advanced" form is always associated with diabetes. Kimmelstiel and Porter acknowledge that a few cases with typical "nodular" lesions were not known to be diabetic. Some of these may have had such mild diabetes as to escape notice. Rifkin *et al.* (1948) refer to two such cases. However, Bell (1946) has seen only one exception—a patient with primary hypertension who was studied for several months before death and at no time showed either hyperglycaemia or glycosuria. Bell also believes that the hyaline masses of chronic glomerulonephritis are easily distinguishable from the nodular diabetic lesions.

Recent studies have tended also to confirm Kimmelstiel and Wilson's observation that a recognizable clinical syndrome is associated with these lesions, of which "the constant features are diabetes, albuminuria, hypertension, and retinal vascular disease" (Newburger and Peters, 1939). Kimmelstiel and Porter find that "in a patient 50 or more years of age with chronic diabetes, nephrotic oedema, and albumin in the urine with a high blood cholesterol one can safely make the diagnosis of intercapillary glomerulosclerosis with 100% accuracy," adding that "advanced retinopathy, specifically of the diabetic type, is more or less regularly associated with intercapillary glomerulosclerosis."

One method of study, however, has shown that proteinuria, urinary infection, and indices of impaired renal function are not of exclusive diagnostic value. Infection, for instance, which is frequent and often asymptomatic in the diabetic (Harrison and Bailey, 1942) is a likely complication of any diabetic renal disease and not a finding which can exclude other conditions as Gauld *et al.* (1948) would seem to suggest. Even in the most severe infection of renal papillitis 12 of the 26 described by Edmondson *et al.* (1947) show Kimmelstiel-Wilson lesions. Uraemia supervened only in one of our cases and in 17.7% of the series reviewed by Kimmelstiel and Porter. We are examining the suggestion of Rifkin *et al.* (1948) that doubly refractile bodies in the urine are of diagnostic importance.

Two other renal conditions not present in our series may closely simulate intercapillary glomerulosclerosis—chronic nephritis and amyloidosis. The nephrotic stage of chronic glomerulonephritis is more likely to occur in the younger age group, and may give a characteristic history of previous acute onset (Newburger and Peters, 1939; Henderson *et al.*, 1947). Kimmelstiel and Porter show that repeated Addis counts should enable the diagnosis of glomerulonephritis to be made, as haematuria of significant degree is not found in intercapillary glomerulosclerosis. Amyloid disease is rare in diabetes (Newburger and Peters), and the characteristic anaemia and symptoms referable to the primary disease would serve to differentiate this condition.

Others have commented upon the four clinical features which we believe to form a recognizable syndrome.

Hypertension with heart failure was noted to be present in the brief clinical notes accompanying the original pathological studies of Kimmelstiel and Wilson and to be common among the cases of Siegal (1940) and Siegal and Allen (1941). Rifkin *et al.*, in a series of 22 necropsies on patients with intercapillary glomerulosclerosis, found that 95% had had systolic

hypertension and 90% had had diastolic hypertension, and 93% were observed to have been in heart failure. Two of those who did not show hypertension had histories and electrocardiographic evidence of recent myocardial infarction. On the other hand, Mann *et al.* (1949), choosing their cases deliberately from younger patients, found that although hypertension was a universal sign it did not become severe until late in the disease—a view held also by Kimmelstiel and Porter.

Widespread oedema was present in four of the original cases described by Kimmelstiel and Wilson, and a "nephrotic syndrome" with oedema and lowered serum proteins has often been described as part of the syndrome (Derow *et al.*, 1939). A "nephrotic syndrome" was present in 1 out of 10 cases described by Herbut (1941) and 3 out of 10 described by Siegal and Allen (1941). Laipply *et al.* (1944) found a nephrotic syndrome in only 6.5% of cases. Kimmelstiel and Porter, summarizing the literature, state that oedema of a nephrotic type is present in less than 10%. Mann *et al.* have suggested that hypoproteinaemia is a relatively late and generally a terminal finding, but that oedema alone was an early sign, and in females often the first. Our series, as those of Rifkin *et al.*, would suggest that the presence of oedema, even if limited to the dependent parts, is significant in conjunction with the other evidence.

Siegal (1940) and Siegal and Allen (1941) first described peripheral neuropathy as part of the syndrome. Others, such as Rifkin *et al.*, have noted simply that peripheral neuropathy was a complication, but do not give details of their records. Rundles (1945) thinks that the coincidental finding of retinopathy and neuropathy is more than fortuitous. In our series we found that subjective symptoms coupled with absent jerks were an almost universal finding.

Newburger and Peters found retinopathy in all their Kimmelstiel-Wilson cases. Kimmelstiel and Porter's analysis of the literature showed retinopathy to have been recorded in 86% of cases. Ashton (1949) has suggested that microscopical examination of the retina would show a higher figure, as he confirms the findings of Ballantyne (1946) that microaneurysms can be found in the retinae of diabetics who did not appear to have clinical retinopathy in life. The severity of the retinopathy is remarked upon by Henderson *et al.* (1947), while Von Bahr (1947) thought that the most severe proliferating type of retinopathy was almost always associated with the Kimmelstiel-Wilson lesions of the kidney. Friedenwald (1948) suggested, and Ashton (1949) agreed, that the intercapillary glomerulosclerosis and diabetic retinopathy are manifestations of the same vascular process.

It is generally agreed that most cases of intercapillary glomerulosclerosis occur between the ages of 50 and 70, and that females are affected twice as often as males (Kimmelstiel and Porter), yet these features are not of diagnostic importance. Cases have been recorded in younger age ranges (Laipply *et al.*, 1944; Goodof, 1945; Mann *et al.*, 1949) and in severe diabetes (Herbut, Mann *et al.*). The question of control is more difficult to assess, depending as it does on long-term continued observations. It is unlikely that any diabetic control is perfect, and satisfactory evidence is not obtainable except of the frequency of the grosser manifestations of bad control. There has always been a clinical impression that badly controlled diabetics were more

likely to suffer from complications such as neuropathy (Rundles) and retinitis proliferans (Waite and Beetham, 1935). Yet others have claimed that the treatment of diabetics had no bearing on the renal involvement (Kimmelstiel and Porter, Laipply *et al.*, Henderson *et al.*).

The duration of the diabetes, though also difficult to assess, seems to be important, and the view has been put forward (Dolger; 1946) that the duration was the most important factor in the development of degenerative lesions. Henderson *et al.* showed that in their series the duration of the diabetes appeared to be short only where the nature of the diabetes was mild, and may well have been present without symptoms for some time. Their series showed that when advanced lesions were present the duration of diabetes averaged 11.2 years, where mild lesions were present 8.1 years, and where no lesions were present 5.2 years. Goodof showed a steady rise in the incidence of intercapillary glomerulosclerosis among diabetics arranged in order of duration after six years had passed. Mann *et al.* also found a significant relation of the lesion with duration of diabetes, the average duration of their younger group of diabetics being 14.8 years.

On the other hand, Croom and Scott (1949) could find no correlation between the severity and control of diabetes and the onset of complications, and showed clearly that degenerative lesions were not inevitable. Their study of 60 diabetics selected to have an average duration of over 15 years showed 15 free from any clinically recognizable degenerative disease, one of whom had been diabetic for 26 years. In their group there were only two with albuminuria and oedema. Thus if degenerative complications are not inevitable with prolonged diabetes, and, less certainly, if control makes little difference, some other factor may be involved. These complications may be due either to prolonged diabetes in some special circumstances with which we are not as yet familiar or to prolonged diabetes of a special type, or to both.

Our study, coupled with an analysis of the literature, leads us to conclude that a syndrome including diabetes, albuminuria, and all the following four features—hypertension with heart failure, diabetic retinopathy or obscuring cataract, peripheral neuropathy, and oedema at least of the dependent parts—will reasonably imply the presence of intercapillary glomerulosclerosis in the kidney.

Summary

Among 43 diabetics examined post mortem the following groups of renal conditions were found: 11 with Kimmelstiel-Wilson lesions (with or without other lesions); three with arteriolosclerosis (without other lesions); four with arteriosclerosis (without other lesions); and four with pyelonephritis (without other lesions). The remaining 21 cases were classed as "other diabetics," without irreversible renal conditions.

Analysis of the associated clinical picture showed that: (a) The Kimmelstiel-Wilson group comprised, especially, elderly females who had had a mild diabetes for many years. (b) All groups with renal disease were associated with proteinuria and, more frequently than other diabetics, with urinary infection. (c) The Kimmelstiel-Wilson group, however, almost universally, showed in addition all the following features: hypertension with heart failure; peripheral neuropathy; oedema at least of the dependent parts; and retinitis or cataract obscuring the retina. This syndrome was not found in any other group.

It is suggested that in any diabetics who show proteinuria the presence of the four additional features listed above implies Kimmelstiel-Wilson lesions in the kidney.

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The First International Congress on Diseases of the Chest, sponsored by the Council on International Affairs, American College of Chest Physicians, held at the Carlo Forlanini Institute, Rome, Italy, September 17 to 22, was attended by approximately 1,000 physicians and their wives. At the inaugural session the College medal was presented to Sir Alexander Fleming for his discovery of penicillin. More than 100 scientific papers were presented during the congress by physicians from 40 countries, including two delegates from the Soviet Union, Professor Pavel Lukomski, who read a paper on "Aetiopathogenesis of Suppurative Diseases of the Lung," and Professor Feodor Uglov, who read one on "Lung Resection Ligation of the Pulmonary Artery in the Treatment of Chronic Suppurative Lung Diseases." Special administrative meetings of the governors and regents of the College from the 40 countries represented at the congress were held. A European Chapter of the College was organized, with Dr. André Meyer, Paris, as the general secretary. The regents of the College in Europe who will serve as the executive council for the Chapter are Professor Gustav Maurer, Davos, Switzerland; Professor Etienne Bernard, Paris, France; Professor Lopo de Carvalho, Lisbon, Portugal; Professor Nicholas Oekonomopoulos, Athens, Greece; Professor Eugenio Morelli, Rome, Italy; and Sir Alexander Fleming, London, England. Delegates from England who attended the congress in Rome were Sir Alexander Fleming, Sir Harold Boldero, and Drs. A. J. Benatt, C. K. Cullen, M. L. Dowdard, W. Griffel, W. Paton Philip, R. R. Trail, M. Weinberger. The delegates were received by his Holiness, Pope Pius XII, and a reception was held for the visiting delegates by Signor Salvatore Rebecchini, Mayor of Rome.