TABLE II

Case No.	Age	Globin Insulin in Units	Blood Sugar in Mg. per 100 ml.			
			6 a.m.	Noon	6 p.m.	10 p.m.
1	37	32	175	125	200	
2	30	60	116	—	131	
3	7	38	75	256	118	
4	16	120	112	85	225	
5	65	16	162	—	150	
6	57	60	156	131	93	
7	51	16	150	—	193	
8	50	32	137	143	100	
9	70	40	106	112	243	
10	70	20	106	187	87	
11	55	12	100	131	181	
12	61	42	168	212	137	
13	68	124	181	231	187	
14	63	32	62	93	181	
15	12	28	112	112	125	
16	42	24	106	225	106	
17	19	36	193	100	200	
18	36	32	131	234	156	
19	64	12	112	162	212	
20	21	68	112	140	131	
21	21	68	474	137	200	394

of their reactions. The control was reasonably good, though in some of the cases a readjustment of the dosage or the times of the meals was made before the patient left hospital —e.g., cases 3, 13, 14.

Failures

In a few cases there is an escape of control in the late evening, sometimes lasting all night and causing nocturnal polyuria. Often a redistribution of the times and amount of food rectified it, or a temporary evening dose of 8–12 units of soluble insulin while the globin is being adjusted is indicated ; this can be left off gradually after a week or two. Case 21 (Table II) shows this escape—Case 20 is the same patient after readjustment.

In those few cases in which the blood sugar is low at noon and the evening dose remains necessary a transfer to P.Z.I. alone may solve the difficulty. This has been successful in the cases of two boys.

Discussion and Conclusions

It has been questioned whether, since P.Z.I. and S.I. in various combinations give good results, there is need for a third type of insulin. Rabinowitch *et al.* (1947) discuss this, and after careful studies of ambulant patients on P.Z.I. or G.I. alone, P.Z.I. and S.I. in separate syringes, or S.I. twice a day found that the fasting blood sugar was lower with P.Z.I. alone than with G.I. alone, but the postprandial level was lower with G.I.: they obtained the best control with G.I. in the morning and P.Z.I. in the evening. Roberts and Yater (1947) in a survey of 97 cases recorded a better control with G.I. than with P.Z.I. in 70. Malins (1945), in a clinical study of 36 cases, considered that globin insulin has a limited place in the treatment of mild and moderately severe cases.

My impression has been—and a survey of the notes confirms it—that all types of patient do as well on a single dose of globin insulin each day as on other kinds of insulin, singly or in combination. From the doctor's point of view it is easier to adjust the dose than with the varying combinations of P.Z.I and S.I. even when they are given separately ; when they are mixed in the syringe a stable balance is always difficult.

The speed and efficiency of the clinic is increased. The opportunities for mistakes and confusion in measuring the dose are greatly lessened, as is the time consumed in teaching the patient self-administration. P.Z.I. given alone has the same advantages, but, owing to the longer time which elapses before it begins to act and the prolonged duration of the action, is of limited application.

Nearly all patients who have transferred from another type of insulin to G.I. prefer it on account of its simplicity. Many who, for one reason or another—e.g., being admitted to other hospitals—have been rebalanced on P.Z.I. and S.I. have asked to return to G.I. They say that they feel safer from reactions and that it is much easier and quicker to take.

Globin insulin is, I believe, likely to become the insulin of choice in ambulant uncomplicated cases. It achieves the maximum degree of simplicity so far attainable—one dose of one kind of insulin once a day. Soluble insulin remains the type for use in all emergencies.

Summary

The notes of 366 diabetic cases treated as out-patients with globin insulin are reviewed ; the dosage of insulin in different age groups and the incidence and times of reactions are recorded, and an attempt is made to assess the degree of control obtained.

The opinion is put forward that globin insulin alone is the best type of insulin available at present for uncomplicated ambulant cases of diabetes.

It is a pleasure to thank Dr. Prowse and the other physicians and surgeons of the Royal Sussex County Hospital, and those of the New Sussex Hospital, for the use of notes of cases seen by them before they came under my care.

REFERENCES

Malins, J. M. (1945). *British Medical Journal*, **2**, 318.
Peck, F. B. (1943). *Ann. intern. Med.*, **18**, 177.
Rabinowitch, I. M., *et al.* (1947). *J. Canad. med. Ass.*, **56**, 595.
Roberts, J. T., and Yater, W. M. (1947). *Ann. intern. Med.*, **26**, 41.
Wauchope, G. M. (1940). *Lancet*, **1**, 962.

RENAL COMPLICATIONS IN DIABETES MELLITUS

WITH SPECIAL REFERENCE TO THE KIMMELSTIEL-WILSON LESION

BY

W. R. GAULD, M.D., M.R.C.P.
Assistant Physician, Aberdeen Royal Infirmary

A. L. STALKER, M.B., Ch.B.
Lecturer in Pathology, University of Aberdeen

AND

A. LYALL, M.D., F.R.C.P.
Lecturer in Clinical Chemistry, University of Aberdeen

In the prolonged observation of patients under treatment for diabetes mellitus one of us has been impressed with the relatively frequent occurrence of albuminuria. In a number of these cases clinical and laboratory evidence of progressive renal failure was observed, and the condition was often complicated by retinal changes and hypertension. These changes were earlier interpreted as evidence of progressive vascular degeneration in most instances, but the observation made by Kimmelstiel and Wilson in 1936—that a pathological change in the glomeruli of the kidney seemed to be a typical finding in diabetes—suggested a review of this problem.

Kimmelstiel and Wilson (1936) observed hyalinization of intercapillary connective tissue in the kidney in eight patients, all of whom except one had suffered from diabetes and in whom, terminally, oedema and renal failure had occurred. They named this condition intercapillary glomerulosclerosis. Following on this observation several workers contributed further examples from both the pathological and the clinical aspect. Anson (1938) found six diabetic cases with similar lesions. Derow, Altschule, and Schlesinger (1939) reported a further example, and in the same year Newburger and

Peters (1939) published a review of nine cases, with post-mortem evidence in four. Herbut (1941), in a review of 2,000 consecutive necropsies at the Jefferson Hospital, Philadelphia, found a further nine cases fulfilling all the requirements previously described. Porter and Walker (1941) published the results of an analysis of the clinical and laboratory features of eight cases, with post-mortem verification in six of them. Siegal and Allen (1941) found the characteristic glomerular lesion in 35 out of 105 diabetics, and Horn and Smetana (1942) recorded the finding of 33 cases out of a total of 144 diabetics. Since then there have been publications on this subject by Mauser, Rowe, and Michael (1942), Laipply, Eitzen, and Dutra (1944), and Bell (1946). The last-named devotes an entire chapter of his monograph to it.

In spite of these contributions there seems to be as yet no general recognition of this complication in the diabetic life, and so far as we are aware no review of this subject has appeared in the British literature. This may not be surprising, since most of the work appeared in America during the war years.

Presentation of Cases

The material analysed in this paper consists of data collected from 24 patients suffering from diabetes mellitus in whom progressive renal complications have been observed and in seven instances followed to necropsy. In the majority the clinical manifestations were diabetes for a longer or shorter period followed by hypertension, arteriosclerosis, retinopathy, albuminuria, and chronic uraemia, although not always definitely in that order.

The cases, presented in the accompanying Table, are provisionally divided into groups, although in a few instances overlapping may occur: (1) twelve patients showing the onset of hypertension and renal failure after a prolonged diabetic state; (2) three patients who developed symptoms and signs of subacute nephritis during the course of diabetes; (3) six patients who at the time of their initial complaints were found to have coincident diabetes, arteriosclerosis, retinopathy, and renal damage; (4) three patients with diabetes and intercurrent urinary infections resulting in renal failure.

Group 1

All the patients in this group with one exception were over 50 years of age, and all with one exception had a long history of diabetes, having been observed over the course of the disease by one of us. The average duration was 10 years. The degree of diabetes was moderately severe in all but two cases. The incidence of diabetic coma as an episode was low in this group. In Case 2 the onset of the disease was with severe diabetic acidosis, and in Case 3 diabetic coma had occurred once. Incidents of sepsis occurred occasionally, but only in Case 2 could these be classed as numerous.

Details of Cases

Case No.	Age and Sex	Diabetes		Hypertension		Retinitis	Urine			Urea Conc. Test Max. Value	Blood				Oedema	Effusions	Mode of Death	Necropsy Reports
		Duration Years	Insulin Units	B.P.	Duration Years	Duration Years	Albumin	Casts	R.B.C.		Urea	Proteins	A/G Ratio	Haemoglobin				
Group 1																		
1	62 F	17	15–15	190/100	12	10	++	+	—	—	75	—	—	86	+	+	Uraemia	K.W. lesions, Grade 1. Nephrosclerosis
2	43 M	13	28–28	155/85	3	2	+	+	+	1·6	60	5·4	1·7/1	82	Slight	—	Coronary thrombosis	
3	52 F	13	30–25	175/105	3	1	++	+	—	1·04	126	—	—	—	..	—	Uraemia	K.W. lesions, Grade 1. Pyelonephritis. Nephrosclerosis
4	60 F	12	24 P.Z.I.	250/110	1	1	+	+	+	1·74	86	7·6	1·9/1	76	..	—	Alive	
5	59 F	3	15–15	250/110	½	?	+++	++	+	1·3	120	5·5	1·3/1	94	+++	+++	Uraemia	K.W. lesions, Grade 3. Subacute nephritis. Nephrosclerosis
6	67 F	10	15–15	205/105	5	Present	++	+	—	1·56	49	—	—	98	+	+	Congestive heart failure	K.W. lesions, Grade 2. Nephrosclerosis —slight
7	55 F	11	17–17	170/110	?	2½	++	+	+	0·94	93	5·1	0.54/1	81	+	—	Cerebral haemorrhage	No P.M.
8	66 M	14	30–30	208/100	12	Present	++	++	+	1·38	64	—	—	—	+	—	Cerebral thrombosis Uraemia	No P.M.
9	61 M	7	12–12	160/100	4	—	++	+	+	1·0	207	—	—	—	+	—	Uraemia	No P.M.
10	66 M	17	30 P.Z.I.	190/130	8	8	++	+	+	—	66	—	—	—	+	+	?	No P.M. } Died out of hospital
11	69 F	7	Nil	240/110	6	?	++	+	+	—	71	—	—	—	—	—		No P.M. }
12	71 F	15	10 P.Z.I.	165/95	Not known	Not known	+++	—	—	—	185	—	—	60	++	—	Uraemia	K.W. lesions, Grade 3. Nephrosclerosis
Group 2																		
13	38 M	15	32–32	174/90	12	—	++	++	+	2·1	71	4·85	—	—	++	++	,,	Subacute nephritis
14	28 M	14	32 Globin	145/100	1	?	+	+	+	—	—	—	—	—	+	—	,,	No P.M. Died out of hospital
15	34 F	18	28 P.Z.I. –10	170/105	7	Nil	+	+	—	2·3	41	6·56	1·5/1	76	+	—	Alive	
Group 3																		
16	75 M	1	Nil	168/80	1	1	++	+	+	1·4	46	7·61	2·2/1	100	Slight	—	,,	
17	61 M	4	24 P.Z.I.	255/100	4	Present	Trace	+	+	—	40	—	—	—	++	+	,,	
18	40 F	½	14 P.Z.I.	190/110	½	½	++	++	+	1·4	60	—	—	68	Slight	—	,,	
19	56 M	2	12	205/105	2	?	+	+	+	1·8	186	—	—	68	+	—	Uraemia	No P.M. Died out of hospital
20	61 F	10	8–8	200/110	10	1	+++	+	+	—	47	5·6	1·5/1	100	++	++	Coronary thrombosis	No P.M.
21	60 F	2	18 P.Z.I.	190/90	2	Not known	++	+	—	1·0	—	—	—	90	+	—	Uraemia	No P.M. Died out of hospital
Group 4								Pus	Organ.									
22	66 F	12	16 P.Z.I.	210/110	5	4	+	+	*B. prot.*	—	132	—	—	64	+	—	Alive	
23	62 F	1/12	18–18	—	—	Nil	+	+	*B. coli*	1·7	74	—	—	70	—	—	Uraemia	K.W. lesions, Grade 1. Pyelonephritis. Nephrosclerosis
24	70 F	8	6	230/120	8	Nil	+	+	*B. coli*	1·7	93	6·86	1·4/1	64	++	—	Alive	

Hypertension was of the more severe degrees in all except three instances, and only in two was the diastolic pressure below 100 mm. Hg. In seven instances hypertension appeared relatively late in the disease, from five to ten years after the onset of diabetes. Retinal changes usually appeared at periods of one to two years after hypertension was observed. Albuminuria was noted quite early in the disease in several instances, being sometimes transient but usually present when hypertension was established. Evidence of failing kidney function could nearly always be found by urea-concentration or urea-clearance tests in the earlier stages. Moderate increases in blood urea were usually present for about three years. The later stages of renal failure were nearly always accompanied by hypochromic anaemia of mild degree. Oedema, at first of the feet, occurred early in the onset of renal failure and was usually accompanied by hypoproteinaemia where this was investigated. In most cases generalized oedema occurred and in three cases was severe, being accompanied by ascites and pleural effusions. Detailed descriptions of Cases 1 and 5 illustrate the course and mode of termination of this group.

Case 1

This patient was first seen in 1926 complaining of loss of weight, thirst, polyuria, and pruritus of a few months' duration. The urine contained sugar but no acetone or albumin. Both eyes showed central conical nebulae, but peripheral fields were full and no fundal changes were present. A sugar-tolerance test showed moderately severe diabetes with blood-sugar values of 0.202, 0.256, 0.271, 0.306, 0.271%. The patient was treated by diet alone and continued in fair health for the next five years. In 1931 she was admitted to hospital complaining of pain in the left renal angle. There was a moderate degree of cardiac enlargement and the blood pressure was 172/94. No evidence of a renal calculus was found. Treatment with insulin (15+15 units) was started and the blood sugar was kept within the limits of 0.142 to 0.177%. Examination of the eyes showed a few retinal haemorrhages.

From 1931 to 1934 the patient attended the diabetic clinic regularly. Her weight increased from 138 to 142 lb. (62.6 to 64.4 kg.) during this period. The blood sugar remained within the limits of 0.139 and 0.201%. The Wassermann reaction was negative and a test meal showed achlorhydria. No albumin was found in the urine during this time. The blood pressure increased to 185/100. Vision showed gradual degeneration from lens opacities, vitreous opacities, retinal haemorrhages, and exudates. The blood urea was 21 mg. per 100 ml.

In 1935 and 1936 the blood sugar was less easily controlled, the value increasing to 0.279%. The blood pressure rose to 190/100 and the blood urea increased to 44 mg. per 100 ml. During 1937 to 1939 the patient began to lose weight and to

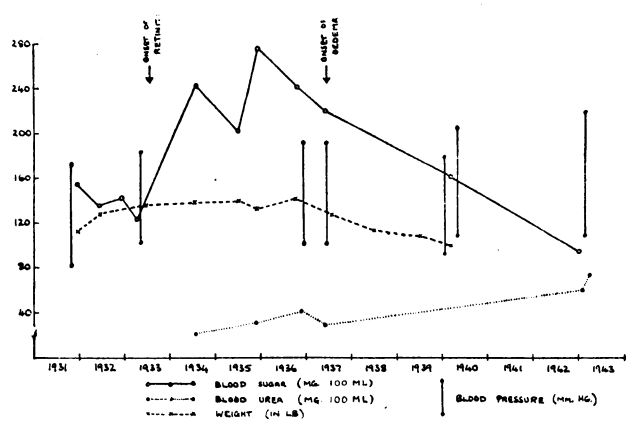

FIG. 1.—Showing progress of disease in Case 1.

have transient oedema of the ankles. In 1940 her weight fell to 110 lb. (49.9 kg.); there was oedema of both ankles, sepsis of the right great toe, and albuminuria, with pus cells and granular casts in the urinary deposit. The blood sugar was kept under good control (in the region of 0.1%), but the blood urea had increased to 63 mg. per 100 ml. In 1943 the patient was admitted to hospital, weak, tired, drowsy, and with sickness, vomiting, and oedema. The blood sugar was normal and the blood urea 75 mg. per 100 ml. The urine showed much albumin and numerous hyaline and granular casts. She lapsed into coma

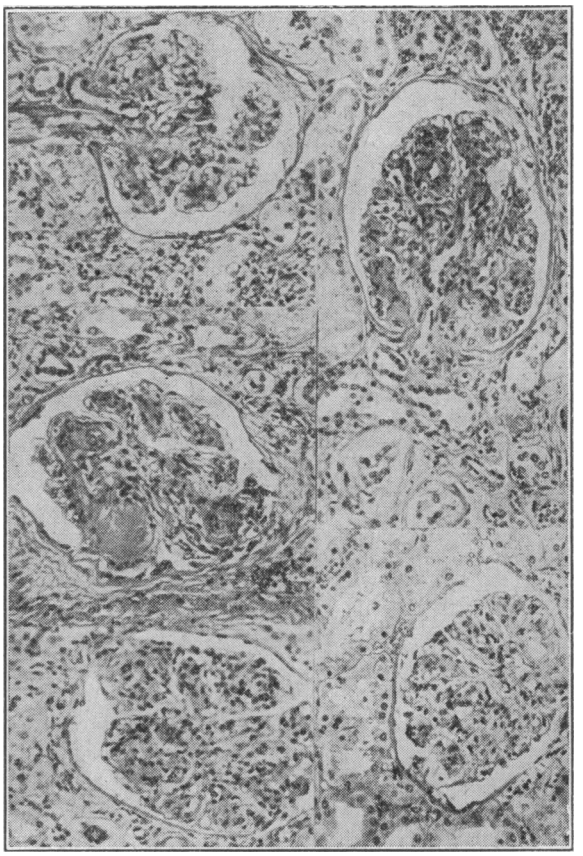

FIG. 2.—Case 1. Composite photomicrograph ×140 H. and E.

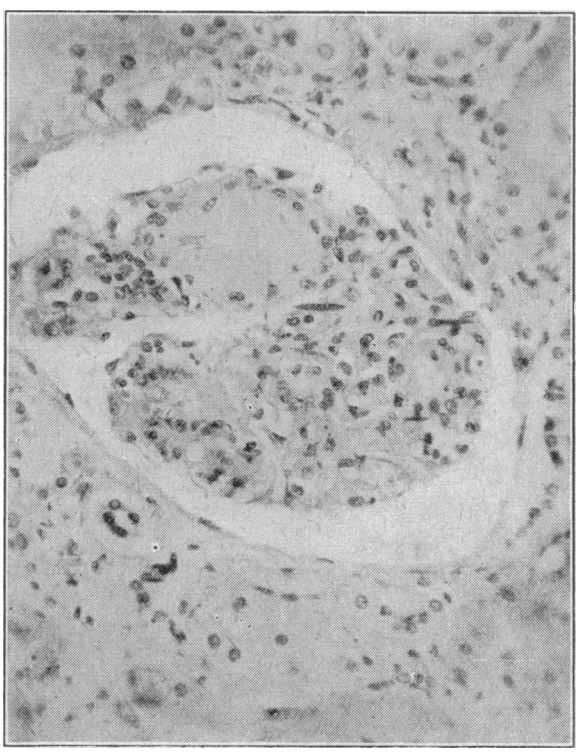

FIG. 3.—Case 1. Photomicrograph ×260. H. and E.

of the uraemic type and died. Graphically the course of the disease is presented in Fig. 1.

At necropsy oedema of subcutaneous tissue, pleural effusion, and gelatinous oedema of the meninges were found. The kidneys were enlarged, firm, and tense under the capsule. The naked-eye appearance was of chronic nephritis or nephrosclerosis with subacute glomerulonephritis superimposed. Dr. Jane Davidson's report on the microscopical changes was : "The glomeruli are of very unequal size, some hypertrophied and others completely functionless and transformed into hyaline foci. Many of the glomeruli show the presence of homogeneous eosinophilic material, which does not stain for amyloid and presumably represents hyaline thickening of the glomerular capillaries. Some of the afferent arterioles show thickened walls in which the same eosinophilic hyaline material is present, diminishing their lumina." Figs. 2 and 3 illustrate the pathology of the kidney.

In summary, this case showed diabetes of moderate severity for 17 years, with onset of hypertension and retinopathy after five years and of albuminuria after 14 years —low-grade subacute nephritis terminating in uraemia with oedema and the kidneys showing changes which are now described as intercapillary glomerulosclerosis.

Case 5

This patient, aged 59, visited the Eye Institute complaining of failing vision in February, 1945, and a diagnosis of diabetic retinitis was made. Questioning elicited a history of polydipsia, polyuria, and neuritic pains of some months' duration, and she was referred to the diabetic clinic, where the diagnosis of diabetes mellitus was confirmed. At this time there was a trace of albumin in the urine. A diet of 1,500 calories was prescribed, and during the next year the patient's condition improved, the albuminuria disappeared, and glycosuria was minimal.

On Jan. 2, 1947, she was admitted to hospital with swelling of the legs and abdomen, fatigue, and frequency of micturition. She had not been adhering strictly to her diet. She was plethoric and dyspnoeic, but there was no cyanosis. The blood pressure was 250/110, with a pulse rate of 100. A small effusion was present at the right base, with bilateral basal rales. The heart was enlarged to the left clinically. The abdomen showed oedema of the abdominal wall and ascites. The liver edge, though just palpable, was not tender. Fundal examination revealed macular changes and numerous haemorrhages—a diabetic retinopathy. A lens opacity was noted on the right side. The urine showed much sugar and albumin but no acetone, and microscopy revealed epithelial cells, pus cells, and granular casts. The blood sugar was 0.306%, blood urea 38 mg. per 100 ml., plasma CO_2 58 vols.%, total plasma proteins 5.41 g.%, with an A/G ratio 2.7/1. Radiograph of chest showed fluid at both bases.

Insulin, 15 units twice daily, was prescribed, and within one week the urine became sugar-free and the blood sugar fell to normal levels. The albuminuria persisted throughout the course of the illness and the oedema and ascites increased in spite of mercurial diuretics, paracentesis, and the intermittent application of Southey's tubes to legs and thighs. During April, 1947, 20 pints (11.36 litres) were withdrawn by these methods, and in May, 1947, 42 pints (23.86 litres) were evacuated. The blood pressure remained high.

A urea concentration test was carried out on May 7, showing a maximum concentration of 1.3% with a standard clearance of 17%, and the blood urea rose slowly to 120 mg. per 100 ml. The specific gravity of the urine varied from 1010 to 1020, and the urinary deposit always showed hyaline and granular casts and occasionally epithelial cells, pus cells, and red blood cells. The plasma CO_2 was continually between 52 and 61 vols.%. The protein content of the oedema fluid was 0.7 g.% initially, falling steadily to 0.47 g.% on June 29. The A/G ratio of the plasma altered from 2.7/1 to 1.3/1 before the patient's death on July 19. Necropsy showed Kimmelstiel–Wilson lesions Grade 3, nephrosclerosis, and subacute nephritis (Figs. 4 and 5).

Group 2

This group consists of three patients aged 28 to 38, all of whom developed diabetes in early life and complained later of swelling of the feet and legs—during the course of pregnancy in Case 15. The clinical picture in the later stages, especially in that of Case 13, was very similar to that of Case 5, with diabetes, albuminuria, and hypoproteinaemia, the intense oedema requiring relief by Southey's

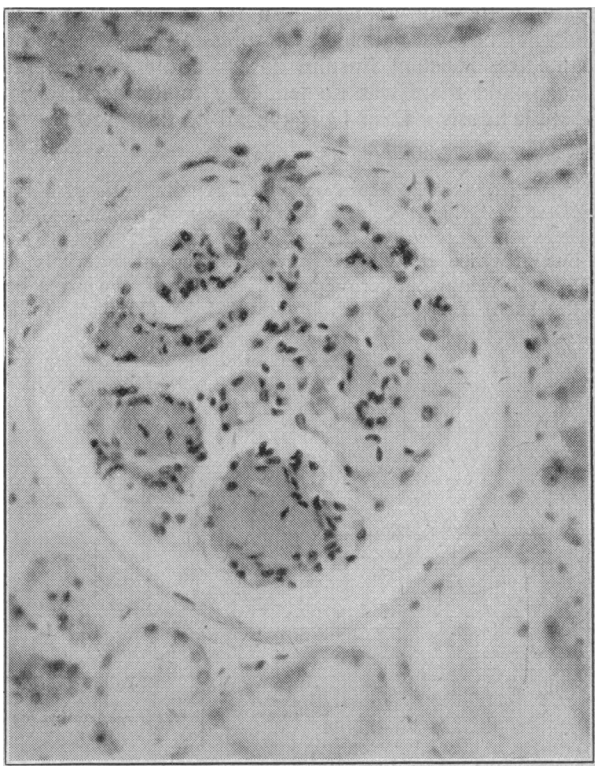

FIG. 4.—Case 5. Photomicrograph ×260. H. and E.

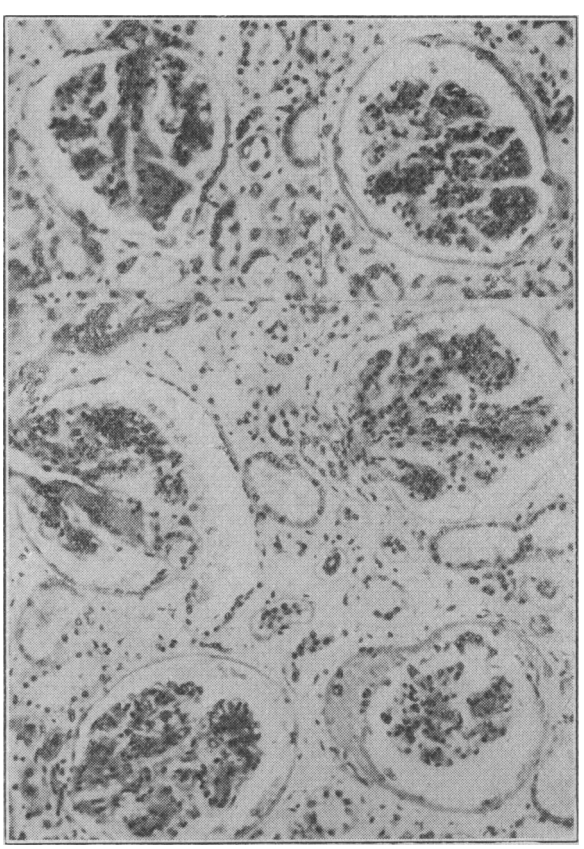

FIG. 5.—Case 5. Composite photomicrograph ×140. H. and E.

tubes and the ascites necessitating repeated paracentesis. The only real difference between the two cases was the absence of retinal haemorrhages and exudates in Case 13 and the lower blood-pressure readings during the later phases of the disease. The course taken after subacute nephritis supervened was similar to the history of that disease in the non-diabetic. So far as the diabetic state was concerned we gained the impression that the diabetes became less insistent (insulin dosage could be moderately reduced) and there was no tendency to the occurrence of diabetic acidosis. Case 13 is typical of this group.

Case 13

The patient was 24 years old when the diagnosis of diabetes was first made in 1929, the blood sugar then being 0.302%. He was stabilized on a diet of 2,316 calories, with 10 units of insulin twice daily. He was observed at intervals until 1932, and during this period control was good, the urine being usually sugar-free. His weight was 161 lb. (73 kg.). In 1933

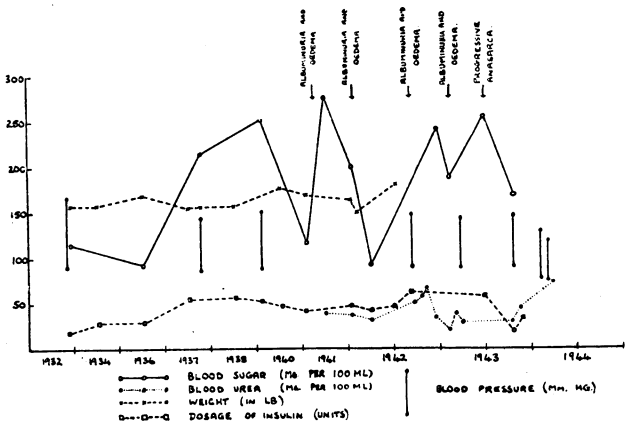

FIG. 6.—Showing progress of disease in Case 13.

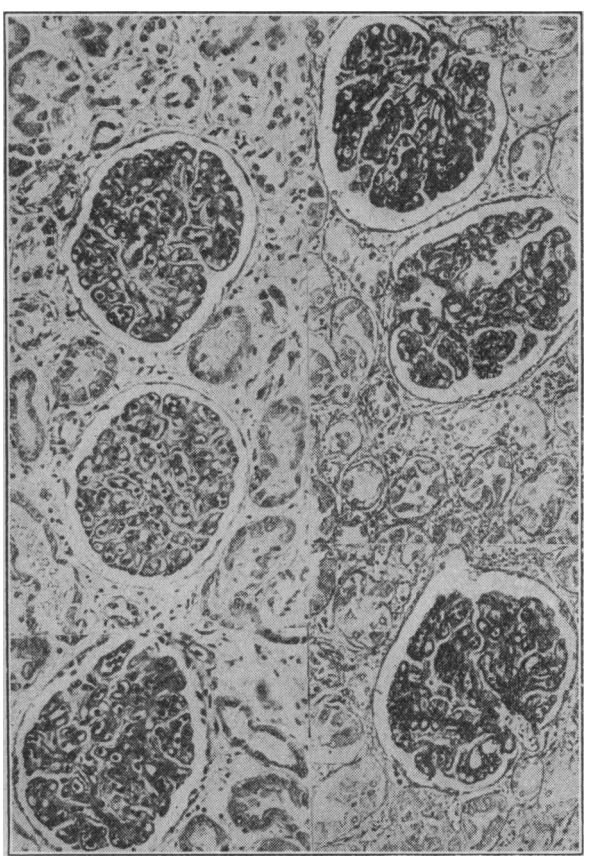

FIG. 7.—Case 13. Composite photomicrograph ×140. Right half: aniline blue, orange G. Left half: H. and E.

he had cervical adenitis and, later, an attack of shingles. For a short time thereafter the pulse rate was fast. Between 1934 and 1937 he continued to follow his work as a cabinet-maker and his weight increased to 174 lb. (78.93 kg.).

In 1937 he complained of being easily tired and of weakness of the legs, and was admitted to hospital for observation. Diabetes was found to be well controlled on insulin, 32 units twice daily. There was no oedema, muscular weakness of the legs, or neurological phenomena. The fundus oculi was normal, the pulse rate 80, and the blood pressure 145/80. During 1937 and 1938 the patient was twice admitted to hospital with mild hypoglycaemia, and insulin was reduced from 36 units twice daily to 32 units twice daily. In 1939 his weight had increased to 182 lb. (82.55 kg.). In 1940 he had German measles, and a few months later developed transient arthritis of the fingers and wrists.

In 1941 he complained of swelling of his feet and was admitted to hospital. There was generalized oedema of a moderate degree. The urine showed much albumin, with a deposit containing epithelial casts. The blood urea was 45 mg. per 100 ml., plasma protein 4.13 g.%, plasma chloride 555 mg. per 100 ml., and blood sugar 0.246%. The oedema disappeared with rest in bed and mild diuretics, and the albuminuria cleared a little later. Insulin dosage was reduced to 20 units twice daily. In 1942 albuminuria recurred with slight oedema. Renal function tests at this time showed urea concentration up to 3.1% and blood urea 31 mg. per 100 ml. The albuminuria rapidly cleared on this occasion but recurred six months later, when the patient was again admitted to hospital (September, 1942) with generalized oedema. The blood pressure was 164/115, blood urea 64 mg. per 100 ml., and the urine contained much albumin and a number of granular and hyaline casts and red blood cells. The plasma chloride was 526 mg. per 100 ml. and plasma protein 4.85 g.%. Fundal examination showed no abnormality. Insulin dosage was 24 units twice daily. Various methods were tried to deal with the oedema, including mercurial diuretics and Southey's tubes. After six months his improvement was only moderate but he was allowed out of hospital, only to be readmitted later in 1943 with intense oedema which terminated in septic infection of the legs, pleural and ascitic effusions, pulmonary congestion, and terminal pneumonia. The course of the disease is presented graphically in Fig. 6. Post-mortem examination revealed evidence of subacute nephritis without K.W. lesions (Fig. 7).

Group 3

This group consists of six patients, all in the later decades with one exception; in these the history of the diabetic state is short, and the whole clinical picture of diabetes, hypertension, retinitis, albuminuria, and renal damage was already present when the cases first came under observation. So far as the clinical manifestations go they are indistinguishable from cases in Group 1 except for the short history of diabetes, but they may be quite different in pathogenesis, the whole picture, including diabetes, being the result of one degenerative process. Since this group is well recognized among clinicians it is deemed unnecessary to describe any case in detail.

Group 4

In this group are three patients with a diabetic history and urinary infections resulting in pyelonephritis and renal failure. These cases are differentiated by the typical urinary findings, and should not be confused with groups already described.

Summary of Pathological Findings

Pathological reports on the seven cases which came to necropsy are given below. Focal glomerular lesions of the type described by Kimmelstiel and Wilson are defined on the basis of the criteria suggested by Siegal and Allen (1941) and classified according to the method of Bell (1946), Grade 1 being scanty and Grade 3 frequent.

Case 1 (Figs. 2 and 3).—Both kidneys were enlarged (combined weight 450 g.). The capsules stripped easily, leaving a

finely granular surface. The cortices were narrow and the small renal vessels thickened. *Histology*:—"Foci of glomerulosclerosis alternate with areas in which there is proliferative glomerulitis. Capsular adhesions are numerous. The glomerular capillaries show hyaline thickening. The collecting tubules contain hyaline casts. Arteriosclerosis and hyaline arteriolosclerosis are prominent. Lesions of Kimmelstiel–Wilson type (K.W. lesions), Grade 1. This is a case of subacute nephritis (associated with nephrotic oedema) probably occurring in a nephrosclerotic kidney."

Case 3.—The kidneys were small, with granular surfaces. The cortices were narrow. *Histology*:—"There is severe glomerulosclerosis, much of which is recent, resembling a glomerulonecrosis in the process of hyalinization. Arteriosclerosis and hyaline arteriolosclerosis are severe. Pyelonephritis is also present. K.W. lesions, Grade 1. This is the scarred kidney of a chronic nephritis."

Case 5 (Figs. 4 and 5).—The kidneys were enlarged (combined weight 530 g.). The cortices were pale, the medullae congested. The capsules stripped readily. *Histology*:—"There is a moderate degree of glomerulosclerosis. The surviving glomeruli show capsular adhesions and hyaline thickening of the capillaries. There is exudate in Bowman's spaces, partially organized in some glomeruli. The collecting tubules contain hyaline casts. Arteriosclerosis and hyaline arteriolosclerosis are prominent. K.W. lesions, Grade 3. This is a case of subacute nephritis (associated with nephritic oedema) which has possibly occurred in a nephrosclerotic kidney."

Case 6.—The kidneys were of normal size. The capsules stripped easily. There was no abnormality of renal architecture. *Histology*:—"There is slight focal glomerular hyalinization. Arteriosclerosis is slight, arteriolosclerosis is of moderate degree. K.W. lesions, Grade 2. This is a nephrosclerosis of trivial degree."

Case 12.—The kidneys were reduced in size and the capsules were adherent. The surfaces were granular. *Histology*:—"There is gross glomerulosclerosis, many glomeruli being only recently hyalinized. Interstitial fibrosis, arteriosclerosis, and hyaline arteriolosclerosis are all severe. There is a concomitant pyelonephritis. K.W. lesions, Grade 3. This is a severe nephrosclerosis."

Case 13 (Fig. 7.)—Both kidneys were enlarged (combined weight 420 g.). The cortices were wide and pale. The medullae were congested. The capsules stripped easily. *Histology*:—"The glomerular capillaries are thick, hyaline, and patent. There are frequent capsular adhesions. There is no glomerulosclerosis, and arteriosclerosis and arteriolosclerosis are both insignificant. The collecting tubules contain hyaline casts. K.W. lesions absent. This is a subacute nephritis (associated with nephrotic oedema)—histologically of the 'nephrosis' pattern."

Case 23.—There was bilateral hydronephrosis, and abscesses were noted in the medulla of the left kidney. *Histology*:—"Left kidney—pyelonephritis is marked. There is slight glomerular hyalinization and arteriosclerosis. Hyaline arteriolosclerosis is severe. K.W. lesions, Grade 1. This is a severe pyelonephritis."

Discussion

During the past decade increasing attention has been drawn to renal failure as a later complication in diabetes. The earlier publications on the subject were largely concerned with observations in post-mortem material of hyaline degenerative changes in the glomeruli of the kidney, to which Kimmelstiel and Wilson (1936) assigned the term "intercapillary glomerulosclerosis." With wider recognition of this condition, attention turned naturally to the clinical manifestations and their correlation with the pathological changes. Newburger and Peters (1939) described four cases showing diabetes, albuminuria, oedema, nitrogen retention, and retinopathy in which the clinical history was known and the typical hyalinization of renal glomeruli was found at necropsy. They also described five other cases, clinically similar, but without pathological confirmation.

Porter and Walker (1941) analysed the clinical and laboratory features of eight cases of intercapillary glomerulosclerosis where the diagnosis was verified in six instances. Albuminuria was severe, blood pressure usually over 200, blood proteins much reduced, oedema of significant degree; and anaemia, nitrogen retention, and retinal haemorrhages were prominent in this group. They suggested that the renal changes represented an instance of a predilective degenerative process in diabetes culminating in the syndrome described. Herbut (1941) reviewed 2,000 necropsies and found nine cases fulfilling all the requirements described and showing glomerular lesions. Albuminuria in these cases varied in amount in direct relation to the degree of oedema, while the occurrence of casts in the urine was unrelated to the presence of glomerular hyalinization. Siegal and Allen (1941) studied 105 diabetic necropsies and correlated the history of hypertension with the presence of glomerulosclerosis. In 60 cases without hypertension glomerulosclerosis occurred 12 times, in 27 with hypertension the lesion was found nine times, and in 18 with the complete renal syndrome glomerulosclerosis was present in 14.

Up to this point it would seem that the authors quoted tended to consider that intercapillary glomerulosclerosis was the cause of renal failure.

Horn and Smetana (1942) pointed out that, although glomerulosclerosis in its more advanced state was seen only in cases of diabetes, it was not of necessity associated with a particular clinical syndrome. Laipply and his co-authors (1944) studied the necropsy reports and clinical notes of 124 diabetic patients and recognized areas of glomerular hyalinization in 79 instances. In general the lesion was relative to the duration of diabetes in its occurrence and degree. Although in some cases hyaline degeneration was of less marked degree and although 64 patients showed albuminuria, the nephrotic syndrome occurred in only five of this series. This would cast some doubt upon the conception that glomerular hyaline degeneration is of prime aetiological significance in the pathology of renal failure in these conditions.

A new point of view was adopted by Bell (1946), who found that glomerulosclerosis was well correlated with arteriosclerosis. In 189 necropsies on patients with diabetes but without arteriosclerosis no glomerular lesions were found. In 148 diabetic cases with arteriosclerosis 67% showed hyaline glomerular lesions. He concluded that in most instances the degree of hyalinization was proportional to the severity of the arteriosclerotic changes.

It is obvious from the conclusions of previous authors that considerable difficulty arises in attempting to correlate clinical signs with pathological findings in this condition.

From the evidence presented in this paper it seems quite clear that, apart from surgical lesions of the renal tract, at least four types of renal failure may occur in the diabetic. The series in Group 1 corresponds closely to most of the material previously described. So far as post-mortem evidence goes in this group there exist in each case examined widespread pathological changes in the kidney, other than glomerulosclerosis of this type, which might result in uraemia. This leads us to conclude that diabetic glomerulosclerosis is in itself incidental and is not the primary cause of renal failure.

Cases in Group 3 show the same clinical picture but with this important difference, that widespread vascular changes and diabetes occur practically simultaneously. Owing to the absence of post-mortem proof it is impossible to say whether the typical pathological renal changes are in fact present. If further evidence shows that glomerular

hyaline degeneration is present in these cases—as is probable—it would seem that this degenerative change is not due to the diabetes itself but to associated vascular lesions. In any case we are of the opinion that widespread arterial degeneration can produce the whole clinical picture within a short space of time.

With regard to Group 2, where incidental oedematous nephritis occurred in diabetes, the differential diagnosis is practically impossible during life. The clinical picture is the same, with the exception of occurrence earlier in life and perhaps the absence of retinal haemorrhage.

Prognosis.—The onset of albuminuria, apart from that associated with a precomatose state in diabetic patients, is usually of serious import and must be taken as a warning of impending renal complications. When retinitis and oedema occur the outlook is bad, and within two years death usually supervenes from uraemia, cardiac failure, or a combination of both. It is doubtful whether, in the present state of knowledge, any steps can be taken to defer these changes or to deal effectively with them when they occur.

Summary

Twenty-four cases of renal failure occurring in diabetic patients are described.

Classification shows four groups, including those associated with the Kimmelstiel–Wilson lesion.

Pathological details and photomicrographs illustrate the paper.

We are indebted to Mr. Norman Mowat for preparing the composite photomicrographs and to Mr. George Cheyne for technical help.

REFERENCES

Anson, L. J. (1938). *Sth. med. J.*, **31**, 1272.
Bell, E. T. (1946). *Renal Diseases*. Kimpton, London.
Derow, H. A., Altschule, M. D., and Schlesinger, M. J. (1939). *New Engl. J. Med.*, **221**, 1012.
Herbut, P. A. (1941). *Arch. Path.*, **31**, 501.
Horn, R. C., and Smetana, H. (1942). *Amer. J. Path.*, **18**, 93.
Kimmelstiel, P., and Wilson, C. (1936). Ibid., **12**, 83.
Laipply, T. C., Eitzen, O., and Dutra, F. R. (1944). *Arch. intern. Med.*, **74**, 354.
Mauser, C. L., Rowe, A. H., and Michael, P. P. E. (1942). *Ann. intern. Med.*, **17**, 101.
Newburger, R. A., and Peters, J. P. (1939). *Arch. intern. Med.*, **64**, 1252.
Porter, W. B., and Walker, H. (1941). *J. Amer. med. Ass.*, **116**, 459.
Siegal, S., and Allen, A. C. (1941). *Amer. J. med. Sci.*, **201**, 516.

DIABETIC COMA

BY

R. H. MICKS, M.D., F.R.C.P.I.

Physician, Sir Patrick Dun's Hospital

From Jan. 1, 1940, to Jan. 1, 1946, Root treated 188 cases of diabetic coma in the New England Deaconess Hospital, with 6 deaths; and from Jan. 1, 1946, to Jan. 1, 1948, he treated 55 cases with no deaths. He has published a very full description of his methods of treatment (Root, 1945). My authority for the recent statistics is a personal communication from him. Few physicians or clinics have published their death rate in diabetic coma, and no recorded results are so good as this.

My essay in discipleship is prompted by the wish to make this line of treatment more widely known, for it has received sadly little attention from writers of textbooks in Europe, and some of the textbooks that are deservedly popular in this country advocate methods which include those very sins of commission and omission which Root has shown to be responsible for failure to save the more severe cases of coma. The chief sin of omission is not to appreciate the urgent need for large doses of insulin and the fact that insulin-resistance increases as the condition progresses. The chief sins of commission are the early administration of glucose and the use of the oral route for the administration of fluids.

This paper is based on bitter personal experience, for I have made many mistakes myself, and have learnt what happens when sufficient insulin is not given soon enough, when gastric aspiration is omitted or fluids are given by mouth, and when glucose-saline is given intravenously instead of simple normal saline.

Undoubtedly much of the credit for the good results of Root and his colleagues must be given to their personal skill and to the 24-hour laboratory service maintained in their hospital. But even the worst cases can be saved by physicians of less experience and in the absence of blood analysis. Root (1945) states: "No plan of treatment based on mathematical calculations of the blood sugar and carbon dioxide will take the place of constant bedside observation of the patient and adjustment of treatment to the patient's changing condition."

Nomenclature and Diagnosis

The accepted meaning of the word "coma" is a state in which the patient does not respond to any external stimulus. In this sense of the word the term "diabetic coma" is a misnomer, for it is only very rarely that the patient when first seen is in a state of true coma; usually the mental state is one of mild, moderate, or severe confusion with marked drowsiness.

The term diabetic coma is in fact by general agreement applied to severe *rapidly progressive* diabetic ketosis, and its diagnostic features are increasing drowsiness and confusion (ending eventually in true coma) with increasing hyperpnoea, dilatation of the stomach, and eventually circulatory failure due to electrolyte and water depletion. The biochemical findings are characteristic. It is readily induced even in the controlled diabetic by acute infections or alimentary tract disturbances. It is not so much a complication of diabetes as the end-stage of diabetes, and the treatment of coma is the treatment of diabetes—namely, insulin.

The condition is easy to recognize, a mistake being in fact almost impossible. One essential feature which distinguishes it from other causes of coma in diabetics is that in diabetic coma "unconsciousness" does not supervene till after a progressive and characteristic illness lasting as a rule several days. The diabetic who is found "unconscious" without any preliminary illness may be a case of hypoglycaemia or he may have had a stroke, but he is certainly not a case of diabetic coma.

Summary of Treatment

In most cases it is possible to bring about a striking improvement in from three to six hours, and during this period constant hard work at the bedside is necessary. The only factor in bringing about this improvement is insulin. Two other measures are important—gastric aspiration and the intravenous administration of normal saline.

The chief point in treatment is to ensure, even at the risk of giving more than may be needed, that the patient gets enough insulin within the first three hours. Of course in many cases some infective process is present and must be treated too.

Insulin Dosage

There are four points of fundamental importance. The first is that it is the insulin which cures diabetic coma: though other measures are necessary they are not curative. The second point is that insulin resistance increases so long