RENAL FUNCTION IN SCLERODERMA

BY

L. URAI, M.D. Z. NAGY, M.D.

G. SZINAY, M.D. AND W. WILTNER, M.D.

From the Third Department of Medicine, University of Budapest, Hungary

It has been known for some time that changes caused by scleroderma—progressive systemic sclerosis¹⁰—appear not only on the skin but also in the internal organs, especially the gastro-intestinal tract, lungs, and heart. Only few cases in which the kidneys were certainly involved have been published in the literature, such involvement leading to early death with symptoms of renal failure.^{1-9 16-18 20-22 25-34}

Morphology of Kidney

According to Calvert and Owen⁶ the morphological pattern of the scleroderma kidney is characteristic. In the proximal part of the interlobular arteries a mucoid thickening of the intima with gross reduction in lumen is seen, whereas in the distal part there is fibrinoid necrosis involving also the arterioles. Depending on the severity of the vascular changes, a more or less pronounced ischaemic necrosis may develop in the renal cortex, constituting what has been called a "true scleroderma kidney."

In the reports mentioned above little evidence is presented to suggest previous renal involvement. From a survey of 150 cases Leinwand *et al.*¹⁹ concluded that until the final phase there is little indication that the kidneys are affected. In the few cases in which a patient suffering from scleroderma died of undoubted renal failure, death usually ensued within one to six weeks of the onset of renal symptoms. In these cases normal laboratory findings (analysis of urine, non-protein nitrogen estimation, creatinine clearance) were followed by an acute deterioration accompanied by the appearance in the urine of protein (albumin), white and red blood cells, and granular casts. The non-protein nitrogen level rose rapidly, as also did the blood pressure, and an increasingly severe oliguria developed. Accompanying the development of azotaemia the hitherto consistently normal blood pressure rose to very high levels (240–260/150 mm. Hg), changes in the optic fundus appeared, and death ensued from anuric uraemia.

During the past three years we have observed 45 patients suffering from scleroderma. In a woman aged 43 fatal renal failure rapidly developed after steroid ("neosterone") treatment had been instituted for polymyositic lesions. While in hospital she suffered from sclerodermal symptoms for about a year. The clinical history in this case, as well as the morphological findings at necropsy, were identical with those described as occurring in scleroderma kidney (see Fig.).

Photomicrograph showing characteristic intimal proliferation narrowing the lumen of an interlobular artery. Peripherally, fibrinoid necrosis predominates in the artery and in the pre-arteriole originating from it. (Endes's combined staining.)

According to Moore and Sheehan,²⁵ the relation of the special morphological changes to the acutely developing clinical picture should be interpreted as follows. The intimal thickening of the interlobular arteries appears to be the result of a process starting two to four weeks before death. This would gradually lead to a tubular atrophy, coinciding in time with the development of oliguria. The other characteristic morphological change—fibrinoid necrosis of the distal part of the intralobular arteries and of the afferent arterioles—and the consequent cortical necroses, are presumed to develop as late as a few days before death.

Present Investigation

In more than one case the post-mortem examination of patients suffering from scleroderma but who died from some non-renal complication had revealed not only a rather severe mucoid intimal thickening but also a fibrinoid necrosis of the renal arteries without any evidence of impaired renal function.^{11 22 30} On the other hand, when analysing the history of our case mentioned above we were struck by the fact that, despite normal findings in the urine, the effective renal plasma flow (R.P.F.), as measured by the P.A.H. clearance test (C_{P.A.H.}), was reduced as compared with the normal and the filtration fraction (F.F.) was increased. Thus it seems reasonable to assume that scleroderma—progressive systemic sclerosis—producing changes in most of the internal organs, would also affect the kidneys, and the characteristic pattern of "true scleroderma kidney," instead of developing only at the terminal stage, might have its origin in some earlier renal affection.

We assumed that the use of more sensitive tests might reveal more or less marked pathological changes in renal function before signs of renal involvement were detectable by clinical methods. To elucidate this point 25 patients suffering from scleroderma of varying degrees of severity were tested for R.P.F. by the P.A.H. method and for glomerular filtration rate (G.F.R.) by the endogenous creatinine clearance (C_{Cr}) method, and from these the F.F.s were computed. In general, averages were taken of data obtained from blood tests made at the beginning and end of each clearance period. In cases where the withdrawal of blood was difficult, samples were taken halfway through the period, it being considered that, as the level of P.A.H. was constant, this would not endanger accuracy. Determinations, representing the beginning of clearance periods, were made 20 minutes after the infusions were started. At the beginning of the infusions patients received 200–500 ml. of water to induce hydration. The length of a single clearance period depended on the volume of diuresis; usually periods of 15–20 minutes were found satisfactory. With a few exceptions each case had two to three clearance periods, and if the results agreed sufficiently well they were evaluated. Creatinine clearance was estimated by the method of Popper, Mayer, and Mandel, and P.A.H. clearance by that of Bratton and Marshall.

In order to facilitate evaluation of the data obtained values were corrected to 1.73 sq. metres of body surface, surface area being calculated from weight and height, with the help of appropriate tables, in the usual manner. The filtration fraction was computed from the equation $C_{Cr}/C_{P.A.H.} \times 100$. The results are summarized in the Table.

It will be seen that only two of the 25 patients had C_{P.A.H.} values which could be accepted as normal. Clinically, these two cases were the least severe, exhibiting "acro-sclerosis" of short duration. In three cases the reduction in C_{P.A.H.} was moderate and in six cases average, while in 14 cases C_{P.A.H.} was much reduced (150–300 ml. per minute). In 23 of the 25 cases the G.F.R. as measured by C_{Cr} was within normal limits, and in the other two cases it was only moderately reduced.

No unidirectional, unequivocal correlation could be established between the results of renal function tests on the one hand, and the duration, severity, and extent of the clinical disease on the other.

Conclusions

From the above results two conclusions can be drawn.

1. The reduction in R.P.F. indicates the presence of scleroderma changes in the kidneys long before the usual clinical tests, including analysis of the urine, would show any sign of renal involvement. Obviously, the arterial changes observed histologically (thickening of the intima, narrowing of the lumen to fibrinoid necrosis) are responsible, at least in part, for the reduction in the R.P.F.

2. Whereas $C_{P.A.H.}$ was reduced in more than 80% of the cases, the G.F.R. was normal in all but two. Consequently

the F.F. would be expected to be greater. Indeed the F.F. was much increased in 19 out of the 25 cases. This indicates that in these cases the anatomical changes in the pre-glomerular arteries were associated with spasm of the efferent vessels. Similar phenomena can be observed in cases of impaired renal function due to other causes than scleroderma.^{12-15 23 24}

Thus it can be assumed that in patients suffering from scleroderma, also, the spasms accompanying the anatomical changes serve as a compensatory mechanism aimed at the maximum possible maintenance of glomerular function in the presence of renal vascular lesions. This would explain

Results of Renal Function Tests in 25 Cases of Scleroderma

Case No.	Sex	Age (Years)	P.A.H. Clearance (ml. per minute)		Creatinine Clearance (ml. per minute)		Filtration Fraction
			Actual	Calculated per 1.73 sq. m. Body Surface	Actual	Calculated per 1.73 sq. m. Body Surface	
1	F	19	560 560	616 616	96 83	106 91	17 15
2	F	43	520 505	666 648	97 100	124 128	19 20
3	F	59	416 448	532 574	77 83	99 106	19 19
4	F	42	457 420	560 516	106 96	130 118	23 23
5	F	43	415 415	532 532	90 74	115 95	22 18
6	M	49	435 392 393	502 452 453	106 100 95	119 115 110	24 25 24
7	F	19	374 374 350	446 446 418	92 92 88	110 110 105	25 25 25
8	M	47	396 373	426 400	110 87	118 93	28 23
9	F	48	380 312	487 397	110 88	140 112	29 28
10	F	44	344 394	379 433	84 114	93 125	24 29
11	F	49	294	403	71	98	24
12	F	42	390 340	427 372	90 85	98 93	23 25
13	F	52	298 292 254	380 372 323	85 78 71	108 99 91	28 27 28
14	F	44	390 320	385 316	104 92	103 91	27 29
15	F	57	280 274 270	328 321 316	79 79 82	92 92 96	28 29 30
16	F	37	298 276	331 306	103 99	114 110	34 36
17	M	59	308 267 210	398 347 273	83 75 65	108 98 85	27 28 31
18	F	50	244 268 262	303 331 324	88 89 77	109 110 95	36 33 29
19	F	59	343 306 300	353 315 309	99 88 94	102 90 97	29 29 31
20	F	57	296 314	380 405	91 74	117 96	31 24
21	F	53	320 270	406 342	109 87	141 110	35 32
22	F	40	224 260 240		64 72 97		29 28 40
23	F	42	204 155	283 216	40 35	55 49	20 23
24	F	60	230 204	263 234	74 70	85 80	32 34
25	F	26	150 127 107	175 148 124	51 49 48	59 57 56	34 38 48

why the usual clinical tests fail at an early stage, and may even fail completely, to show the presence of diseased kidneys. Once this equilibrating mechanism is upset, for whatever reason, renal function will rapidly deteriorate and uraemia develop. The morphological manifestation of this train of events constitutes what has been termed a "true scleroderma kidney."

Summary

In a small percentage of cases scleroderma produces characteristic morphological changes in the kidney. These consist of mucoid proliferation, accompanied by gross reduction in lumen, of the proximal parts of the interlobular arteries, while the distal parts of these arteries exhibit a fibrinoid necrosis extending to the arterioles. In the parenchyma of the renal cortex ischaemic necroses occur.

The case is reported of a woman aged 43 who developed acute renal failure shortly after the institution of steroid therapy for polymyositis. The renal histology followed the pattern seen in "true scleroderma kidney."

Out of 25 patients suffering from scleroderma of varying severity 80% showed a reduced $C_{P.A.H.}$ (for the estimation of R.P.F.), normal $C_{Cr.}$, and increased F.F. From this it is concluded that the finding of a reduced R.P.F. furnishes an earlier indication of sclerodermal renal involvement than do the commonly used clinical tests.

Reduced $C_{P.A.H.}$, normal $C_{Cr.}$, and increased F.F. indicate that the anatomical changes in the preglomerular arteries are accompanied by spasm of the efferent vessels. The presence of a compensatory mechanism serving to maintain, so far as possible, maximum glomerular function in the presence of a diseased renal vascular system is suggested.

REFERENCES

- Allen, A. C. (1952). *The Kidney*. Churchill, London.
- Banks, B. M. (1941). *New Engl. J. Med.*, **225**, 533.
- Bartels, E. D., Christensen, L. K., and Ohlsen, A. S. (1955). *Acta path. microbiol. scand.*, Suppl. **105**, 174.
- Beigelman, P. M., Goldner, F., and Bayles, T. B. (1953). *New Engl. J. Med.*, **249**, 45.
- Bevans, M. (1945). *Amer. J. Path.*, **21**, 25.
- Calvert, R. J., and Owen, T. K. (1956). *Lancet*, **2**, 19.
- Conestable, E., and Natale, P. (1953). *Progr. med. (Napoli)*, **9**, 41.
- Enticknap, J. B. (1952). *Lancet*, **1**, 316.
- Glaser, R. J., and Smith, D. E. (1953). *Amer. J. Med.*, **14**, 231.
- Goetz, R. H. (1951). *Angiology*, **2**, 555.
- Goldman, I. R., Young, J. M., and Knox, F. H. (1954). *Dis. Chest*, **25**, 94.
- Gömöri, P. (1949). *Kisérlet. Orvostud.*, **1**, 35.
- (1952). *Mag. Tud. Akad. Bol. orv. Tud. Osztal. Közl.*, **3**, 157.
- Földi, M., and Szabó, G. (1952). *Mag. belorv. Arch.*, **3**, 105.
- and Komáromy, I. (1950). *Ibid.*, **3**, 111.
- Gonzalez Salvatierra, A. (1955). *Rev. méd. Chile*, **83**, 162.
- Hannigan, C. A., Hannigan, M. H., and Scott, E. L. (1956). *Amer. J. Med.*, **20**, 793.
- Kampmeier, R. H. (1950). *Amer. Practit.*, **1**, 113.
- Leinwand, I., Duryee, A. W., and Richter, M. N. (1954). *Ann. intern. Med.*, **41**, 1003.
- Luneth, J. H., Baker, L. A., and Shifrin, A. (1951). *A.M.A. Arch. intern. Med.*, **88**, 783.
- Masuzi, M., and Yä-Shu (1938). *Virchows Arch. path. Anat.*, **302**, 39.
- Mathisen, A. K., and Palmer, J. D. (1947). *Amer. Heart J.*, **33**, 366.
- Menne, F., and Fritsch, M. (1956). *Z. klin. Med.*, **153**, 550.
- Hillenbrand, H. J., and Hoeltzenbein, J. (1956). *Klin. Wschr.*, **34**, 125.
- Moore, H. C., and Sheehan, H. D. (1952). *Lancet*, **1**, 68.
- O'Leary, P. A., and Erickson, J. G. (1953). *J. Amer. med. Ass.*, **152**, 1695.
- Pagel, W., and Treip, C. S. (1955). *J. clin. Path.*, **8**, 1.
- Platt, R., and Davson, J. (1950). *Quart. J. Med.*, **19**, 33.
- Pollack, A. D. (1940). *Arch. Path. (Chicago)*, **29**, 859.
- Rodnan, G. P., Schreiner, G. E., and Black, R. L. (1957). *Amer. J. Med.*, **23**, 445.
- Rossier, P. H., and Hegglin-Volkman, M. (1954). *Schweiz. med. Wschr.*, **84**, 1161.
- Sharnoff, J. G., Carideo, H. L., and Stein, I. D. (1951). *J. Amer. med. Ass.*, **142**, 1230.
- Spühler, O., and Morandi, L. (1949). *Helv. med. Acta*, **16**, 147.
- Talbot, J. H., Gall, E. A., Consolazio, W. V., and Coombs, F. S. (1939). *Arch. intern. Med.*, **63**, 476.

ONSET ENURESIS

BY

J. D. PAULETT, M.R.C.S.

AND

E. TUCKMAN, M.B., D.C.H., D.T.M.&H.

General Practitioners, St. Paul's Cray, Kent

No distinction is usually made between those enuretics who have always been wet at night and those who have once been dry and then have subsequently recommenced bed-wetting (onset enuresis). This report describes a study of children with onset enuresis in two practices on a post-war L.C.C. housing estate. The practices are similar in all respects and are contiguous geographically.

Case Finding

During the years 1950-5, 24 children with onset enuresis were brought for advice in the normal manner to one of us (J. D. P.), it being known among his patients that he was "interested" in the problem of enuresis.

On the N.H.S. list of the other of us (E. T.) there were on January 1, 1955, 317 families with a child or children under the age of 21, the family sizes being as shown in Table I. The total number of 677 children consisted of

TABLE I.—Family Size

No. of children in family	1	2	3	4	5	6	7	10
No. of families	101	137	50	13	8	2	4	-

331 girls and 346 boys. During the year 1955 the mother of each family was personally interviewed by E. T. and asked in respect of each child the age at which it had become dry at night, and the details of any relapses; and, in the case of those still wet, whether there had been any bouts of dryness, when these had occurred, and how long they had lasted. The incidence of enuresis (this being defined as one or more wet beds a week) revealed by this survey is shown in Table II, and is similar to that in previously published

TABLE II.—Incidence of Enuresis

Age in yrs.	-1	-2	-3	-4	-5	-6	-7	-8	-9	-10	-11	-12	-21
No. of children	25	24	42	48	60	66	70	64	50	35	37	15	141
No. still wet	25	21	27	12	13	9	9	6	7	0	3	2	4
Percentage still wet	100	87	64	25	22	13	13	11	14		6		3

reports (Bransby, Blomfield, and Douglas, 1955; Blomfield and Douglas, 1956). Of the 478 children of 5 years of age or over, 438 were dry at the time of questioning. The ages at which they had become dry at night are shown in Table III

TABLE III.—Ages When Becoming Dry

	No. of Children	Percentages at Years:					
		1½	2	2½	3	4	5
First child	268	28	55	72	76	82	88
Second child	144	28	55	71	74	81	86
Third and subsequent children	66	57	77	87	88	91	93
All children		33	59	75	79	85	87

as a percentage of each age group according to birth order. Of the 31 children over the age of 6 who were still wet, 9 (29%) had previously been dry for at least three months, the average period of dryness being two years. In addition, 11 children, dry at the time of questioning, had had relapses