# Changes in Renal Function During Reactive Phases of Lepromatous Leprosy[1, 2, 3]

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Davison ([6]) described the occurrence of acute edema in lepromatous and tuberculoid leprosy in association with reactive phases of leprosy while Wheate ([21]) described the phenomenon in lepromatous, tuberculoid and borderline (intermediate) leprosy during reactive episodes. Cochrane ([5]) noted edema of the hands and feet as a condition often associated with "progressive reaction." Gokhale and Kurkure ([9]) carried out phenol red excretion tests on a series of leprosy patients and they suggested that there was some impairment of renal function during reactive episodes.

One of us (A.B.A.K.) observed that bilateral pitting edema during "reaction" in lepromatous leprosy is often associated with an apparent increase in the cellular content of urinary sediment, suggesting the possibility of changes in renal function. In order to document such changes, a study of the functions of the kidney during reactive phases was undertaken.

## MATERIALS AND METHODS

Samples were drawn from the patients who were admitted to the Schieffelin Leprosy Research Sanatorium, Karigiri, during the period November 1966 to January 1968, to constitute material for the study. Thirty-five lepromatous leprosy patients in reaction, 32 lepromatous patients during quiescent phases (i.e., following subsidence of reaction), 26 patients with uncomplicated lepromatous leprosy, and 20 healthy controls were studied. Daily record of clinical status was maintained for patients who were admitted during reaction and intensive studies were carried out after the subsidence of reaction in these patients.

In order to provide some objectivity in recording the clinical status in reaction, a four-point scale as described in Table 1 was used.

Urinalysis, urinary creatinine clearance, blood urea, serum sodium, potassium and serum creatinine were determined during the acute period of exacerbation and, thereafter, at monthly intervals. Urine was also cultured in a sample of cases in each study group. Among those with abnormal renal function, Congo red test ([20]) was carried out to exclude amyloidosis.

Urinalysis was carried out every day during the period of reaction by the following method: 2 to 3 ml. of a fresh, mid-stream specimen of urine were centrifuged at 2,000 revolutions per minute for 10 minutes. One drop of sediment was transferred from the plastic centrifuge tube to a clean microscope slide and examined, under a cover slip, under both low (10X) and high power (43X) magnifications using (10X) eyepieces. A record was made of the number of casts observed in the specimen under low power magnification and the number of red and white corpuscles seen per high power field.

The urine was examined for protein by heating the top centimeter or two in a test tube, acidifying with a few drops of 3 per cent acetic acid and reheating to boiling point, followed by naked eye examination for a precipitate which, if present, was quantitatively assessed according to the system of grading given by Davidsohn and Wells ([7]).

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TABLE 1. *Grading of reactional status.*

| Grade | Symptoms and signs | | | | | Oral temperature (°F) |
|---|---|---|---|---|---|---|
| | ENL | Subcutaneous nodules | Periosteitis neuritis and arthritis | Edema | Others | |
| 1+ | Few nodules, superficial, not tender | Nil | Pain but no tenderness | Minimal | — | 99.0–101 |
| 2+ | Scattered nodules, mostly superficial, slightly tender | ± | With some tenderness | Moderate | — | 99.0–103 |
| 3+ | Multiple nodules, superficial and deep, painful and tender | Tender | Painful and tender | Gross | Iritis<br>Tender and painful lymphadenitis | 99.0–105 |
| 4+ | Multiple superficial and deep nodules, very painful and tender, necrotic | Tender | Very painful and tender | Gross | Iritis<br>Very painful and tender lymphadenitis.<br>Toxic state with distress | 99.0–105 |

Serum and urine creatinine were estimated utilizing Jaffe's reaction (4) and Unicam (SP 600) spectrophotometer. The creatinine clearance test was carried out and the clearance value calculated using routine methods described by Henry (10). (No correction was made for body surface area.)

Practical difficulties with patient supervision assuring prevention of fluid intake made it difficult to carry out tests of tubular function such as concentration-dilution tests.

Blood urea was estimated by the Van Slyke and Cullen method (19) and serum sodium and potassium were determined at the same time using an EEL flame photometer according to the procedure described by King (14). Serum protein was determined using cellulose-acetate strips and a Shandon Universal electrophoretic apparatus (15, 18).

## RESULTS

**Urinalysis.** The number of persons with urinary red cell counts of more than 5 per high power field (HPF) and the number with white cell counts of more than 10 per high power field in the various groups under study are shown in Table 2. Patients in "reaction" had their urine examined daily. The values obtained during the peak of reaction have been utilized in this study.

The number of patients with raised red cell counts in the urine observed in uncomplicated lepromatous leprosy was significantly lower than the number seen in reactive and quiescent phases ($P<0.01$). There was no significant difference between the various groups of patients regarding the number of patients with raised urinary white cell counts. None of the control subjects had raised red cells or white cells in the urine.

The number of patients with casts and significant proteinuria in the various groups is shown in Table 3.

Pus cell casts and proteinuria of 1+ and over were observed in a significantly higher number of cases in grade 3+ to 4+ reaction than they were in milder cases of reaction or in quiescent phases ($P<0.01$).

TABLE 2. *Urinary red cell and white cell counts.*

| Group | Number of patients studied | Per cent | |
|---|---|---|---|
| | | Urinary red cell counts > 5 HPF | Urinary white cell counts > 10 HPF |
| Reaction grade 3+ and 4+ | 19 | 53 | 26 |
| Reaction grade 1+ and 2+ | 16 | 38 | 31 |
| Quiescent | 30 | 27 | 13 |
| Uncomplicated lepromatous | 24 | 13 | 25 |
| Controls | 20 | 0 | 0 |

TABLE 3. *Casts in the urine and proteinuria.*

| Group | Number studied | Per cent | |
|---|---|---|---|
| | | Casts | Proteinuria 1+ and over |
| Reaction grade 3+ and 4+ | 19 | 53 | 37 |
| Reaction grade 1+ and 2+ | 16 | 13 | 6 |
| Quiescent | 30 | 10 | 3 |
| Uncomplicated lepromatous | 24 | 0 | 0 |
| Controls | 20 | 0 | 0 |

In none of the uncomplicated lepromatous leprosy patients and in none of the controls was significant proteinuria or casts recorded.

**Urinary Creatinine Clearance.** The findings were as presented in Table 4 and Figure 1.

Though the number of abnormal values for creatinine clearance (less than 76 ml./min.) was greatest in the severe reaction groups the differences were not statistically significant. However, there was significant lowering of creatinine clearance in lepromatous leprosy patients both in the uncomplicated phase as well as the "reaction" phase as compared with healthy controls.

**Blood urea and serum electrolytes.** No significant changes were observed in these characteristics during reactive episodes.

**Serum creatinine.** No abnormally high levels were recorded in either patients or controls, the values falling within normal limits.

**Urine Culture.** It was possible to culture the urine at peak of reaction in a sample of cases in each of the groups under study. The findings are recorded in Table 5. About one-third of the urine cultures did not show any growth. Another third showed coliform bacilli while the remainder showed organisms such as *Streptococcus faecalis, Klebsiella,* and *Pseudomonas pycocyaneus.*

**Blood pressure.** No significant changes were observed in either systolic or diastolic blood pressure during reactive phases.

**Fundus.** Examination did not show any changes in the patients in reaction nor in patients with uncomplicated lepromatous leprosy.

**Edema.** Was observed in 22 of the 35 patients in reaction as classified in Table 6. It was minimal in five, moderate in 11 and gross in the remaining six patients. Five out of the six grossly edematous cases were from the severe reaction group.

The relationship between edema and al-

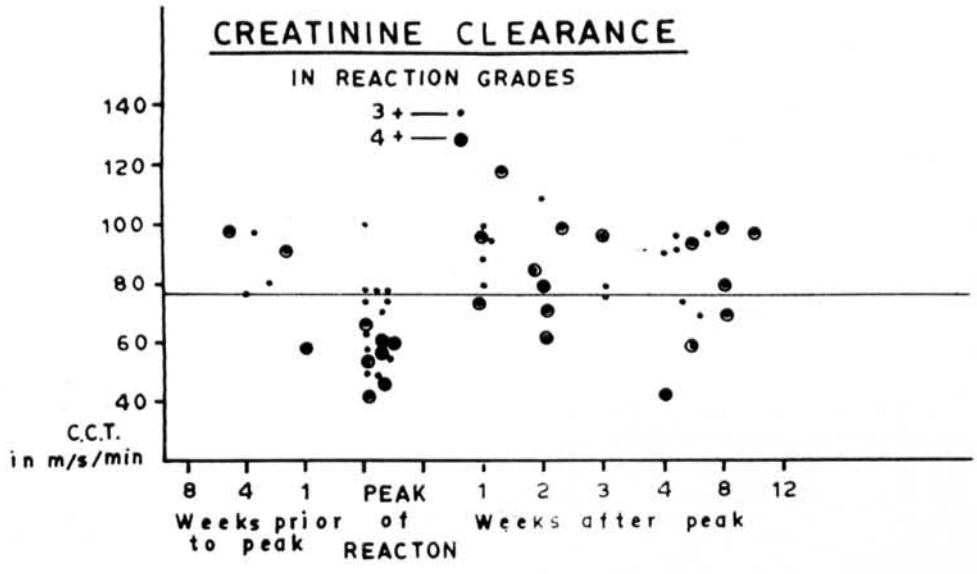


FIG. 1. Creatinine clearance in lepromatous leprosy before, during and after peak of reactive phases of lepromatous leprosy.

bumin and creatinine clearance is shown in Table 7 and in Figure 2.

In four of the six grossly edematous cases, both impaired creatinine clearance and hypoalbuminemia were present.

## DISCUSSION

There appear to be certain similarities between the so-called "collagen diseases" (systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, etc.) and the reactive phases of leprosy as judged by the presence of clinical features of acute-rheumatoid-arthritis-like exudative arthritis ([12]), lupus erythematosus cell phenomenon ([3]), antinuclear factor ([3]), thyroglobulin antibodies ([2]) and increased gamma globulin in the serum. Renal involvement in these "auto-immune" diseases has been well documented ([1, 17]). It is, therefore, possible that the renal involvement in leprosy may, in part, be due to a similar "auto-immune" phenomenon. The relatively common appearance of microscopic hematuria, occasionally associated with clinical appearance of petechiae, arthralgia, arthritis and erythema nodosum, suggest "Henoch-Schonlein" phenomenon as another possible mechanism of renal involvement.

On the other hand, the presence of bacteriologically proven pyelonephritis in one-third of the cases is a pointer to the possibility of exacerbation of "pyelonephritis" as another mechanism of impairment of renal function in the erythema nodosum group. It has been observed that specific treatment of the urinary infection with appropriate antibiotics or chemotherapy, often results in subsidence of the erythema nodosum leprosum reaction, suggesting a possible causal relationship between these two conditions ([11]). This suggestion is further substantiated by the autopsy findings in patients who have died in our hospital. Morbid anatomic evidence of interstitial nephritis and pyelonephritis has been found in 70 per cent of lepromatous leprosy patients ([8]).

Significantly frequent involvement of the kidney has been reported in the past by Mitsuda ([16]) and Kean ([13]) who described "nephritis of all kinds" in their individual series of autopsies. Both these series were reported prior to the introduction of sulfone therapy in the management of leprosy; it is therefore unlikely that the sulfones could be incriminated for the "nephritides" that have been recorded in patients with leprosy.

TABLE 4. *Urinary creatinine clearance in various groups.*

| Group | Number | Subnormal value (<76 ml/min) | |
|---|---|---|---|
| | | Number | Per cent |
| Reaction grade 3+ and 4+ | 18 | 11 | 61 |
| Reaction grade 1+ and 2+ | 14 | 4 | 29 |
| Quiescent | 27 | 6 | 22 |
| Uncomplicated lepromatous | 22 | 9 | 41 |
| Control | 20 | 0 | 0 |

TABLE 5. *Organisms grown in urine culture (percentages are shown in parentheses).*

| Group organism | Reaction grade | | Quiescent | Uncomplicated lepromatous |
|---|---|---|---|---|
| | 3+ & 4+ | 1+ & 2+ | | |
| Nil | 4 (40.0) | 2 (28.5) | 1 (20.0) | 1 (50.0) |
| Coliforms | 4 (40.0) | 4 (57.2) | 3 (60.0) | 1 (50.0) |
| Streptococcus faecalis, Klebsiella | 2 (20.0) | 1 (14.5) | 1 (20.0) | — — |
| Total | 10 | 7 | 5 | 2 |

TABLE 6. *Edema related to severity of reaction.*

| Degree of edema | Total | Reaction | |
|---|---|---|---|
| | | Grade 1+ & 2+ | Grade 3+ & 4+ |
| Nil | 13 | 8 | 5 |
| Minimal | 5 | 2 | 3 |
| Moderate | 11 | 5 | 6 |
| Gross | 6 | 1 | 5 |
| Total | 35 | 16 | 19 |

During the acute phase of erythema nodosum leprosum in those patients who had significant proteinuria, microscopic hematuria, cell casts in the urine, and edema, we did not find elevation of antistreptolysin titer nor any significant change in the blood urea and electrolytes, which is unlike the usual glomerulonephritis of Ellis type I. No significant change in blood pressure was recorded in any of these patients nor changes in the fundus.

It is obvious that no simple explanation is available to account for the changes in renal function or for the occurrence of edema during reactive phases of leprosy. In the majority of cases, the latter appears to be associated with diminished creatinine clearance and hypoalbuminemia. The renal changes may be due to changes in the nephron similar to those described in autoimmune diseases, be due to exacerbation of pyelonephritis or, be attributable to "Henoch-Schonlein" like phenomenon which damages the nephron. To date, specific granulomatous lesion of the kidney due to *Mycobacterium leprae* has not been recorded though the presence of acid-fast bacilli in the urine is common among lepromatous leprosy patients.

It is noteworthy that in none of the cases reported here could we find evidence of amyloidosis.

TABLE 7. *The apparent causes of edema.*

| Apparent cause | Degree | | | Total |
|---|---|---|---|---|
| | Minimum | Moderate | Gross | |
| Low creatinine clearance | — | 3 | — | 3 |
| Hypoalbuminemia (ALB < 3 gm) | 2 | 3 | 1 | 6 |
| Both low creatinine clearance and hypoalbuminemia | 2 | — | 4 | 6 |
| Neither low creatinine clearance nor hypoalbuminemia | 1 | 5 | 1 | 7 |
| Total | 5 | 11 | 6 | 22 |

Further studies with renal biopsies obtained during the reactive episodes of lepromatous leprosy may yield more definitive data regarding the pathogenesis of renal changes in this phase of the disease.

## SUMMARY

An attempt is made to study alterations in the functions of the kidney that occur during the reactive phases of leprosy as a possible etiologic factor in the appearance of edema which is a frequent accompaniment of "reaction" in leprosy. Significantly impaired creatinine clearance and/or hypoalbuminemia has been found in 75 per cent of cases. Bacteriologically proven pyelonephritis was also found in two-thirds of the patients in reaction. It is suggested that the renal damage may be the result of one or more of the following mechanisms: (1) exacerbation of chronic pyelonephritis (2) "Henoch-Schonlein" phenomenon involving the kidney (3) auto-immune damage of glomerulus as seen in "collagen diseases."

## RESUMEN

Se hizo un intento de estudiar las alteraciones de las funciones del riñón que se presentan durante las etapas reaccionales de la lepra como un posible factor etiológico en la aparición del edema que acompaña frecuentemente a la "reacción" en lepra. En un 75% de los casos se encontró un clearance de creatinina significativamente alterado y/o hipoalbuminemia. También se encontró, en dos tercios de los pacientes en reacción, una pielonefritis comprobada bacteriológicamente.

Se sugiere que el daño renal puede ser el resultado de uno o más de los siguientes mecanismos: (1) exacerbación de pielonefritis crónica; (2) un fenómeno de "Henoch-Schönlein" que comprometa el riñón; (3) una lesión autoinmune de los glomérulos, como se ve en las "enfermedades del colágeno."

## RÉSUMÉ

Une tentative a été faite pour étudier les altérations de la fonction du rein qui surviennent au cours des phases réactionnelles de la lèpre. On a essayé de mettre en évidence la signification étiologique possible de ces altérations dans l'apparition de l'oedème qui accompagne fréquemment la réaction lépreuse. Chez 75 pour cent des cas, on a observé, soit des troubles significatifs dans le clearance de la creatinine, soit une hypoalbuminémie, soit ces deux manifestations ensemble. Une pyélonéphrite confirmée par la bactériologie a également été observée chez deux tiers des malades en réaction.

On suggère que la lésion rénale peut résulter de l'un ou de plusieurs des mécanismes suivants: (1) une exacerbation de la pyélonéphrite chronique; (2) un phénomène de "Henoch-Schonlein" au niveau du foie; (3) un trouble auto-immunitaire des glomérules tel qu'on en observe dans les maladies du collagène.

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