Renal Amyloidosis in Leprosy. Functional and Histopathologic Studies


Kidney involvement in leprosy is frequent. A wide spectrum of pathologic manifestation has been reported (12, 13, 18, 19, 21, 24). Chronic pyelonephritis is commonly observed (12, 13). Secondary amyloidosis, however, occurs almost only associated with the lepromatous type of leprosy (12, 13, 18, 19, 21, 24), the kidney being the organ more often involved. The patients so affected die eventually in uremia.

The amyloid deposit may be found in glomeruli, tubules and vessels. Liver involvement with amyloidosis is frequent as is also the digestive tract. Tests to evaluate the function of these organs do not clarify the severity of the functional derangement nor the structures involved. The kidney, nevertheless, offers unique characteristics. A virtual functional dissection can be performed by means of different tests. Within certain limits the inulin clearance evaluates the glomerular function, the functional capacity of the tubules may be estimated by the ability to eliminate an acid overload, to concentrate and to dilute the urine, as well as by the maximal capacity to transport glucose and para-amino-hippuric acid, etc. The clearance of diodrast and p-amino-hippuric acid serves to measure effective renal plasma flow.

In those patients with evidence of renal damage disclosed by albuminuria and alterations of the urinary sediment the suspicion of the existence of amyloid deposits should be raised, especially if no other change responsible for the disorder is found.

The present investigation was initiated to evaluate the degree of functional disturbance of patients with lepromatous leprosy presumed to have renal amyloidosis because of albuminuria and abnormal urinary sediment and having no evidence of other disease process possibly responsible for these changes, and to relate this disturbance to the different parts of the nephron. Twenty-one patients were investigated. Eleven refused to be biopsied and three did not have their diagnosis of renal amyloidosis confirmed by histologic criteria. Only the seven cases histologically proven to have amyloidosis are the object of this report.

PATIENTS, MATERIALS AND METHODS

Description of the patients. Case 1. White male, 51 years, with lepromatous leprosy of four years duration, whose first manifestation of the disease was an episode of erythema nodosum leprosum (ENL). He was admitted a number of times for reactive phases of ENL. Blood pressure was 120/80. Liver edge was felt one centimeter below the right costal margin. Urinalysis revealed proteinuria of 0.04 gm/l (+) and normal sediment. Total proteins 6.2 gm/l; albumin 3.06, globulin 3.14 gm/l; hematocrit 44%. Blood creatinine 1 mg/100 ml; hemoglobin 12 gm/l; 100 ml. Red blood cell count was 4,300,000/mm.

Case 2. Japanese farmer from Okinawa, age 62 years, lepromatous leprosy for 19 years and blind for 15 years. He suffered numerous episodes of ENL and developed cardiac failure three years prior to these studies. A chest x-ray then revealed infiltration of the lower lobe of the left lung. Blood pressure was 140/90. Urinalysis showed proteinuria of 0.148 gm/l and huy

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line, granular and waxy casts; blood creatinine 2.3 mg/100 ml.

Case 1. Negro male, 49 years old, farmworker, lepromatous leprosy for 16 years. For the previous six years he had a number of admissions for treatment of plantar ulcers. He never had any episode of ENL. Blood pressure was 160/110. Stool examinations revealed ova of Ascaris lumbricoides, Ancylostoma duodenale and larvae of Strongyloides stercoralis. Total protein was 4.1 g/ml; serum albumin 1.6, globulin 2.5; urinalysis revealed 5.2 g/ml, hemoglobin and waxy casts, blood creatinine was 9 mg/100 ml.

Case 2. Negro female, 64 years old, housewife, with lepromatous leprosy for 34 years; living in a sanatorium since 1944. She had frequent episodes of ENL and developed functional disturbances. Blood pressure was 160/90. Urinalysis revealed proteinuria of 5.1 g/ml, granular, hyaline and waxy casts. Blood creatinine was 8.7 mg/100 ml, total proteins 2.5 g/ml. Red blood cell count was 3,700,000/mm$^3$, hemoglobin 9 gm/100 ml. She died about one month after the clearance studies.

Case 3. Negro male, 49 years old, farmworker, with lepromatous leprosy for 27 years. He suffered many episodes of ENL and presented plantar ulcers. Three years prior to this study the right lobe of the thyroid increased in size but there were no associated functional disturbances. Blood pressure was 190/110. Urinalysis disclosed specific gravity 1.012, proteinuria of 2.3 g/ml, granular, hyaline and waxy casts; blood creatinine 7.8 mg/100 ml, red blood cell count was 3,400,000/mm$^3$ and hemoglobin 10 gm/100 ml, hematocrit 28%.

Case 4. Negro male, 49 years old, farmworker with lepromatous leprosy for 20 years. He suffered many episodes of ENL. His vision has been declining since the beginning of the illness. He never had plantar ulcers. Blood pressure was 100/60. The urine was positive for protein, and the sediment contained hyaline, granular and waxy casts. Blood creatinine was 1.8 mg/100 ml. He died of bronchopneumonia some time after these studies.

Case 5. White male, 49 years old, with lepromatous leprosy at the age of eight years. Parents, one brother and one sister also had the disease. He was considered cured in 1953. During his illness he had many episodes of ENL. Plantar ulcers occurred on many occasions; at the time of the renal studies they were healed. Blood pressure was 200/120. The urine was positive for protein and the sediment contained hyaline, granular and waxy casts; blood creatinine was 2.3 mg/100 ml.

Renal studies. The clearance determinations for inulin and p-amino-hippuric acid (PAH) were done simultaneously. Two or three clearances were performed sequentially and their average reported as the result. The urine was collected for periods of 30 minutes for each clearance. The collections were begun after a steady plasma concentration of inulin and PAH acid had been reached, between 10 and 20 mg/100 ml for the former and between 1 and 2 mg for the latter. The bolus of the initial injection containing inulin and PAH acid and the concentration of these substances in saline infusions for maintaining these plasma levels were calculated on the basis of previous clearance of creatinine, taking this clearance as similar to the one of inulin. The clearance of PAH acid was estimated as being five times that of inulin. Treatment with sulfones was interrupted during the week preceding the day of the test in order to avoid false results in the determination of the concentration of PAH acid. Beginning two hours before and during the test, 200 ml of water was given every half hour. Special care was observed in collecting the urine which was obtained through a Foley catheter inserted into the bladder. The latter was fully emptied prior to the collection and washed with saline. This procedure was repeated at the end of each period of urine collection when air was also introduced into the bladder to assure full emptying. Blood was drawn, using heparin as anticoagulant, at the beginning, middle and end of each collection. Before the injection of inulin and PAH acid, enough plasma was obtained to serve as the blank and also to prepare the standard curves of these substances. This procedure was followed in all cases. The determination of the concentration of inulin and PAH acid followed the standard methods (26, 32)

The urine concentration test was done according to Fishberg (1') and the osmolarity was measured in the osmometer of Advanced Instruments, immediately after the samples
Table 1. Clinical data and renal function studies.

<table>
<thead>
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<th>Case 1</th>
<th>Case 2</th>
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<td>Sex</td>
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<tr>
<td>Age</td>
<td>51</td>
<td>62</td>
<td>49</td>
<td>64</td>
<td>69</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>4</td>
<td>19</td>
<td>16</td>
<td>34</td>
<td>27</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>ENL</td>
<td>many</td>
<td>none</td>
<td>several</td>
<td>many</td>
<td>many</td>
<td></td>
<td></td>
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<tr>
<td>BP (highest mm Hg)</td>
<td>120/80</td>
<td>140/90</td>
<td>210/110</td>
<td>160/90</td>
<td>190/110</td>
<td>140/80</td>
<td>200/120</td>
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<tr>
<td>Planter ulcers</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
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<tr>
<td>Blood creatinine (mg/100 ml)</td>
<td>1.0</td>
<td>2.3</td>
<td>9.0</td>
<td>8.7</td>
<td>7.8</td>
<td>1.8</td>
<td>2.3</td>
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<td>Total protein (gm/100 ml)</td>
<td>6.2</td>
<td>4.0</td>
<td>2.5</td>
<td>2.3</td>
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<td>Albumin (gm/100 ml)</td>
<td>3.06</td>
<td>2.64</td>
<td>1.6</td>
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<td>Globulin (gm/100 ml)</td>
<td>3.14</td>
<td>1.70</td>
<td>2.4</td>
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<tr>
<td>Proteinuria (gm/l)</td>
<td>0.04</td>
<td>0.14</td>
<td>5.2</td>
<td>5.1</td>
<td>2.3</td>
<td>++++</td>
<td>0.16</td>
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<td>Inulin clearance (ml/min)</td>
<td>98.73</td>
<td>42.15</td>
<td>8.89</td>
<td>11.61</td>
<td>38.88</td>
<td>38.02</td>
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<tr>
<td>PAH clearance (ml/min)</td>
<td>476.12</td>
<td>203.01</td>
<td>10.48</td>
<td>12.70</td>
<td>44.89</td>
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<td>159.40</td>
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<td>Filtration fraction</td>
<td>0.207</td>
<td>0.207</td>
<td>0.847</td>
<td>0.640</td>
<td>0.258</td>
<td>0.353</td>
<td>0.238</td>
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<td>Maximal urinary concentration (mOsm/l)</td>
<td>921</td>
<td>not done</td>
<td>372</td>
<td>350</td>
<td>362</td>
<td>524</td>
<td>419</td>
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</table>

a Gamma globulin.
b Not corrected for body surface.

were obtained. The highest result was taken as the maximal capacity of the kidney to concentrate the urine.

The biopsies were performed percutaneously. The specimens were kept in Zinsser's solution until processed. The sections were stained with hematoxylin and eosin and Congo red. The latter preparations were examined under polarized light for determination of green birefringence which is the hallmark of amyloid deposit (1). The material of the only case coming to autopsy (No. 6) was preserved in 10% solution of neutral formaldehyde and similarly stained.

RESULTS

Table 1 presents the main clinical data and the results of the functional tests. Table 2 summarizes the main pathologic findings. The biopsy and single autopsy reports on the kidneys follow.

Case 1. Biopsy (Fig. 1). Normal renal architecture. Many glomeruli show a clear mesangial axis with slight increase in the number of cells, usually in small clusters in the middle of a dense acidophilic stroma. The capillary loops are permeable. An artery of small caliber shows discrete, subendothelial fibrous thickening. There is no abnormality in the interstitial tissue. The basal membrane of the medullary tubules is slightly positive for amyloid deposit (1). The material of the only case coming to autopsy (No. 6) was preserved in 10% solution of neutral formaldehyde and similarly stained.
TABLE 2. Major pathologic findings in the kidney.

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<th>Case 1</th>
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<td>Amyloid deposit</td>
<td>-</td>
<td>(+)</td>
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<tr>
<td>Endothelial cellularity</td>
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<td>Mesangial cellularity</td>
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<td>Mesangial sclerosis</td>
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<td>Amyloid deposit</td>
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<td>Arteriosclerosis</td>
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<td>Cortical tubuli</td>
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<td>Medullary tubuli</td>
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<td>Amyloid deposit</td>
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FIG. 1. Case 1. Discrete peritubular amyloidosis. The tubular architecture is well preserved. The amyloid deposit follows the contours of the tubules near the basal membrane. Congo red stain. Magnification X63.

FIG. 2. Case 2. Marked peritubular amyloidosis. Renal medulla shows peritubular deposit deposition of amyloid material in thick and irregular hyaline bundles and areas of atrophy of the tubular epithelium reduced almost only to its contours marked by the amyloid deposit. Congo red stain. Magnification X25.
FIG. 3. Case 3. Intense glomerular amyloidosis. Group of glomeruli with diffuse deposits of the amyloid substance. The glomerular tuft is increased in size. The amyloid material located in the mesangial axis entirely blocks the lumen of the loops of the capillary vessels. Discrete capillary fibrosis and atrophy of the adjacent renal tubuli. Congo red stain. Magnification X63.

FIG. 4. Case 4. Glomerular and vascular amyloidosis. Glomerulus with focal amyloid deposition in the capillary subendothelium and along the mesangial axis. On top of the glomerulus a small vessel with the amyloid deposit obstructing partially its lumen is seen. Congo red stain. Magnification X63.

linized and present fibrous thickening of the capsules. There is moderate vascular amyloidosis and intense amyloid deposition in the basal membrane of the medullary tubules.

Case 3. Biopsy (Fig. 3). Renal tissue with altered architecture due to interstitial fibrosis and tubular atrophy. Only the cortex is seen in the biopsy fragment. Small foci of mononuclear inflammatory infiltrates are present in the interstitial tissue. There is generalized involvement of the enlarged glomeruli with amyloid deposits. The majority of the glomeruli show hyalinization of the tuft and fibrous thickening of the capsules. Amyloid deposit is also seen in the vascular subendothelium. Some arterioles present hyperplasia of the muscular layer and fibrous thickening of the intima. No amyloid deposit is observed in the tubules.

Case 4. Biopsy (Fig. 4). Altered renal architecture. Diffuse interstitial fibrosis and atrophy of the tubules. There is diffuse but discrete mononuclear inflammatory infiltrate in the interstitial tissue. The enlarged glomeruli are generally filled with amyloid deposits. Foci of hypercellularity are present in the middle of the amyloid substance. Adhesions of the glomerular tuft are also observed. There is intense deposition of amyloid in the subendothelium but discrete deposition in the basal membrane of the cortical and medullary tubules. The small arteries show subendothelial fibrous thickening.

Case 5. Biopsy. Impaired renal architecture. Tubular atrophy and interstitial fibrosis are observed. The glomeruli are enlarged and there is pronounced amyloid deposition frequently associated with hypercellularity of the glomerular tuft, adhesions and proliferation of Bowman’s capsule. Rare glomeruli show atrophy and hyalinization. There is intense deposition of amyloid in the vessels and in the cortical tubules. Foci of mononuclear inflammatory infiltrate are seen in the interstitial tissue. There is no medullary tissue in the fragment of the biopsy.

Case 6. Necropsy. The renal architecture is altered. Areas of interstitial fibrosis and tubular atrophy alternate with areas of dilated tubules. There is pronounced deposition of amyloid in the glomeruli, subendothelium of the vessels and in the basal membrane of the tubules, especially in those located in the medulla. Some glomeruli show hyalinization and atrophy with capillary fibrosis. Discrete arteriosclerosis is observed.

Case 7. Biopsy. Small fragment of renal tissue showing six glomeruli. There is marked alteration of the architecture. Interstitial fibrosis with atrophy of the tubules and areas of tubular dilation are observed. Diffuse mononuclear inflammatory infiltrate in the interstitial tissue is present. Three glomeruli are hyalinized showing residual
sions of hypercellularity and a central block of amyloid deposit. The remainder of the glomeruli present discrete mesangial hypercellularity with hyaline and acidophilic thickening of the mesangial axis. The walls of the arterioles are thick and hyalinized. Amyloid deposits are present in the subendothelium of the arteries in the middle of fibrous proliferation with decrease of the lumen of the vessels. Some tubules show discrete amyloid deposition in the basal membrane.

**DISCUSSION**

The seven lepromatous leprosy cases reported suffered in the past from *eritema nodosum leprosum*. None, however, was in reaction at the time of this study. Alterations of kidney function have been reported (14, 24) during active ENL. Four patients, cases 3, 4, 5, and 7, presented or had a history of plantar ulcers of long duration. Cases 3, 4, and 5 were in an advanced phase of their illness and in frank uremia. In these circumstances, the insulin and the p-amino-hippuric acid clearances do not reflect the glomerular filtration rate nor the effective renal plasma flow, especially the latter (10).

In the case of the clearance of p-amino-hippuric acid, the assumption that 90% of this substance should be extracted in its passage through the kidneys is not observed. The tubular mass seriously damaged is incapable of effectively excreting the p-amino-hippuric acid. This is the main reason for the rise of the filtration fraction and not the diminution of the effective renal plasma flow. In these three patients the tubular functional involvement, measured by the capacity to concentrate the urine is very marked. The histologic study of these kidneys reveals extensive and uniform damage of the whole organ.

Case 1, however, showed excellent functional reserve; the glomerular filtration rate was normal, his ability to concentrate urinary solutes was good, but the filtration fraction was somewhat augmented, probably indicating a vascular involvement greater than that of the glomeruli, or a vascular involvement associated with deficient tubular excretion. Histologically, the vessels did not show amyloid deposit and the tubules showed only minor alterations.

The other three cases (2, 6, and 7) presented an intermediate type of involvement.

The filtration fraction was slightly augmented suggesting greater vascular involvement. The incidence of amyloidosis in patients with lepromatous leprosy is variable; low in India and Mexico (15, 16, 24), high in the U.S.A. (27, 28). Williams and co-workers (24), studying comparable groups in the United States (101 patients) and Mexico (119 patients), estimated the incidence of this complication as between 40% and 50% in the former group and 6% in the latter (diagnosis made by necropsy, gingival biopsy, tests of retention of Congo red). These authors observed a great discrepancy in the ingestion of animal fat, which in the American group was much greater than in the Mexican group, although the latter consumed much more calories. The frequency of this complication in Brazil is still undefined. Preliminary studies in the Hospital de Dermatologia Sanitaria Lauro de Souza Lima, Bauru, Sao Paulo, however, suggest a high incidence (14).

Those patients having lepromatous leprosy and albuminuria not explainable by other renal disease must be suspected of harboring amyloid deposits in the kidney. If a renal biopsy is not feasible, gingival or rectal biopsy (2.4, 8, 10), especially the latter, can confirm the diagnosis, and with almost absolute certainty it may then be concluded that the kidney is also involved. Functional evaluation should then be mandatory. For practical purposes, the clearances of inulin and p-amino-hippuric acid can be substituted by the clearances of creatinine and phenolsulfonphthalein and the determination of the specific density of the urine can be substituted for the measurement of the urinary osmolality since these tests are much easier to perform in a clinical laboratory.

There is some evidence in the literature that the amyloid deposition is reversible with the amelioration of the primary illness (14, 16). This being so, the periodic performance of tests to evaluate the renal function would be a valuable means of following the evolution of amyloid deposition in the kidney. The follow-up of the cases reported in this paper and the periodic functional evaluation of other patients with renal amyloidosis secondary to lepromatous leprosy may confirm the validity of this hypothesis.
SUMMARY

Seven cases of renal amyloidosis secondary to lepromatous leprosy are reported. Six had the diagnosis confirmed by biopsy and one by necropsy. One patient had only mild tubular involvement, three were in a far advanced stage and the other three were moderately affected. Five had a previous history of repeated episodes of erythema nodosum leprosum (ENL), three of ENL and plantar ulcers, and one of plantar ulcers without episodes of ENL. None were in active phase of ENL during the renal studies.

Renal function was evaluated by the clearances of inulin (to measure the glomerular filtration rate), p-amino-hippuric acid (to measure the effective renal plasma flow) and by the maximal capacity of the tubules to raise the urine osmolarity after water deprivation.

The patient with only slight deposits of amyloid in the tubules showed excellent functional reserve. The three advanced cases presented serious impairment of the glomerular filtration rate, effective renal plasma flow and tubular capacity to concentrate the urine. The three cases with intermediate type involvement showed an increase of the filtration fraction suggesting a greater vascular involvement or this associated with a deficient capacity of the tubules to transport the dye.

The authors suggest that those patients with lepromatous leprosy and albuminuria not explainable by other illnesses should be suspected of harboring amyloid deposits in their kidneys. If renal biopsy cannot be performed a gingival or rectal biopsy would confirm the diagnosis of amyloidosis and kidney involvement could be assumed since this organ is affected in over 80% of the cases with systemic amyloidosis. Renal function evaluation should then be mandatory.

The more practical tests of creatinine clearance, phenol red excretion and measurement of the specific gravity of the urine after water deprivation could be substituted for the clearances of inulin and p-amino-hippuric acid and measurement of urine osmolarity, respectively. The periodic performance of these tests should be a valuable means of following the amyloid deposits in the kidney, since there is evidence in the literature that these deposits may be reversible.
de l'autopsie. Un de ces malades présentait seule-
ment une atteinte tubulaire légère; trois étaient-
dans un état beaucoup plus avancé; les trois
derniers n'étaient que modérément affectés.
CinQ de ces malades présentaient une histoire-an-
térieure d'épisodes répétés d'erythème nou-
xes lépreux (ENL); trois d'ENL et d'ulcères pla-
ntaires, et un ulcère de jambe sans épisodes d'ENL.
Aucun de ces maladies n'était atteint de la phase
aigue de l'œdème noueux durant le cours de
cette étude.

La fonction rénale a été évaluée par le claire-
ance de l'inuline, afin de mesurer le taux de filtration
glomérulaire, la mesure de l'acide p-aminoph-
parique pour évaluer de débit du plasma rénal ef-
fectif, et la capacité maximale tubulaire pour
l'élaboration de l'osmolarité urinaire après prêvi-
tion d'eau.

Le malade qui ne présentait que de faibles
dépôts amyloïdes dans le système tubulaire présenta
une réserve fonctionnelle excellente. Les trois malades au stade avant présentaient
une détérioration grave, tant en ce concerne le
 taux de filtration glomérulaire, que le débit
plasmatique rénal effectif ou et la capacité
 tubulaire à concentrer l'inuline. Les trois cas pré-
 sentant une atteinte de type intermédiaire, mon-
traient une augmentation de la fraction de filtrat-
tion qui suggérait une plus grande atteinte
vasculaire, ou bien une association avec une
capacité déficiente des tubules à transporter le
chloure.

Les auteurs suggèrent que ces malades, at-
teins à la fois de l'épisode leptomélatrète et d'abru-
tomnie ne pouvant être expliquées par d'autres
affections, devraient être soumises de prévi-
sé des dépôts amyloïdes dans les reins. Si
l'est possible de pratiquer une biopsie rénale,
it faudrait procéder à une biopsie gingival ou
rectale qui pourrait confirmer le diagnostic d'amy-
loidose, ou pourrait être lors présumé que le
rein est également atteint, car cet organe est af-
fecé dans plus de 80 pour cent des cas prêten-
tant une amyloidose systémique. Il devrait être
impératif de procéder à une évaluation de la fonc-
tion rénale. Les épreuves plus pratiques de clair-
ance pour la créatinine, d'excrétion du rouge phénol,
de même que la mesure de la gravité spéci
cifique de l'urine après prêvention d'eau, pour-
raient remplacer les clairances de l'inuline et de
l'acide aminophosphique, de même que la mesure
de l'osmolarité de l'urine. La répétition péri-
dique de ces épreuves pourrait constituer une
méthode fort utile pour suivre les dépôts de
substance amyloïde dans le rein, puisqu'il existe
dans la littérature des données que montrent que
ces dépôts peuvent être réversibles.

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