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PREVENTION OF RENAL DISEASE

*U Bengtsson*

University Hospital, Lund, Sweden

Analgesic nephropathy is one of the best examples of preventable renal disease. In Sweden the incidence of analgesic nephropathy reached a maximum during the late 1950's. The compound used by the great majority of Swedish patients presenting with analgesic nephropathy contained phenacetin, phenazone and caffeine. Few patients had used phenacetin-containing compounds including salicylates. At the beginning of 1961 came the prescription law, and phenacetin-containing drugs were no longer available over-the-counter, NAPAP or paracetamol was included in the restriction. The total consumption of phenacetin fell to less than 10% and has remained at a low level.

The clinical panorama started to change during the first few years of restriction. Voiding of papillary tissue in the urine became infrequent, and repeated pyelonephritic attacks precipitated by obstruction of the urinary tract also became less frequent [1]. Anaemia was a more pronounced feature in analgesic nephropathy when the abuse was still going on than after 1961. The number of new cases of analgesic nephropathy diminished.

After some years the incidence of uraemia due to analgesic nephropathy started to fall. In Göteborg renal transplantation has been the first choice in treatment of terminal uraemia. Table I shows how the percentage of analgesic nephropathy has continued to decrease over the years. It will still take several years before phenacetin-induced nephropathy has disappeared as a cause of uraemia, because the progress of renal impairment is slower in analgesic nephropathy than in other kinds of chronic renal disease, provided that hypertension and urinary tract in-

<table>
<thead>
<tr>
<th>Year</th>
<th>AN/total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965–69</td>
<td>33/165</td>
<td>20.0</td>
</tr>
<tr>
<td>1970–72</td>
<td>22/186</td>
<td>11.8</td>
</tr>
<tr>
<td>1973–75</td>
<td>16/183</td>
<td>8.7</td>
</tr>
<tr>
<td>1976–78</td>
<td>9/160</td>
<td>5.6</td>
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</table>
fections are adequately treated and that analgesic abuse has ceased.

The relative frequency of analgesic nephropathy in patients accepted for dialysis or transplantation has decreased in Denmark in a similar way as in Sweden according to the EDTA Registry (Table II). Denmark also restricted the sale of phenacetin in the early 1960's. In Switzerland, the country where analgesic nephropathy was first described, the frequency of analgesic nephropathy has increased, and phenacetin-containing drugs are still freely available in every drug store.

**TABLE II. The Relative Frequency of Analgesic Nephropathy in Patients Accepted for Dialysis or Transplantation**

<table>
<thead>
<tr>
<th></th>
<th>1970</th>
<th>1976</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Sweden</td>
<td>9.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Denmark</td>
<td>14.0</td>
<td>6.6</td>
</tr>
<tr>
<td>Switzerland</td>
<td>16.7</td>
<td>19.7</td>
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</tbody>
</table>

(EDTA)

The most serious complication of analgesic abuse is the development of renal pelvic carcinoma. Ten per cent of the patients with analgesic nephropathy I have followed have developed this kind of tumour. The induction time for such tumours is very long, with an average of 22 years and a great spread [2]. Thus, the tumour has been diagnosed several years after the withdrawal of drug abuse. The number of such tumours reached a maximum in 1970 (Figure 1). Even the total number of uro-epithelial tumours was higher during this period. Patients are nowadays reluctant to give a history of analgesic abuse. The finding of papillary necrosis in some of the other patients makes it probable that analgesic drugs was an aetiological factor even in them.

The story of phenacetin-containing drugs is probably not unique, and there are reasons to watch carefully for the effects of other analgesics. So far we have no evidence in Sweden that other analgesics have caused chronic nephropathy, but every case of interstitial nephritis should be analysed as regards analgesic or any other chronic drug consumption, especially self-medication. Paracetamol is now available over-the-counter, and we do not know what consequences this might have. If renal lesions should appear, restriction of sale should be introduced.

Another drug-induced nephropathy which has been discussed during the last few years is lithium nephropathy. That lithium causes a concentration defect has been known from the very beginning of its use in therapy. However, in 1977 it was reported in a biopsy study from Århus in Denmark that chronic renal lesions can develop during long-term therapy with lithium [3]. Interstitial fibrosis and tubular atrophy were the findings.

This report has led to similar studies elsewhere. In the mental hospital in Lund 33 patients on lithium therapy were studied [4]. Seven patients had a slightly reduced GFR. So far no patients have been reported to have progressed to terminal renal failure. However, this might happen in the coming decades. What can
be done to prevent such a development? Lithium cannot easily be withdrawn from patients for whom this kind of therapy is essential. Controls of the blood concentration of lithium should be performed regularly. Since a concentration defect is common, everything should be done to prevent disturbance in water balance, whenever these patients catch intercurrent infections, diarrhoea etc. Additional blood levels should then be done in order to adjust the dose.

Not only drugs but many toxic environmental factors must be taken into consideration in prevention of renal disease. Cadmium is one example.

We usually associate toxic agents with tubular lesions, but during recent years data have accumulated indicating that organic solvents or fuels might be involved in the pathogenesis of glomerular disease. This applies to Goodpasture’s syndrome and non-systemic glomerulonephritis. In a study in Lund it was shown that the frequency of a heavy or moderate exposure to organic solvents was more than twice as high in patients with glomerulonephritis as in controls with non-glomerular renal disease or appendicitis [5]. During follow-up, patients who had discontinued the exposure demonstrated a more favourable course than patients with continuous exposure.

Since exposure to organic solvents is common and glomerulonephritis is a
relatively uncommon disease, a genetic trait or other co-factors must be assumed. Much more research work is needed but already, at the present time, it seems reasonable to discuss whether patients with glomerulonephritis and exposure to organic solvents should try to avoid further exposure.

Hypertensive renal disease is a disease which should be preventable. As far as essential hypertension is concerned more than a slight reduction of renal function should not be seen with adequate treatment. An unavoidable cause for development of severe hypertension is renal artery stenosis. Arteriosclerotic plaques can sometimes cause occlusion of one or both renal arteries leading to rapid deterioration of renal function (Figure 2). The only measure which can save renal function in this situation is reconstruction of the renal arteries [6].

![Diastolic BP Graph](image)

![Serum creatinine Graph](image)

**Figure 2.** The course of blood pressure and renal function in a 53 year old man developing renal artery stenosis and occlusion. The arrow indicates time of artery reconstruction.
In most forms of chronic renal disease hypertension is one of the most important factors leading to deterioration of renal function. In a long-term follow-up of patients with chronic pyelonephritis [7], the progress of renal impairment was much faster in patients who at some time developed severe hypertension (Table III). Only cases with a GFR below 40ml/min were analysed. The patients with severe hypertension had been out of control for some period, and half a year may be enough to lead to an unsatisfactory turn of the clinical course.

| TABLE III. Annual Reduction in GFR in Chronic Pyelonephritis Prospective Study |
|-----------------------------------|------|---------|
| Number of Patients | ml/min |
| Normotension | 12 | 1.3 ± 1.8 |
| Hypertension grade 1-2 | 70 | 1.4 ± 1.6 |
| Hypertension grade 3-4 | 7 | 6.2 ± 6.1 |
| (p < 0.05) |

A retrospective study was then made of patients with uraemia due to chronic pyelonephritis (Table IV). These were patients in the transplantation programme in Göteborg, coming from several parts of the country. No less than 36% had had hypertension of grade 3 or 4 for shorter or longer periods and the deterioration of renal function had also been faster in this group. The majority had either not been followed continuously or the antihypertensive treatment had been inadequate. With continuous control and adequate treatment such a development need not occur.

The problems are similar in chronic glomerulonephritis and in most other chronic renal diseases. In diabetic nephropathy hypertension develops with few exceptions and there is convincing experience that a high blood pressure accelerates renal impairment [8]. As far as diabetes is concerned there are many clinical, epidemiological and experimental studies indicating that good metabolic control prevents or delays the development of diabetic complications including nephropathy.

Professor Kerr has discussed reflux nephropathy in children, and I will give some data on a study of reflux nephropathy in adults in Lund. The majority are young females, but there are patients up to 60 years of age. Forty-seven patients have been followed up for 5 to 10 years after antireflux operations. All except 4 had pyelonephritic changes with blunted calyces and cortical scars. In the majority there was reduced kidney size, usually unilaterally. The main indication

| TABLE IV. Annual Reduction in GFR in Chronic Pyelonephritis Retrospective Study |
|-----------------------------------|------|---------|
| Number of Patients | ml/min |
| Normotension | 7 | 4.5 ± 1.2 |
| Hypertension grade 1-2 | 68 | 4.7 ± 2.5 |
| Hypertension grade 3-4 | 43 | 8.0 ± 5.0 |
| (p < 0.001) |
for surgery was repeated bouts of acute pyelonephritis. During the follow-up only 4 patients had an isolated attack of pyelonephritis and the majority had no signs or symptoms of urinary tract infection. The patients with normal serum creatinine remained at a normal level of function (Table V). In patients with an initially raised serum creatinine renal impairment progressed in all but one patient. We have no comparable controls and although the number of patients in the second group is small, the tentative conclusion is that an anti-reflux operation should be performed before a rise in serum creatinine. When renal impairment accelerates, the patients sometimes demonstrate increasing proteinuria and glomerular involvement probably due to an autoimmune mechanism.

Prevention of acute nephropathies and acute renal failure has been omitted in this survey as have items outside the author's experience.

TABLE V. Follow-up of VUR After Surgery

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Initial S–creat. (\mu\text{mol/l} )</th>
<th>Years of follow-up</th>
<th>(\Delta S–\text{creat. } \mu\text{mol/l/year} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean</td>
<td>range</td>
</tr>
<tr>
<td>38</td>
<td>&lt;110</td>
<td>7.3</td>
<td>(5–10)</td>
</tr>
<tr>
<td>11</td>
<td>110–230 (mean 150) (median 135)</td>
<td>6.5</td>
<td>(2–10)</td>
</tr>
</tbody>
</table>

References


Open Discussion

HANSEN (Aarhus) I would like to comment about lithium nephropathy. In our last series, consisting of 110 and 257 patients respectively studied at 2 centres we did find a reduced renal concentrating ability in about 25% of all patients treated for more than 2 years. In the first year in the 110 patients renal biopsies were made in patients with impaired renal concentrating ability and the same findings as presented 2 years ago were found. Concerning glomerular filtration rate, lithium-induced nephropathy seems to be characterised by severely impaired renal concentrating ability with a disproportionate preservation of glomerular
filtration rate. Reduction in glomerular filtration rate develops late. Second, concerning measures which could prevent some toxic nephropathies. You have to realise that with compounds excreted in urine mainly, the daily dose has to appear in the urine, if you have a steady state balance. Studying for example lithium-induced nephropathy, you normally find approximately 10 to 20 mmols lithium per litre of urine. During concentration tests in patients on lithium treatment you will find up to 70 mmols per litre during the period of water deprivation. That means that concentration in urine and in some parts of the nephron will become approximately 20 to 45 times the lowest plasma toxic level.

BURCK (Kiel) Both speakers stressed the important role of hypertension in pyelonephritis. Higher grades of hypertension result in a poorer prognosis. Do you know whether sufficient diagnostic efforts are made to rule out in these cases that the underlying disease was not pyelonephritis but rather glomerulonephritis? I ask this question since we found in our own studies that in 100 cases who died with the diagnosis of pyelonephritis 45% had died from glomerulonephritis in the years when there was no intermittent haemodialysis programme. Does one of the speakers have experience as to the occurrence of additional glomerulonephritis in the late course of chronic pyelonephritis, which then might be the reason for severe grades of hypertension?

BENGTSSON: I think the proportion of patients in whom this would be an explanation is not very high in my study, because hypertension was an early feature in many of the patients. Of course they were not biopsied, but about half of them did not have proteinuria and in the other patients, proteinuria was very discrete, but we had a few patients developing an increasing proteinuria with increasing impairment.

KERR In our series we have diagnosed pyelonephritis only in the patients with gross radiological change, but our only proof that they have not a glomerular nephritis as well is that we do look at their urine at each visit to the hospital and they almost never have casts in the urine, except when they have malignant hypertension.

GOLDSMITH (Liverpool) During the past 5 years we have seen 2 middle aged male patients in close industrial contact with solvents who presented as surgical emergencies with acute unilateral renal vein thrombosis starting within the kidney and spreading outwards. Is this a coincidence or a result of solvent intoxication?

BENGTSSON Is there anybody in the auditorium, who has any experience of this?

KERR I have no experience. Since publications began to appear stressing the influence of renal vein thrombosis in glomerulonephritis we are finding a lot more than we used to.

GOLDSMITH But our cases were rather unusual in presenting with shock and large painful loin masses.

STRUYVENBERG (Utrecht) In the Netherlands the increased use of paracetamol
has led to a marked increase in the number of fatal suicides caused by liver necrosis. Is this also the experience in Sweden and the UK?

BENGTSSON Yes, we have seen not many, but we have seen these cases of hepatic necrosis, and we warned the state authorities that they should not withdraw the prescription rule for paracetamol, but they said that pediatricians wanted to have it available and now we are watching the situation very closely.

KERR In the UK paracetamol is the commonest fatal drug overdose nowadays.

PUGSLEY (Adelaide) I wonder if I could ask Professor Bengtsson to amplify her remarks a little on the subject of nephron sparing surgery in renal artery stenosis. One might get the impression that if you see renal function failing, that it is just a matter of cutting out the stenosis or by-passing it, but I think many cases may have, after all, atheroma upstream or downstream. It might be a little more difficult in these to recommend that course of action, I wonder what your feelings are about that?

BENGTSSON Yes, many of these patients have other atheroma, but in the examples I have shown there was the question of saving the renal function. Without surgery they would have been uraemic in a few days or weeks.

PUGSLEY What I am trying to draw you into saying is that when you see renal function failing in people who have renal arterial disease of this nature which is usually arteriosclerotic and bilateral, will you always recommend surgery, or do you think your selection has to be more careful?

BENGTSSON No, I will not always recommend that. There are many things to discuss in every such case and I cannot give any general advice. They should not be operated only on the indication of hypertension, if hypertension can be managed by medical treatment, but when renal function is threatened then I think we should operate.

MALLUCHE (Los Angeles) In regard to the issue of renal vein thrombosis brought up by Dr Goldsmith, I would like to refer to a study done in our unit which shows that the incidence of renal vein thrombosis is relatively high in patients with membranous and membranoproliferative glomerulonephritis and nephrotic syndromes, due to the coagulopathy. It might be that Dr Goldsmith’s patients were nephrotic due to their intoxication.

KURUVILA (India) Would you recommend surgical correction of vesico-ureteric reflux in children where renal function is severely impaired?

KERR I don’t think we can answer that from our data or from the literature. I think surgeons have been reluctant to do the operation in the presence of renal failure.

ANDREUCCI (Naples) Do you suggest surgical treatment of children with reflux nephropathy but already on RDT, who are to have a kidney transplantation?

BENGTSSON If they had repeated attacks of acute pyelonephritis I think it
would be better to remove the kidney and the ureters.

KERR If you look for reflux in all transplant recipients there is a rather high incidence of reflux, even in people who do not have pyelonephritis as the primary illness, and we certainly don’t remove their kidneys, but it has been our policy to remove the kidneys and ureters of children with a history of recurrent infection and pyelonephritis, but I don’t think anybody has done a controlled trial to see what it does to transplant results.

CRASWELL (Brisbane, Australia) Queensland is the most northerly of the Australian states and is the State with the highest incidence of analgesic nephropathy. This agrees with what Dr Bengtsson says about the effects of temperature. What screening measures does Dr Bengtsson employ to detect uro-epithelial tumours of the renal tract?

BENGSTSSON We follow the urinary sediment very closely and when there is haematuria, even if it is only a few red cells, then you should screen the urine for malignant cells, even if there are a few patients who develop carcinoma without haematuria, so I think once a year in those patients, I screen with cytological tests, even if they don’t have haematuria.

GELIN (Göteborg) As there have been some surgical questions I might interfere in this discussion concerning reflux and renal infection. It must be emphasised that reflux without an obstructing mechanism involved does not produce renal infection and should not be treated. For stenotic renal arteries an early correction should be aimed at, to prevent renal hypertension from crippling the patient. In cases of multiple and distal stenosis they can safely be treated with the extra-corporeal procedure. Finally let me re-emphasise Professor Bengtsson’s statement that removal of phenacetin has prevented both nephritis and uroepithelial tumours. But from the figure shown by Professor Bengtsson I should like to ask someone from Switzerland, what are you going to do about it?

BRUNNER (Basel) Dr Gelin wants me to make a comment on the availability of phenacetin in Switzerland. The Swiss Association of Nephrologists has many times asked the Health Authorities to ban this drug. They have told us to provide full information on the adverse effects of any drug which is likely to replace phenacetin. So it is still available in Switzerland and Hoffmann La Roche continues to make a profit of 40 million Swiss Francs a year on this drug.