PHENACETIN NEPHRITIS: INTERSTITIAL NEPHRITIS AND NECROTIZING PAPILLITIS ASSOCIATED WITH THE CHRONIC INGESTION OF PHENACETIN

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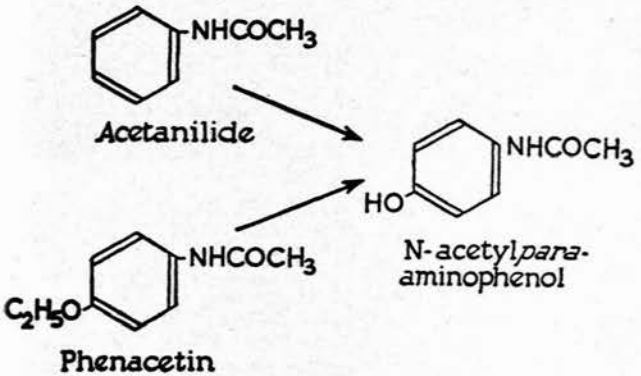
Phenacetin is a coal-tar derivative, related to acetanilid, which has been used in medicine since 1886. It and its main breakdown product, N-acetyl para-aminophenol,



have been incorporated into many headache and analgesic compounds. It is used extensively by the public who, in South Africa, are able to obtain it in more than 61 different brands of proprietary preparations.

In view of the widespread use of phenacetin and its compounds, it is surprising to note the dearth of information in the English and American literature regarding its harmful effects. In marked contrast to this, numerous reports have appeared in the Swiss and Scandinavian literature[1-8] stressing the kidney damage associated with the chronic ingestion of compounds which contain phenacetin. Recently we have studied two patients with severe phenacetin-induced renal disease.

Case 1

Mr. B., aged 39 years, was admitted to the professorial medical unit of the Johannesburg General Hospital on 25 April 1961. His past history was that since 1945 he had been complaining of peptic ulcer symptoms which became steadily worse and were not relieved by usual medication. Following a haematemesis he underwent gastrectomy which also failed to improve his symptoms. At the beginning of 1957 he began to take proprietary tablets each containing aspirin (260 mg.), phenacetin (260 mg.) and codeine (8·1 mg.) to relieve the pain. The initial intake was 4 - 6 tablets a day increasing at times to a daily consumption of 24 - 28 tablets. This habit continued daily for approximately 3½ years with an average intake of 15 - 20 tablets daily.

In March 1961 he was admitted to hospital with complaints of headache, vomiting, diarrhoea, weakness, and polyuria of 3 weeks' duration. On examination he was found to be dehydrated, lethargic, and pale with a blood pressure of 130/70 mm.Hg. The remainder of the physical examination was negative. Examination of a specimen of urine showed a trace of protein, and on microscopy of a centrifuged specimen there were 2 - 3 leucocytes per high-power field, and no casts. His blood findings were as follows: Urea 464 mg./100 ml.; sodium 130 mEq./l.; potassium 6 mEq./l.; carbon dioxide 15·5 mEq./l.; chloride 100 mEq./l.; haemoglobin 9·8 G./100 ml. blood; and erythrocyte sedimentation rate 18 mm. per hour (Wintrobe). Liver-function tests were normal. On expectant treatment there was a symptomatic improvement.

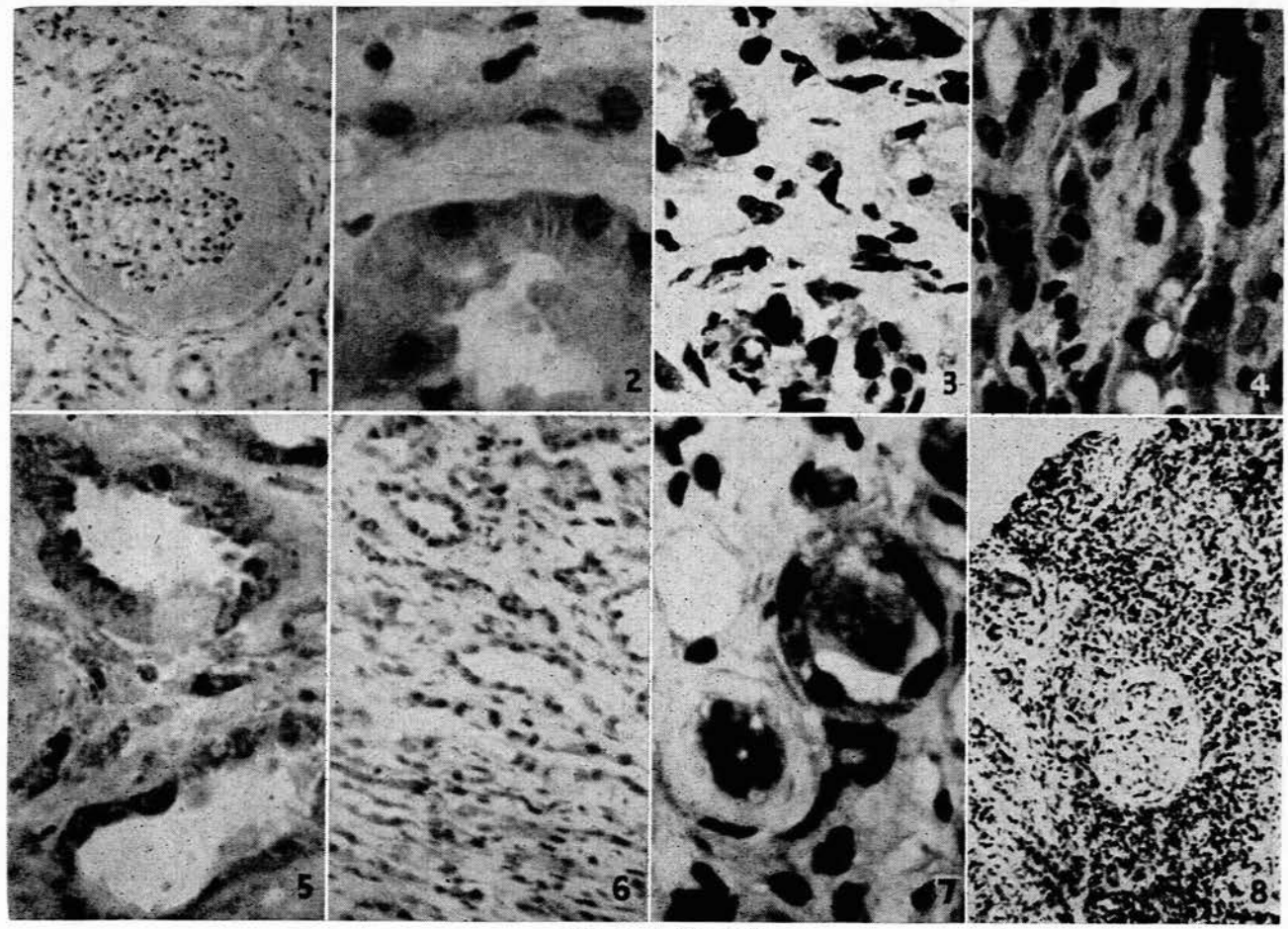
He was readmitted a month later in a stuporose condition having been vomiting persistently for some 3 days. On examination he was extremely pale. His blood pressure was 200/110 mm.Hg and there was slight left ventricular enlargement. There were no localizing signs on examination of the central nervous system, but the plantar responses were both extensor. The fundi were normal. On lumbar puncture the pressure was 110 mm. of fluid and there was no block.

Laboratory Investigations

The cerebrospinal fluid was clear and was normal on microscopic examination. The protein level was 55 mg./100 ml.

Blood. Blood sugar 170 mg./100 ml.; urea 286 mg./100 ml.; sodium 138 mEq./l.; potassium 5·7 mEq./l.; chloride 106 mEq./l.; carbon dioxide 7·6 mEq./l.; calcium 6·8 mg./100 ml. serum; and phosphorus 5·2 mg./100 ml. plasma. Haemoglobin 10·6 G./100 ml.; leucocyte count 33,000 cells/c.mm. No methaemoglobin or sulphaemoglobin was present.

C-reactive protein and LE cells were absent. Plasma proteins 6·8 G./100 ml.; albumin 4·6 G./100 ml.; globulins 2·2 G./100 ml., with a normal electrophoretic pattern. The



Figs. 1—8. See text.

erythrocyte sedimentation rate varied between 33 and 66 mm. per hour (Wintrobe).

Urinalysis. No proteinuria or glycosuria. Microscopic examination of a centrifuged specimen showed 3 leucocytes per high-power field, but no erythrocytes or casts were present.

Renal-function tests (normal values in brackets[9]). Glomerular filtration rate (C_{inulin}) 15·2 ml./min. (125). Effective renal plasma flow (C_{pah}) 114 ml./min. (633). Filtration fraction 0·14 (·198). Addis count,[10] red cells 51,850/hour, white cells 25,700/hour. No casts were seen. Coliform bacilli (sensitive to neomycin and nitrofurantoin) were isolated.

Renal biopsy. A percutaneous needle biopsy was performed and the tissue obtained was examined using the following stains: haematoxylin and eosin, periodic-acid Schiff, Masson's, Perls' and Pickworth's.

The glomeruli showed tamponade — an increase of fluid in Bowman's space — but were otherwise relatively normal (Fig. 1). This fluid was rich in carbohydrate as shown by the PAS stain. Occasional foci of haemosiderin pigmentation were present in the epithelium of Bowman's capsule and the glomerular capillaries. The epithelial cells of the proximal convoluted tubules showed the greatest reaction, but these changes were variable (Figs. 1 - 4). There was eosinophilic degeneration of the tubular epithelium, the cells being swollen and granular and their free margins irregular and desquamating into the tubular lumen (Fig. 2). Frank necrosis of some proximal tubular epithelial cells was observed with evidence of nuclear pyknosis, karyorrhexis and karyolysis. Desquamated tubular epithelial cells were seen lying at lower levels of the nephron, i.e. loops of Henle and distal convoluted tubules (Fig. 3). Occasional groups of cells in the descending loops of Henle showed large vacuoles in the cytoplasm (Fig. 4).

An interesting finding in very occasional proximal epithelial cells was the presence of a fine granular pigment which stained positive with the Pickworth stain. These cells were distended and their cytoplasm filled with pigment (Fig. 5). In the surrounding interstitial tissue there was fine granular material, staining blue with the Pickworth stain. The interstitial tissue showed a marked increase in fibrous tissue, fibroblasts, and scattered foci of nongranular cell infiltration (Fig. 6). Blood vessels throughout the biopsy were normal histologically.

X-rays. The skull, chest and abdomen were normal. Tomograms showed that the kidneys were normal in size, the left being slightly larger than the right.

Retrograde pyelography revealed minor irregularities in the pelvis and calyceal system of each kidney. The urine obtained on catheterizing the ureters contained occasional red and white blood cells, and was sterile.

Progress. Despite conservative therapy there was a steady rise in his blood urea with a gradual deterioration in the patient's general condition after discharge from hospital.

Case 2

Mr. R., aged 31 years, had been suffering from headaches since 1951. For relief of an attack he would take 20 tablets of a preparation containing aspirin (337 mg.), phenacetin (162 mg.) and caffeine (32·5 mg.) per tablet. Four years ago he began taking an analgesic containing 250 mg. phenacetin per tablet to the extent of 60 tablets weekly. Two years later he experienced pain in the right renal angle accompanied by a fever of 104°F. and severe vomiting. A retrograde pyelogram performed at this time showed no abnormality. A similar

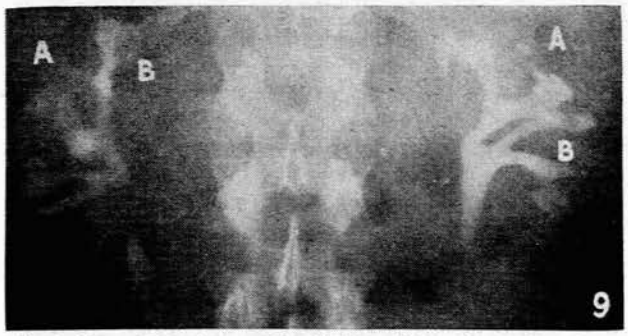


Fig. 9. Retrograde pyelogram (Case 2). There is loss of normal anatomy of all calyces. Particularly on the right side there is clubbing of calyces with extravasation of dye into the renal substance. There is (A) cupping of calyces with rounded filling defects in the necks of calyces (B) which is associated with a dye-filled tract draining such an area (left lowest calyx). These changes are typical of papillary necrosis.

attack occurred in February 1960. A repeat cystoscopy and ureteric catheterization was carried out and debris was removed from both sides. No calculi were present. Since then he had had intermittent loin pain with dysuria and pyrexia and on occasion complained of 'passing pieces of dried blood' in the urine. On histological examination one of these was found to be an extruded necrosed papilla. A retrograde pyelogram at this stage showed the characteristic features of severe papillary necrosis (Fig. 9).

On physical examination his blood pressure was 140/110 mm.Hg. There was no pallor or cyanosis suggestive of methaemoglobinaemia. There were no abnormal physical signs.

Laboratory Investigations

Blood. Haemoglobin 14·4 G./100 ml.; leucocyte count 16,600 cells/c.mm.; erythrocyte sedimentation rate 4 mm. per hour (Wintrobe); sodium 137 mEq./l.; potassium 5·6 mEq./l.; chlorides 104 mEq./l.; carbon dioxide 16·5 mEq./l.; urea 73 mg./100 ml.; serum calcium 4·6 mEq./l.; serum uric acid 3·4 mg./100 ml.; and serum creatinine 2·6 mg./100 ml.

No methaemoglobin or sulphaemoglobin was present.

Liver-function tests. Thymol turbidity 3·0 units; colloidal red +++; cephalin cholesterol flocculation +++; zinc sulphate turbidity 11·4 units; alkaline phosphatase 10·4 units; serum bilirubin 0·4 mg./100 ml.; serum albumin 3·9 G./100 ml.; serum globulin 2·9 G./100 ml.

Urinalysis. No proteinuria or glycosuria. Microscopic examination of a centrifuged specimen showed occasional leucocytes and bacteria per high-power field; Addis count,[10] red cells 114,000/hour, white cells 86,000/hour, casts 1,700/hour. Coliform bacilli, sensitive to streptomycin, neomycin and nitrofurantoin, were isolated.

Renal-function tests. (Normal values in brackets[9]). GFR 32·6 ml./min. (125); ERPF 144 ml./min. (633); T_m PAH 33·4 mg./min. (79); FF 0·23 (·198).

$\frac{GFR}{T_m PAH}$ = 0·95 ml./min. (1·6) (Ratio of glomerular to proximal tubular function).

$\frac{ERPF}{T_m PAH}$ = 4·16 ml./min. (8) (Blood supply of functioning renal tissue).

Renal biopsy. The glomeruli showed some degree of variation in pattern. Some appeared histologically normal while others showed total hyalinization of glomerular capillaries. The glomerular tamponade observed in Case 1 was absent in this biopsy.

The major changes in the tubular system were in the proximal convoluted tubules and loops of Henle where the epithelium showed granular eosinophilic degeneration.

The basement membranes of some of the tubules of the loops of Henle showed marked thickening (fibrosis) (Fig. 7). The tubular epithelial cells within this thickened basement membrane had undergone marked eosinophilic necrosis with karyorrhexis and karyolysis of their nuclei.

There was a golden-brown pigment within the tubular epithelial cells. This pigment was similar to a pigment found in liver-biopsy material as described below.

The interstitial tissue, predominantly in the cortex of the kidney, was increased showing much fibrosis (Fig. 7). There was an area of massive tubular necrosis present indicating necrotizing papillitis.

Focal areas of chronic pyelonephritis were present, consisting of some periglomerular fibrosis, colloid casts in slightly dilated tubules, and marked lymphocytic infiltration (Fig. 8). These areas appeared quite separate from those of chronic interstitial nephritis. There was hyalinization of small arterioles and mild proliferative arteritis of larger vessels. A liver biopsy showed diffuse, fine, golden-brown, granular pigment within the hepatic parenchymal cells. This pigment was similar to that seen scattered in the renal tubular epithelial cells. Investigation of the pigment in these two sites showed negative results for iron, haemoglobin and bile, but gave a positive result with the Schmorls' ferric-ferricyanide method.

The pigment showed a yellow/orange autofluorescence, was feebly PAS-positive and negative to Sudan Black B. These results indicate a highly oxidized lipofuscin.

Progress. Despite vigorous antibiotic therapy and withholding of phenacetin, the patient has continued to pass necrosed papillae in his urine. He has persistently impaired renal function.

DISCUSSION

There is little doubt that renal disease present in the above 2 cases was associated with a large intake of phenacetin-containing drugs. The total amount consumed by the 2 patients described was 7 and 5 kg. in 4 and 9 years respectively. This corresponds well with the quantity ingested by other patients who have been shown to be suffering from this condition.[3,8] Although the association of kidney damage with an excessive intake of phenacetin has been recognized since 1950[1] and a large Continental literature has appeared, the exact role of phenacetin in the aetiology of interstitial nephritis is still uncertain.[4] Some workers[11,12] found that phenacetin alone did not produce predictable pathological changes in experimental animals even when the phenacetin was given in large doses for many months. Tholen,[3] however, found histopathological effects following the administration of phenacetin to mice, but these animals were possibly pre-infected with *Clossiela muris*[13] which may have been responsible for causing pyelonephritis. It was later admitted, on the basis of the existing evidence,[4] that phenacetin administration does render the kidney more susceptible to infection and thus predisposes to the development of chronic pyelonephritis. Sorensen[14] found that patients who had consumed more than 1 kg. of phenacetin over many years did not have impaired creatinine clearance when compared with a control group. However, he did not separate those who had taken the very large amounts of phenacetin usually associated with renal damage from those with moderate consumption.

The pathological changes in the kidneys of patients with phenacetin nephritis are thought by Zollinger[4] to be fundamentally different from those seen in pyelonephritis. He pointed out that in interstitial nephritis there is a diffuse increase in interstitial tissue causing compression of parenchymal tissue and blood vessels without necessarily destroying them. It follows from this that papillary necrosis, which is the other common manifestation of

phenacetin damage to the kidney,[5,7] is probably due to the resulting medullary ischaemia. In the second case described pathological changes of chronic pyelonephritis were present as well as those of interstitial nephritis.

The origin of the interstitial fibrosis is not clear from the pathology of the 2 cases discussed in this paper. Although these probably represent different grades of severity of the condition there is no progressive pattern which would give a clue to the sequence of the histopathological changes. The presence of proximal tubular necrosis may indicate that the primary lesion is cellular degeneration resulting in the escape of toxic material such as phenacetin, its by-products, or altered haemoglobin pigment into the interstitial tissue, as has also been suggested by others.[3,16]

In the first case described there was marked proximal tubular epithelial necrosis. As seen in Fig. 3 the epithelial cells may become markedly distended, apparently from the accumulation in the cytoplasm of the cells of a granular pigment staining positively with the Pickworth stain. Owing to the presence of methaemoglobinaemia and sulphaemoglobinaemia in patients with phenacetin intoxication, this pigment is probably a haemoglobin product. The accumulation of the pigment may have a deleterious effect on the function of the cells. Gilman *et al.*[17] have shown that the renal tubular epithelium is extremely susceptible to agents which combine with or oxidize sulphydryl groups, and Harrison *et al.*[18] have demonstrated that methaemoglobin may act as an oxidant and thus may possibly catalyse the oxidation of sulphydryl groups in the renal epithelial cells. Moreover, Bing[19] has shown that in acidotic dogs methaemoglobin solutions produce renal injuries characterized by hydropic degeneration in the proximal convoluted tubules and necrosis in the distal convoluted tubules.

The alternative suggestion is that phenacetin or its derivatives have a direct toxic effect on the intersitial tissue causing fibrosis and thus resulting in secondary ischaemia of the renal tubules. This hypothesis is compatible with the results of renal-function tests in our patients.

It has been put forward that a contaminant, acetic-4-chloranilide, formed during the manufacture of phenacetin from 4-nitrochlorbenzol, may be the toxic substance responsible.[13] The reason for this suggestion is that it is only since this manufacturing method has been in use that the renal toxicity of phenacetin has been recognized. However, phenacetin made in accordance with the *British Pharmacopoeia,* in which the acetylation of phenetidin is described, would not contain this contaminant.

In the absence of gross urinary-tract infection the urine characteristically shows little abnormality.[7] The low Addis counts in both patients and the persistently low protein excretion (trace to one-plus albumin) confirms these findings. However, in patients who have papillary necrosis, blood clot or tissue which consists of necrosed papillae may be passed in the urine, as in the second case discussed here.

There is no consistent pattern of functional renal damage. The filtration fraction may be increased or decreased. The finding of a diminution of glomerular filtration rate in the presence of normal glomeruli histologically is in favour of glomerular ischaemia. An increased filtration fraction until late in the disease is also compatible with this observation. In the second case it would seem that there was a greater reduction in plasma flow and glomerular filtration than in functioning tubular mass as measured by the T_m PAH. This could be interpreted as evidence against primary tubular disease with consequent effects on the interstitial tissue.

In the absence of necrotizing papillitis there are no radiological signs helpful in the diagnosis of phenacetin nephritis. Possibly at a certain stage in the progression of the disease the unusually normal size of the kidneys, relative to the degree of uraemia, may be helpful. This is contrasted with the contracted kidneys seen in a comparable degree of uraemia caused by chronic pyelonephritis.[16] This was so in the first case, where it was noted that the kidneys were normal in size when the blood-urea level was 180 mg./100 ml. In patients with papillary necrosis the appearance on intravenous or retrograde pyelography may be diagnostic. As described by Rutner,[15] in the papillary form of the condition there is penetration of the contrast medium into the area of necrosis producing haziness and irregularity of the calyceal cup, and late sequestration of the necrosed area may occur (as seen in Case 2). In the medullary form of the disease there is an irregular sinus tract leading from the calyx to the medullary cavity. Furthermore, when the necrosed material becomes encrusted with calcium salts, the radiological appearance of a calculus with a translucent centre may be simulated.

Owing to the nature of the pathology it is not surprising that treatment is unsatisfactory. Withdrawal of the drug is essential to prevent progression of the lesion, and antibiotics are administered because of the complicating pyelonephritis.

The other toxic manifestations of phenacetin have been well documented, especially those caused by methaemoglobinaemia, sulphaemoglobinaemia, and haemolysis,[20-22] the latter particularly occurring in the presence of renal insufficiency. Furthermore, a case of auto-immune haemolytic anaemia associated with acute renal failure has been described.[23] However, in contradistinction to the other complications, this followed small doses of phenacetin.

It is difficult to assess accurately the amount of phenacetin consumed in this country. There are approximately 61 proprietary preparations available containing phenacetin, usually in association with aspirin and caffeine, and the total consumption of these as well as the pharmacopoeial preparations of phenacetin must be tremendous. Over and above this, figures obtained from one sick benefit fund show that 2,000,000 G. of phenacetin are ordered annually for consumption by their 400,000 members, of whom approximately 160,000 are adults. This represents an annual consumption among the adults of 12,500 mg. of phenacetin each. The effect of the drug in producing headache, nervous irritability, depression, tremor, weakness and debility may encourage further ingestion for the relief of the symptoms which it has produced,[16] and it is this feature which may be important in producing a form of habituation. Moreover, as Moolten and Smith[16] point out, phenacetin habitues resemble narcotic addicts in the secretiveness with which they surround their compulsive use of the drug.

The problem of abuse of phenacetin has been intensively

investigated, particularly in Switzerland and Denmark. It has been stated that in Zurich nearly 25% of patients with pyelonephritis give a history of phenacetin habituation. The consumption of phenacetin in Switzerland is of the order of 45,000 kg. annually.[24] This problem has been emphasized by Spuhler[25] and confirmed by Sandring and Welin,[26] who collected 42 cases of patients who abused phenacetin; 28 of these had renal damage and 4 died in uraemia with postmortem findings of chronic interstitial nephritis and papillary necrosis. In the light of this it is chastening to note that the first case of phenacetin nephritis in the USA was only reported in 1960[16] despite the fact that the average consumption of phenacetin there is said to be 22 G. per person annually.[27]

It would seem from the figures which are quoted above, that South Africans consume a similar amount of phenacetin per head of the population, and thus there must be numerous cases of chronic toxic renal damage from this drug which are being overlooked or misdiagnosed. A patient with phenacetin nephritis was recently reported[28] in South Africa, the condition having been found at necropsy. Perhaps the most disturbing factor is that this potential source of serious ill-health is freely available to the public. Moreover, modern advertising techniques have stimulated the sale of these drugs to reach enormous proportions. Repeated pleas have been made in vain by several authors recommending that the sale of the drug should be restricted in some way. It is obvious that while one or two phenacetin-containing tablets will certainly not harm anyone, its ready availability renders it a potentially dangerous drug.

It would seem that the use of phenacetin is based mainly on tradition and that it could be removed from analgesic tablets without decreasing their efficiency. Moreover, there is little pharmacological basis for adding phenacetin to preparations of aspirin when an analgesic effect is required.

Both phenacetin and its forerunner, acetanilid, were introduced into therapeutics in a rather fortuitous manner.[29,30] Perhaps now, some 75 years later, these drugs, in contrast to their unheralded arrival, should be actively removed from their position as safe household remedies.

SUMMARY

1. Two patients with chronic renal disease associated with the prolonged intake of large quantities of phenacetin are described. The diagnoses were confirmed on renal biopsy.

2. The effects of phenacetin habituation are discussed and reasons are given for the abandonment of phenacetin as a therapeutic agent.

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