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The nephrotoxicity of analgesics

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IN recent years there has been increasing suspicion that prolonged or excessive use of analgesics may result in progressive renal damage very similar to that produced by chronic pyelonephritis. Phenacetin (acetophenetidin) has been widely incriminated as the offending drug, mainly because it was common to all the analgesic mixtures mentioned in the early reports. Histologically and functionally the renal lesions are predominantly tubular, with interstitial fibrosis, tubular degeneration and atrophy and a high incidence of papillary necrosis and pyelonephritis (Rubenstein, Abrahams, Stables & Levin, 1964).

PHENACETIN

Although phenacetin has been present in analgesic mixtures abused in most recent reports of chronic interstitial nephritis, no case has yet been reported in which phenacetin was the only drug taken. Other drugs, including the salicylates, the antipyrine group, caffeine, codeine and barbiturates have also been taken concurrently, and the potential toxicity of these other drugs does not seem to have been adequately assessed. It is also possible that drugs other than those already mentioned may cause renal damage after prolonged use. Kasanen & Vasama (1964) noted prolonged use of primidone (Mysoline) and corticosteroids respectively in two patients with unexplained papillary necrosis, and only 14 of the 44 cases of chronic interstitial nephritis reported by Spühler & Zollinger (1953) gave a history of abuse of analgesics. The latter authors felt that sulphonamides and antibiotics were responsible for the renal lesions and in fact did not even mention phenacetin. Similar lesions appear to arise spontaneously in cats (Lucke & Hunt, 1965), mice and rats (see Studer, 1965).

While the "common denominator" theory may implicate phenacetin as a cause of interstitial nephritis, it certainly does not exonerate other drugs taken concurrently. A condition gains an often unjustified "respectability" when a name is given to it, and once the name "phenacetin nephritis" was established, everyone felt much better, but the incentive to look for other causes seemed to be lost. The present situation is far from satisfactory. There is substantial epidemiological evidence to support the theory that abuse of analgesics containing phenacetin *and other drugs* can, in some instances, cause renal damage. It has been argued that patients with chronic bacterial pyelonephritis are likely to suffer from headaches and therefore to abuse analgesics, and that the frequent association between pyelonephritis and analgesic abuse is therefore coincidental (Reubi, 1958, and others). This is unlikely to explain all cases because some do not have clinical evidence of urinary tract infection during their illness, and analgesic abuse has preceded any renal or other

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symptoms, including headaches. In addition, identical renal lesions have occurred in patients without headaches abusing analgesics because of arthritis (Jacobs, 1964; Tan, Rabbino & Hopper, 1964; Beales, 1965; Kennedy, 1965, and many others) or to increase performance at work (Grimlund, 1963).

The association between renal damage and abuse of analgesics is obscured and complicated by the following facts which must be satisfactorily explained by any acceptable theory of the mechanism of toxic action.

1. Extensive studies in animals treated with phenacetin have failed in general to induce renal lesions comparable to those seen in man. This work has recently been reviewed by Studer (1965).

2. Many persons abusing analgesics (including mixtures containing phenacetin) do not seem to suffer renal damage.

3. Many patients with renal impairment associated with abuse of analgesics have had evidence of pyelonephritis. The relationship between urinary tract infection and analgesic nephritis is not clear. Further complication arises from the difficulty in histological distinction between chronic pyelonephritis and analgesic nephritis.

4. With the exception of one isolated report (Nordenfelt & Ringertz, 1961), females have been affected more frequently than males. This is also true in chronic pyelonephritis, but inadequate information is available to indicate the sex ratio of analgesic abuse itself.

5. There are geographical inconsistencies. The reported incidence of analgesic nephritis has been much greater in Scandinavia and Switzerland than in some other countries despite apparently similar overall national consumption of phenacetin (Ross, 1962).

The incidence of "analgesic nephritis" would appear to be low in this country, and the first case was not published until 1964 (Sanerkin & Weaver). However, a total of nine cases has now been recorded (Sanerkin, 1964; Jacobs, 1964; Brown & Pell-Ilderton, 1964; Beales, 1965; Kennedy, 1965), and I myself have already seen 27 cases in Aberdeen including one case of interstitial nephritis in a patient treated with *p*-aminosalicylic acid for tuberculosis. Together with a further group of patients whose analgesic histories have not yet been established, the total number may exceed 40. The true incidence may therefore be high.

p-Chloracetanilide, a usual contaminant of phenacetin, has been suspected of nephrotoxicity. Harvald, Valdorf-Hansen & Nielsen (1960) found that the administration of phenacetin containing 0·13% and 0·30% of *p*-chloracetanilide to patients with advanced renal damage caused a greater increase in the urinary excretion of red blood cells as measured by Addis counts than when pure phenacetin was given. On the other hand, a significant increase in "leucocyte" excretion occurred only with the smaller dose of contaminating *p*-chloracetanilide and the validity of these findings has been questioned (Kup, 1960).

Surprisingly little work seems to have been done to follow this lead and it was not until last year that Schnitzer, Smith & Golden (1965) published

their work on the chronic toxicity of *p*-chloracetanilide in rats. They found no evidence of renal toxicity in a 22 week study, but did observe profound effects on the blood forming tissues. Although this question must still remain open, it seems unlikely that analgesic nephritis is caused by this compound, but it may contribute to the haemolytic anaemia often encountered.

Perhaps we should think about this problem in a different way. *If* phenacetin is the sole nephrotoxic agent, then it seems clear that it can affect only a minority of persons abusing it. To ascertain the mechanisms of toxicity thus becomes more difficult, as it is not unreasonable to suppose that only a minority of experimental animals treated with phenacetin would develop renal lesions. The study of individual animals rather than groups might therefore be more fruitful, but practical considerations limit this approach. There is also the possibility that phenacetin is only nephrotoxic in the presence of other drugs, and further studies might be worth while using more drug combinations. If other drugs taken together with phenacetin are primarily responsible for the renal damage (as for instance the anti-inflammatory drugs or caffeine), some of the difficulties in accepting phenacetin as a cause of analgesic nephritis might be explained.

RECENT FINDINGS

The assumption has been made that if a drug or its metabolites is toxic and causes tubular damage, cell death may occur and result in an increase in the number of *renal tubular cells* appearing in the urinary sediment. Since it is difficult to differentiate reliably between renal tubular cells and leucocytes, these cells are usually counted together as "non-squamous white cells". The large spontaneous fluctuation in the output of leucocytes (Prescott, 1966) therefore makes it difficult to show any but gross changes in the excretion of renal tubular cells. For this reason the Addis count is a relatively crude and insensitive method. By the use of the diaminofluorene-peroxide-phloxine method (Prescott & Brodie, 1964) it is possible to stain these cells differentially and simply, so that small changes in the excretion of renal tubular cells can be demonstrated.

Groups of healthy volunteers (5 male, 5 female) were given the following drugs orally in four divided daily doses: acetylsalicylic acid (aspirin) 3·6 g, phenacetin 3·6 g, A.P.C. (aspirin 1·8 g, phenacetin 1·8 g, caffeine citrate 1·2 g), paracetamol (acetaminophen) 3·6 g, caffeine citrate 2·4 g and a placebo. Excretion rates of renal tubular cells, leucocytes and red blood cells were determined during a 5 day control period and again during 5 days of drug administration (Prescott, 1965a).

The changes in the excretion of renal tubular cells are shown for each treatment group in Table 1. The mean control counts for each group shown in the first column are the mean total renal tubular cells excreted between midnight and 4.00 p.m. during the 5 day control period. The corresponding counts during the treatment periods are shown in the next column. A great increase in renal tubular cells occurred in the aspirin group, and moderately large increases were seen in the A.P.C., phenacetin and caffeine groups. Since only a small (but statistically significant)

TABLE 1. MEAN TOTAL RENAL TUBULAR CELL COUNTS

Tablets administered	Control counts (thousands)	Drug counts (thousands)	% Increase	P*
Placebo	5,814	6,153	+6	N.S.
Paracetamol†	5,645	6,286	+11	<0·05
Caffeine	6,308	8,660	+37	<0·01
Phenacetin	6,064	10,494	+73	<0·05
A.P.C.	6,012	11,435	+90	<0·01
Aspirin	6,065	57,294	+945	<0·01
Mean control count	5,900			
95% confidence interval for control counts	4,845–7,015			

* Two-tailed tests.
† Observations on 21 subjects.

increase took place in the paracetamol group, a further 11 subjects (5 male, 6 female) were given paracetamol, with identical results. Significant increases in the excretion of red blood cells occurred only in the groups receiving aspirin, A.P.C. and caffeine, and none of the drugs appeared to have any significant effect on the excretion of leucocytes.

In this original study, only two of the ten subjects taking phenacetin showed a great increase in renal tubular cells. The response of one of these subjects is shown in Fig. 1. Subsequent studies have resulted in

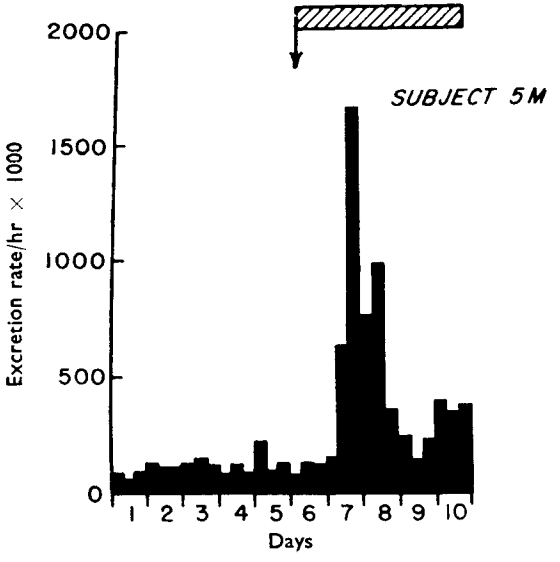

FIG. 1. The effect of phenacetin on the excretion of renal tubular cells in a normal male volunteer. Hatched area: phenacetin 3·6 g/day.

similar marked increases in four of 27 normal persons (15%) given 3·6 g phenacetin daily. In contrast, of 31 persons taking the same dose of paracetamol, only one showed an appreciable increase, and this was much less than the responses seen with phenacetin. In addition, three subjects responding to phenacetin were subsequently challenged with paracetamol.

TABLE 2. RENAL TUBULAR CELL EXCRETION IN 3 SUBJECTS GIVEN PHENACETIN AND PARACETAMOL IN SEPARATE STUDIES

	Phenacetin			Paracetamol		
Subject	Control count (thousands)	Treatment count (thousands)	% Increase	Control count (thousands)	Treatment count (thousands)	% Increase
1	8,792	23,100	+163	8,168	8,352	+ 2
2	6,956	12,372	+ 78	5,336	4,372	−18
3*	8,612	18,592	+116	9,888	15,512	+57

* All subjects received 3·6 g of phenacetin or paracetamol daily for 5 days, except subject 3, who could only tolerate 2·7 g phenacetin.

In two there was no change in cell excretion and in the other, already mentioned above, the increase during the administration of paracetamol was much less than when phenacetin was given. These data are given in Table 2. It is interesting that in this subject, side-effects limited the dose of phenacetin to 2·7 g daily, although 3·6 g paracetamol was easily tolerated. The effect of phenacetin on the renal tubular cell excretion of a patient thought to have analgesic nephritis is shown in Fig. 2. It can be seen that there was a progressive rise in the renal tubular cell counts.

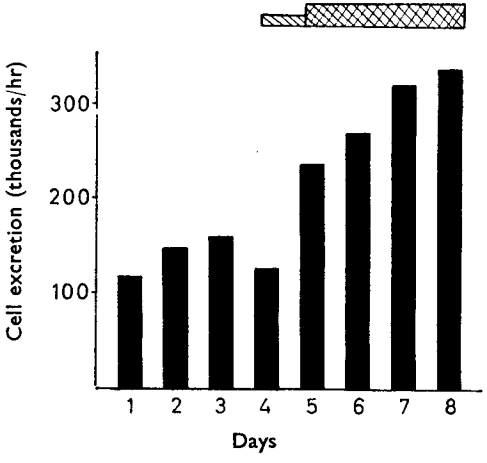

FIG. 2. The effect of phenacetin on renal tubular cell excretion in a patient thought to have "analgesic nephritis". Hatched area: 1·8 g phenacetin daily. Cross-hatched area: 3·6 g/day.

METABOLITES OF PHENACETIN

Since phenacetin is rapidly and extensively metabolised to paracetamol (Brodie & Axelrod, 1949; Welch, Conney & Burns, 1966), this relative lack of effect with paracetamol is of great interest and suggests that either phenacetin itself, or metabolites other than paracetamol, are responsible for this effect. Paracetamol, *p*-phenetidine, 2-hydroxyphenacetin, *S*-(1-acetamido-4-hydroxyphenyl)cysteine and other amines have been identified as metabolites of phenacetin in man (Brodie & Axel-

rod, 1949; Burns & Conney, 1964; Jagenburg & Toczko, 1964; Klutch, Harfenist & Conney, 1966) (Fig. 3), but apart from paracetamol little is known of the renal toxicology of these or other unknown metabolites.

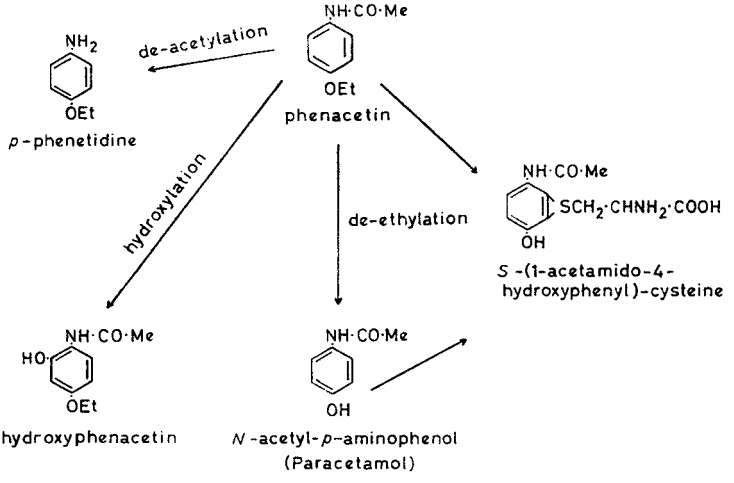

FIG. 3. The metabolism of phenacetin in man.

Preliminary studies (Prescott & Conney, unpublished) have shown no difference in the maximum plasma concentration or half-life of phenacetin and paracetamol after oral administration of phenacetin in subjects showing a marked rise in renal tubular cell excretion compared with those who did not. In nine subjects the mean plasma half-life of phenacetin was 67 min, with a range of 50–90 min. Two subjects with renal tubular cell responses to phenacetin had plasma half-lives of phenacetin of 60 and 70 min. The studies were repeated after drug treatment for 5 days, and although there was wide variation in the peak plasma concentration of phenacetin in the same individual, the half-life was remarkably constant. The combined data are given in Fig. 4.

These findings suggest that only a minority of normal adults is susceptible to the acute renal effects of phenacetin. This effect seems unrelated to the plasma concentrations or half-life of phenacetin, and therefore is unlikely to be due to variations in absorption or to a threshold effect. The possibility that this variation in susceptibility is due to some other metabolic differences, such as the formation of toxic amine metabolites, merits consideration. Although paracetamol is extensively conjugated, de-acetylation and re-acetylation occur in several species and amine metabolites can be formed; in the cat they may account for more than 10% of the administered dose (Welch, Conney & Burns, unpublished). It must be stressed however that although paracetamol apparently does not have a marked nephrotoxic effect in man, it cannot be assumed that it lacks long term toxicity. Caution must also be exercised generally in relating the acute drug effects under discussion to those occurring clinically

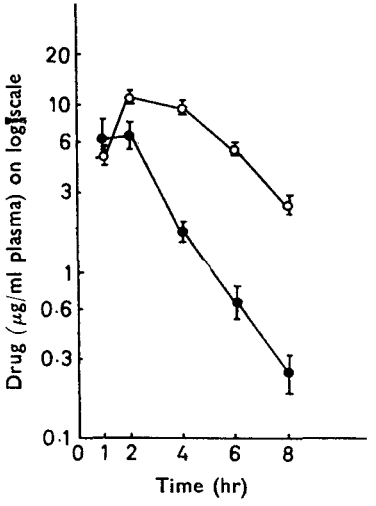

FIG. 4. The mean plasma levels of phenacetin (●—●) and paracetamol (○—○) in 9 normal individuals after 1·8 g of phenacetin by mouth.

following chronic administration. That only a minority of persons is susceptible to the acute renal effects of phenacetin is however in agreement with clinical observations and the possibility of a genetically determined abnormality of phenacetin metabolism is raised. The cell excretion data described are consistent with polymorphism in the renal response to phenacetin (Price-Evans, D., personal communication), and there have been reports of several cases of analgesic nephritis occurring in the same family (Poli, 1955; Ask-Upmark, 1960). One remarkable family history was described by Grimlund (1963) in which six of 11 siblings had analgesic nephritis; three died in uraemia, and several had gastric or duodenal ulceration.

SALICYLATES

Salicylates have long been known to cause renal impairment, and there have been clinical reports of haematuria, proteinuria, increased cells in the urinary sediment, azotaemia, impaired phenolsulphonphthalein excretion, fluid and salt retention, oedema, aminoaciduria, oliguria, anuria, acute tubular necrosis, and papillary necrosis following salicylate administration (see review by Hanzlik, 1927; Lipman, Krasnoff & Schless, 1949; Locket, 1957; Campbell & MacLaurin, 1958; Granville-Grossman & Sergeant, 1960; Harvald, 1963; Scott, Denman & Dorling, 1963; Ben-Ishay, 1964). Tubular atrophy and dilation, interstitial tissue proliferation, decreased resistance to infection, and papillary necrosis have been produced in rats treated with aspirin (Clausen, 1962, 1964; Fellers, Pradilla & Craig, 1965). It is surprising therefore that more attention has not been paid to the renal effects of salicylates. Scott & others (1963) drew attention to the effect of salicylates on the exfoliation

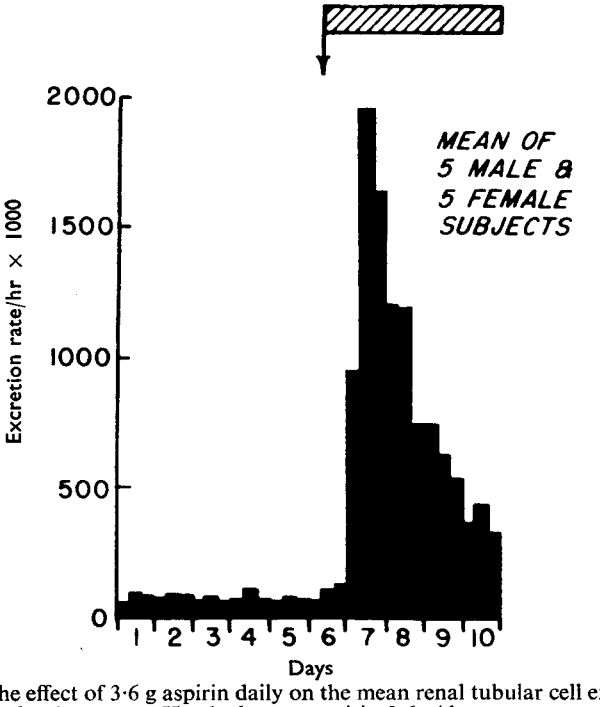

FIG. 5. The effect of 3·6 g aspirin daily on the mean renal tubular cell excretion rates of 10 normal volunteers. Hatched area: aspirin 3·6 g/day.

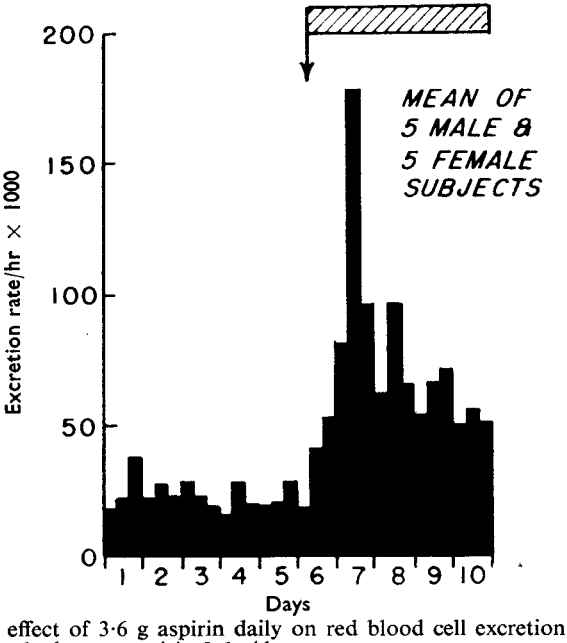

FIG. 6. The effect of 3·6 g aspirin daily on red blood cell excretion in 10 normal subjects. Hatched area: aspirin 3·6 g/day.

of renal tubular cells, and in my recent work, I found that a dramatic increase in the renal tubular cell excretion took place in every subject receiving aspirin. The mean increase in renal tubular and red blood cells is shown in Figs 5 and 6. The increase in both cell types was much greater in females than in males, and this is shown in Figs 7 and 8, which show the individual changes in cell excretion expressed as a percentage of the control counts.

Scott & others (1963) felt that the increased cell excretion was only a transient effect and therefore was unlikely to cause renal drug damage on

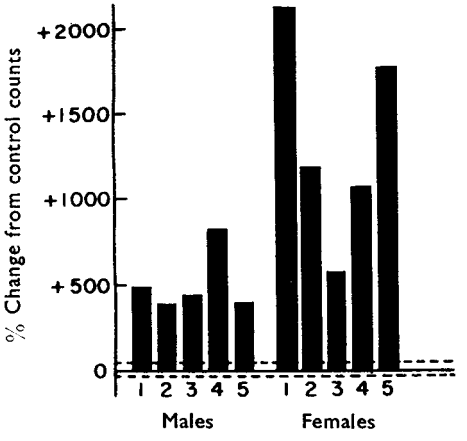

FIG. 7. Individual changes in renal tubular cell excretion in subjects given aspirin 3·6 g daily for 5 days.

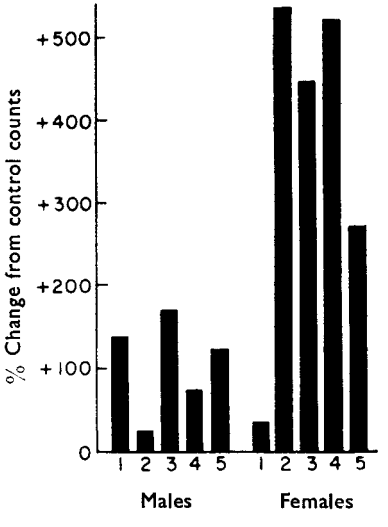

FIG. 8. Individual changes in red blood cell excretion in subjects given aspirin 3·6 g daily for 5 days.

chronic administration. To investigate this further, five subjects (four male, one female) were given 3·6 g aspirin daily for 3 weeks and the excretion of renal tubular cells and red blood cells during this period was compared with the control periods one week before and one week after treatment. The effect on renal tubular cell excretion is shown in Fig. 9

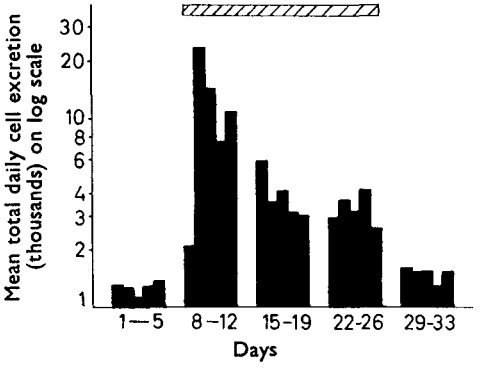

FIG. 9. The effect of aspirin (3·6 g daily for 3 weeks) on the mean excretion of renal tubular cells in 5 subjects (4 male, 1 female.) Hatched area: aspirin 3·6 g/day.

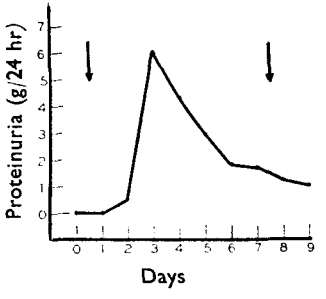

FIG. 10. Mean values for a group of 29 patients with early syphilis receiving bacitracin (400 units/kg) every 5 hr for seven days. Arrows represent beginning and end of treatment.

and it can be seen that although the maximum increase occurred during the first week, the counts were still well above the control levels at the end of the third week of treatment. This phenomenon is not restricted to the salicylates, and an identical response to caffeine was described by Vinci (1914). Renal damage produced by bacitracin results in a rise in urinary cell excretion, proteinuria and impaired renal function (Miller, McDonald & Shock, 1950). In Fig. 10 it can be seen that the maximum urinary protein loss occurs on the second day of treatment, and subsequently falls despite continued drug administration (cf. Fig. 5).

A high incidence of peptic ulceration has been noted in patients with renal damage associated with analgesic abuse. Salicylates are known to cause gastric ulceration and salicylate-induced gastrointestinal bleeding may contribute to the anaemia. Furthermore the unexplained acidosis

reported in many cases of analgesic nephritis could be due to the ingestion of large amounts of salicylates in the presence of renal failure. Phenacetin does not cause acidosis or peptic ulceration.

Patients with rheumatoid arthritis often consume large quantities of analgesics, especially salicylates. Clausen & Pedersen (1961) found that 23% of a series of 80 patients with rheumatoid arthritis had post-mortem evidence of papillary necrosis, and Brun, Olsen, Raaschou & Sørensen (1965) found that nine out of 32 patients with rheumatoid arthritis had chronic interstitial nephritis by renal biopsy. Sørensen (1963) and Allander, Bucht, Lövgren & Wehle (1963), were unable to find any correlation between renal impairment and phenacetin consumption in such patients. Sørensen, however, showed that renal function (as measured by endogenous creatinine clearance, which does not measure tubular function) was progressively impaired with increasing severity of the rheumatoid arthritis. Since those patients with the more advanced arthritis were likely to have received more drugs than those with milder disease, it cannot be stated yet whether the renal lesions (including interstitial nephritis and papillary necrosis) found in these patients are due to the underlying arthritis or induced by analgesic or other drugs. There have been no studies reported in which an attempt has been made to correlate renal damage with salicylate consumption in patients with rheumatoid arthritis.

Apart from the renal effects of the salicylates, other serious toxic effects include gastrointestinal bleeding, ulceration and perforation (Douthwaite & Lintott, 1938; Alvarez & Summerskill, 1958; Duggan, 1965, and others), exfoliation of cells from the gastric mucosa (Croft, 1963), "allergic" phenomena (Locket, 1957; Viguie & Gardies, 1963), aplastic anaemia (Erslev & Wintrobe, 1962; Snijder, Wijnja & Nieweg, 1965) and agranulocytosis (Pretty, Gosselin, Colpron & Long, 1965). In view of the tremendous consumption of salicylates, it is surprising that serious toxic effects are not encountered more frequently.

ANTIPYRINE GROUP AND OTHER ANTI-INFLAMMATORY AGENTS

As salicylates have been largely replaced by the antipyrine group in analgesic mixtures in many European countries with a high incidence of analgesic nephritis, it has been argued that salicylates cannot cause chronic interstitial nephritis. This argument is not valid if the anti-inflammatory drugs which replace salicylates in these mixtures have similar nephrotoxic properties. This indeed may be the case. Antipyrine, aminopyrine, and related pyrazolones are commonly substituted, and we find that the same formidable list of nephrotoxic effects as seen with salicylates has in fact been encountered with the antipyrine group (Lotze, 1934; Aosima, 1940; Axelsson, 1958; Fazekas, Fazekas & Bertok, 1960; Eknoyan & Matson, 1964). The related anti-inflammatory drug phenylbutazone has similar nephrotoxic effects (Lipsett & Goldman, 1954; Steinbrocker, Neustadt & Ehrlich, 1954; Weisman & Bloom, 1955; Bruck, Fearnley, Meanock & Patley, 1954) in addition to other unpleasant effects such as agranulocytosis (see Gsell, 1954). The reported renal

effects of the salicylates, antipyrine and aminopyrine, and phenylbutazone include haematuria, increased cells and casts in sediment, proteinuria, sodium chloride, fluid and nitrogen retention, oliguria, anuria, tubular necrosis and except for phenylbutazone, papillary necrosis. These drugs share many corticosteroid-like actions, and like the steroids, salicylates and phenylbutazone can cause gastric ulceration and fluid retention. Indomethacin, a newer and chemically dissimilar anti-inflammatory drug also seems to cause peptic ulceration and fluid retention, and flufenamic acid (and to a lesser extent mefenamic acid) causes tubular damage and papillary necrosis in animals. It is interesting that many anti-inflammatory agents have been shown to displace corticosteroids from plasma proteins (Maickel, Miller & Brodie, 1965) but it has not been established that this effect is related to anti-inflammatory or toxic effects. Anti-inflammatory action could be the link between toxic renal damage and subsequent pyelonephritis if susceptibility to infection is reduced—an attractive but as yet unproven theory.

CAFFEINE

Finally it is necessary to consider caffeine. This drug has been present in almost all the analgesic mixtures associated with interstitial nephritis and papillary necrosis, and epidemiologically should be as suspect as phenacetin. It is a gastric irritant, capable of producing gastric ulceration (Pfeiffer & Gass, 1962) and there is both clinical and experimental evidence to indicate nephrotoxicity (Vinci, 1914; Wendt, 1938; Boyd, 1959; Boyd, Dolman, Knight & Sheppard, 1965; Prescott, 1965b) Little attention seems to have been given to the possibility that caffeine, abused in analgesic mixtures, or in beverages could have any part in the aetiology of analgesic nephritis. In the present study most persons receiving caffeine showed a rise in renal tubular and red blood cell excretion, although there was no appreciable sex difference in response. Caffeine, like the salicylates, has teratogenic effects (Nishimura & Nakai, 1960; McColl, Globus & Robinson, 1965; Trasler, 1965), and the stimulating effect on the central nervous system would seem a likely explanation of habituation to analgesic mixtures.

SUMMARY

In summary the situation is very confused, but certain points emerge. *If* phenacetin is the only drug responsible for analgesic nephritis, then apparently only a minority of persons abusing it is affected. The evidence discussed supports this hypothesis and suggests that this susceptibility has a metabolic basis. Many more sophisticated experiments will be necessary to establish and demonstrate the precise mechanisms of toxicity. Alternative or additional nephrotoxicity may be contributed by the salicylates, the antipyrine group of drugs, caffeine, and perhaps other drugs.

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Discussion

Dr. A. W. S. Sørensen. In five investigations, I have examined the relationship between consumption of analgesic agents and changes in the kidneys. In a consecutive evaluation of 3 days creatinine clearance in 790 patients, 244 of whom had rheumatoid arthritis, no relation between clearance and consumption of analgesics was found, especially in the groups with heavy consumption where such changes as chronic interstitial nephritis and chronic pyelonephritis were suspected. In 191 women, 50 of whom had rheumatoid arthritis and the remainder other diseases, but all without previous kidney disease or urinary tract complaints, there was no relation between the specific gravity of the urine and the intake of analgesics. In kidney biopsies from 32 patients with rheumatoid arthritis no relation was found between intake of analgesics and the histological picture. In a consecutive controlled investigation, over one year, of the incidence of bacteriuria (more than 100,000 organisms per ml), among 126 consumers of analgesics, compared with the same number who had not taken them, we found the same incidence of 20% in both groups. In a consecutive controlled X-ray study of 1,000 patients from all departments of Copenhagen Commune Hospital, in 1963–64, I found 167 patients (about 17%) with a chronic analgesic consumption. Among these, 8% had papillary necrosis compared with 5% among the other 833 patients. These figures are high and must be reduced because there were cases with obstructions in the urinary tract.

As a clinician I think this problem now requires a quantitative dimension. I should like to know the prevalence of so-called chronic pyelonephritis,