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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,

as we already know the prevalence of asymptomatic bacteriuria and kidney diseases of all kinds among consumers in different geographical regions, without regard to any causality between analgesic agents and renal diseases. I think such a comparison will give the wanted dimension. May I ask Dr. Prescott if he is able to exclude that the increasing desquamation of cells in the tubules in his investigations is a chemical acceleration of a normal phenomenon which is self-limiting? Take the work of Scott and his colleagues (1963)* and the Fig. 9 in the present paper, for instance. Desquamated cells will always be found in the lumen of tubules in a so-called normal biopsy. I agree that these studies of short duration—days or weeks—cannot tell us anything about what will happen in the kidneys during 10, 20 or 30 years consumption of analgesic agents.

Dr. A. Kennedy. My colleague, Dr. Davies, and I have sought answers to the questions: does necrosis in the kidney necessarily produce renal tubular cells in the urine? Does an increase in cells in the urine necessarily indicate necrosis in the kidney? Is there any quantitative relation between these two conditions, and are they directly proportional to one another? We have used known nephrotoxic substances in experimental animals so that we could examine the urine, kill the animals and then examine the kidneys. We have used mercuric chloride which is known to damage the proximal convoluted tubules. A single dose of about 1 mg/kg of mercuric chloride given to rats produced, within 28–48 hr, about a hundredfold increase in the output of cells in the urine, and histologically there was a minimal necrosis in the proximal convoluted tubules. We have also used ethylenimine which causes necrosis of the papillae, a lesion not unlike that described in analgesic nephritis in man. When given to a rat in a dose which is not immediately fatal (it is also a neurotoxic) the papillae can be destroyed and a lesion, histologically very much more severe than the mercury induced lesions of the cortex, is produced. But this produces only about a 10- or 20-fold increase in the output of cells. Not only is the cell excretion not directly proportional to the degree of damage, but it may also depend on the site in the kidney which is damaged by the agent. We would agree that those toxic agents causing necrosis will increase the number of cells in the urine, but we have not yet decided whether it is possible to produce a "cell-uria" in the absence of necrosis. One suggestion why the urinary cell count rises and then falls is that in some kidneys aspirin or phenacetin or a similar drug knocks out older cells which are then desquamated, leaving the younger and more resistant cells behind, so that the cell count gradually falls to normal again.

Is the same sort of cell excreted in response to aspirin that is excreted in response to phenacetin?

Dr. N. G. Sanerkin. The desquamation of renal tubular epithelial cells after the administration of aspirin, phenacetin, or other drugs has no real relevance to the renal lesions occurring in prolonged analgesic abuse. I believe that in such persons the primary lesion is renal papillary or medullary necrosis and that the renal parenchymal contraction ("chronic

* See p. 353 for references.

interstitial nephritis") is merely secondary to the medullary changes (Sanerkin, 1966). Renal medullary necrosis causes disruption of important medullary structures, including Henle's tubules, interrupting nephronal function, and the vasa recta, producing ischaemic damage in the cortex, mainly by interfering with the venous return; it also predisposes the kidney to superimposed infection. As a result of these processes the related cortex undergoes atrophy and fibrosis. An identical view has just been independently expressed by Dawborn, Fairley, Kincaid-Smith & King (1966) who conclude that most of the changes of so-called chronic interstitial nephritis are a direct consequence of renal papillary necrosis, and suggest that the term "chronic interstitial nephritis" should be discarded in cases of analgesic nephropathy. Dr. Kennedy finds that a chemical like carbon tetrachloride, which is toxic to the proximal renal tubular epithelium, causes heavy desquamation of tubular epithelial cells, whereas vinylamine, which produces renal papillary necrosis, causes no significant epithelial desquamation. Obviously the solution to the problem of chronic analgesic nephropathy must be sought not in the immediate effect of suspected drugs on the renal tubular epithelium but in their long-term effect on the renal medulla itself.

Dr. J. T. Scott. I should like to take up this question of aspirin and kidney damage. I am not so concerned about phenacetin, but aspirin is a very useful analgesic and anti-inflammatory drug and we should be careful before we incriminate it in this respect. Now as we showed a few years ago (Scott, Denman & Dorling, 1963), anyone taking aspirin passes a large number of tubular cells in the urine (Fig. 1). This is a

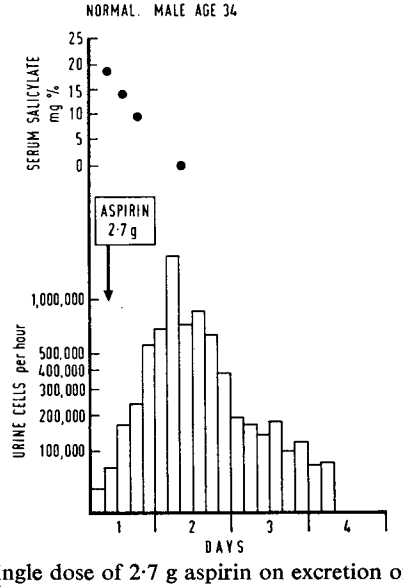

FIG. 1. *Effect of a single dose of 2·7 g aspirin on excretion of renal tubular cells in urine in a normal male.

*Figs 1–4 of this contribution are reproduced from Scott & others (1963), *Lancet*, **1**, 344–348, by permission of the Editor.

universal finding, the only exception being if the subject has taken aspirin previously in recent weeks. A second dose of aspirin taken a few days after the first produces no further exfoliation of cells, but as the time interval between the two doses is lengthened a response is seen to the second dose, though this is still diminished, at least for a month or so (Fig. 2). The shedding of tubular cells is more or less transient and if the administration of the drug is continued the cell count falls to normal levels (Fig. 3). We studied two patients continuously for several weeks, and during the last week the mean cell count in both of them was no higher

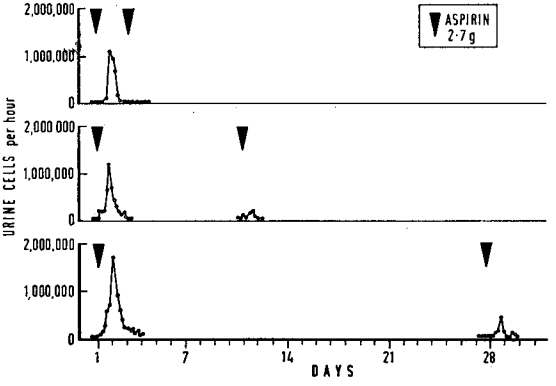

FIG. 2. Effect on excretion of renal tubular cells in urine of single doses of aspirin 2·7 g repeated at different intervals in three subjects.

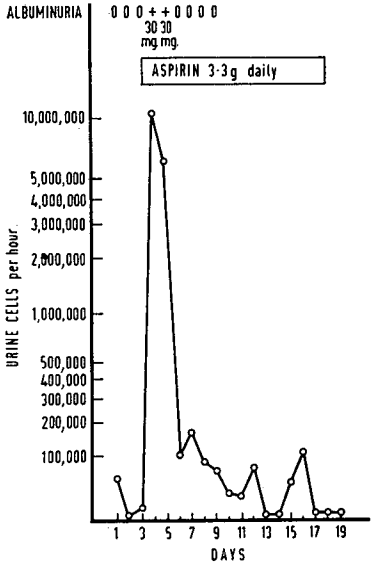

FIG. 3. Effect on excretion of renal tubular cells in urine of continued salicylate in a boy of 11 with rheumatic fever.

than that before aspirin was commenced (Fig. 4). Aspirin celluria is mostly a phenomenon of the early weeks of treatment. It seems likely that aspirin causes the premature desquamation of tubular cells which have attained a certain degree of maturity. Younger cells are not shed and so it is only after several weeks' abstinence from salicylates, during which the cells are permitted to grow, that readministration produced a further celluria.

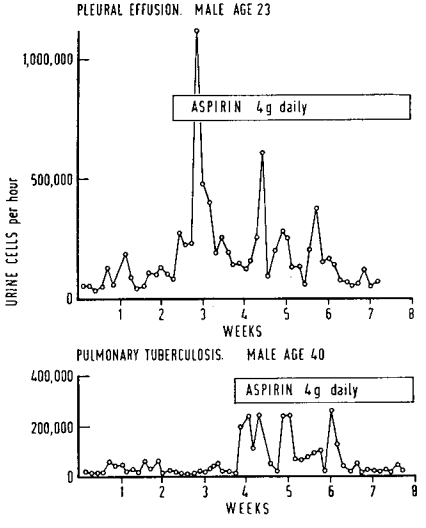

FIG. 4. Daily urine cell-counts in two patients, continued for several weeks of aspirin treatment.

There is really nothing to indicate that this acute tubular cell desquamation—which happens to everyone—has anything to do with chronic renal damage. As animal evidence is so far unsatisfactory we come back to clinical experience. Now Dr. Prescott makes the point that kidney damage has never been reported when phenacetin has been taken alone. But I have never heard of anybody prescribing phenacetin alone. Although it is available as the plain tablet it is nearly always administered in a compound analgesic mixture. This does not apply to aspirin, which is frequently given alone, and in enormous quantities both in this and other countries. As far as I know, however, with the exception of a single individual in a large survey of patients with renal papillary necrosis (Harvald, 1963), there have been no reports of such a condition following the long-term use of aspirin. I do not think the present evidence implicates salicylates as a cause of chronic nephrotoxicity.

Dr. L. F. Prescott. I think Dr. Sørensen's query about the significance of the rise in renal tubular cell excretion has been partly answered by Dr. Kennedy. If a nephrotoxic drug is given, a striking increase in renal tubular cell output occurs, and this can be correlated with histological changes in the kidney. The rise in renal tubular cell count is a more

sensitive indicator of toxic tubular damage than direct histological examination—a small dose of drug may cause increased cell excretion but no obvious histological abnormalities, while larger doses affect more cells and frank tubular necrosis may occur. Increased renal tubular cell excretion is irrefutable evidence of kidney injury (Balazs, Hatch, Zawidzka & Grice, 1963).

When animals (and man) are exposed continually to small doses of acutely nephrotoxic agents such as the heavy metals cadmium and lead, fibrotic lesions similar to those occurring in patients abusing analgesics are seen, and if there has been chronic exposure to *any* substance toxic to the renal tubules I do not consider it unreasonable to propose that this might eventually result in tubular degeneration, atrophy and fibrosis. With regard to the point raised by Dr. Kennedy, the renal tubular cells appearing in the urine following treatment with phenacetin were indistinguishable from those seen with aspirin.

I would like to point out that the 27 cases of analgesic nephritis that I have encountered in Aberdeen have corresponded closely to those reported from Scandinavia and Switzerland in that they had disease clinically similar to chronic pyelonephritis, sometimes with infection and papillary necrosis, sometimes without, often with a history of peptic ulceration or gastrointestinal bleeding and refractory anaemia.

I agree with Dr. Sanerkin concerning the medullary changes. These have been most marked in the preparations that I have examined. In the cortex the appearances may be almost normal with very little fibrous interstitial tissue, while towards the papillae this increases markedly and is often associated with sclerotic papillary necrosis.

With regard to the role of salicylates, I agree that aspirin cannot be blamed solely on the basis of these results. On the other hand, there is overwhelming evidence in the literature that salicylates can produce severe renal damage, and this does not all refer to acute administration of the drug. Can we really ignore this?

Dr. D. V. Parke. I have seen a record which suggests that the toxic side-effects of phenacetin may be genetically determined. The case was of a young girl in Zurich who had cyanosis. The metabolites in the urine of this patient were examined and the 3-hydroxy metabolite, not the 2-hydroxy metabolite, of phenacetin was found—the first time this has been recorded. 3-Hydroxy-4-methoxyaniline was also found, and this substance could give rise to 3,4-dihydroxyaniline (4-aminocatechol) which is an extremely toxic substance. I have fed this substance to dogs at 10 mg/kg and they all died with severe haematuria. Maybe deacetylation of these dihydroxy products could occur in the kidney giving rise to the toxic dihydroxyaniline products. They would probably not be found in the urine because they combine avidly with the organelles of the kidney tissues. The clinical symptoms of this girl were exacerbated, and the 3-hydroxy metabolite in the urine was increased, by treatment with phenobarbitone, which is known to increase the hydroxylation of a number of drugs. This case could be a genetic abnormality, giving rise to an aberration in metabolism of phenacetin.

Mr. T. L. Hardy. We have felt for some time that the antipyrine group of drugs might bear at least part of the blame for many of the renal lesions seen. Many Scandinavian and other continental reports, for example that of Horisberger, have recorded case histories and studies dealing with "phenacetin nephritis". In most of these reports phenazone or a phenazone derivative has been included in the formulations used, as in Saridone. These derivatives may be present in equal proportions to phenacetin, or phenacetin may be absent as in Kafa. Kafa and Saridone were reported by Horisberger and his colleagues (1958) as the most frequently taken preparations noted in his study. Again, Grimlund (1965) repeatedly discusses the effects of phenacetin consumption, in his study of the population of Husqvarna, in Sweden, in subjects taking an equal quantity of phenazone. Recently, during comparative studies of analgesics, including the antipyrine group, we have noted a large and highly significant elevation in the number of renal tubular cells in the urine of rats after the administration of phenazone. This has been accompanied by a proteinuria and in some instances a glycosuria. The cells were identical in morphology to those noted after the administration of known nephrotoxics.

Professor A. H. Beckett. Considering the metabolites of phenacetin, which are implicated in its toxic effects, if it is phenacetin that causes the trouble, and deacetylation is one of the metabolic pathways, surely *p*-phenetidine should be considered as a subject for detailed examination. It only needs the urine of some individuals to be more alkaline than others for reabsorption of this particular metabolite.

Dr. L. F. Prescott. The formation of the 3-hydroxy metabolite of phenacetin has been suspected, although I do not think it has previously been demonstrated in man. De-acetylation of these hydroxylated metabolites may occur, giving rise to 2-hydroxy-4-ethoxyaniline and 3-hydroxy-4-ethoxyaniline, while subsequent dealkylation could yield 4-aminoresorcinol and 4-aminocatechol respectively. The toxicity of these metabolites may therefore be very relevant. Since many patients abusing analgesics also habitually take barbiturates (which are known to increase the activity of several drug metabolising enzymes), it is significant that increased formation of toxic metabolites or their precursors could be demonstrated when the patient described by Dr. Parke was treated with phenobarbitone. Pletscher, Studer & Miescher (1958) have shown that *p*-phenetidine produces a greater reduction in erythrocyte survival time in rabbits than either phenacetin or paracetamol, but little is known of the effects on the kidney.

There would seem to be a convincing epidemiological case against the antipyrine group of drugs on the basis of the high reported incidence of analgesic nephritis in Sweden, Denmark and Switzerland—countries where the consumption of antipyrine is particularly high. In addition, Axelsson (1958) has described papillary necrosis following the abuse of antipyrine so that Mr. Hardy's findings are most interesting.

Dr. A. W. S. Sorensen. On the Continent we have examined the problems of nephrotoxicity of analgesics and a few workers have looked

at the prevalence of these kidney diseases, which I still think to be hypothetical. In some studies, the incidence has been found to be much less than 7%, which is the incidence of renal diseases suspected as causing toxic effects among consumers of analgesics. In our own study of hospital patients we found an incidence of papillary necrosis of 8% among consumers, so the 40 cases of suspect toxic nephritis mentioned by Dr. Prescott I believe to be drawn from at least a thousand consumers in an epidemiological study. It is not possible to prove how many of these 40 cases have had a silent chronic pyelonephritis, a phenomenon forgotten by many doctors. Most of the literature on that problem has described urinary tract infections in from 50–85% among consumers of analgesics with renal disease, so although it is often postulated that these renal diseases are actually cases of toxic nephritis, I think we are dealing with bacterial chronic nephritis rather than a toxic manifestation. The prevalence of chronic asymptomatic bacteriuria in different populations is about 2% in men and 4% in women.

To sum up, I think the prevalence of chronic pyelonephritis and so-called analgesic nephritis has the same dimension and may be the same degree of prevalence as asymptomatic chronic bacteriuria, and that there must be a substantial overlapping between these conditions.

Dr. D. A. Price Evans. Dr. Prescott has presented data that four out of 27 patients were high tubular cell shedders. Before accepting that this might be a pharmacogenetic polymorphism, could not the patients be latent pyelonephritics, in which the drug is acting like a steroid or a pyrogen provocative test? Has Dr. Prescott studied the relatives of high cell shedders to see if this is indeed a genetically determined trait?

Professor O. L. Wade. What was the past experience of these shedders of large numbers of cells in relation to their past phenacetin taking? It seems from the data presented that there are some people who are more liable than others to serious damage when they take drugs, perhaps this only becomes manifest when they have taken drugs, and perhaps methods could be devised for picking out which individuals in our community are liable to this.

Dr. D. I. Macdougall. Only some of those exposed to chronic ingestion of large doses of phenacetin develop renal damage and it seems to be agreed that differences in the metabolic pathway for the drug are the likely explanation of this. It has been assumed that one of its metabolic products is directly nephrotoxic. Is it possible that the primary effect of this metabolite is rather the formation of methaemoglobin (and sulphaemoglobin) in the blood? Resultant impairment of oxygen availability in the renal papilla could account for the necrotising papillitis. All of the three patients I have seen with necrotising renal papillitis and history of phenacetin abuse had the characteristic cyanosis of the methaemoglobinaemia which this drug can produce.

Dr. D. J. Davies. Papillary necrosis during the past 10–15 years has shown striking alterations in reported incidence. It is not really a single disease but may be found in a number of conditions. The number of cases has increased by between 10- and 100-fold. Furthermore, there has

been an alteration in the clinical and the pathological pictures in these cases. The classical lesion which occurs in diabetics with urinary infection usually begins as a wedge of infarction at the base of the medulla, but in patients with presumed analgesic nephritis the lesions tend to be limited to the distal part of the papilla. In this respect the lesions resemble the toxic lesions produced by ethylenimine.

Until recently there has been little evidence that phenacetin and other analgesics are nephrotoxic to animals. Within the past 2 years two papers have appeared, one from Abrahams and his co-workers (1964), the second one more recently in America (Fordham, Huffines & Welt, 1965) where a significant number of medullary as well as cortical lesions were observed in animals that had been given phenacetin alone, and also a mixture of aspirin, phenacetin and caffeine. Abrahams & others observed that if the rats were given aspirin and phenacetin together in the same proportions as in an A.P.C. tablet, there was a lower incidence of renal damage in the former group. This may suggest that caffeine is nephrotoxic.

A third point that I would like to make is that Dr. Sørensen screened rheumatoid patients for chronic renal damage by the use of endogenous creatinine clearance. This is a measure of glomerular function and in medullary necrosis and possibly other forms of tubular damage this test may remain normal for some time; the earliest evidence of impaired tubular function is shown by impaired regulation of the osmolarity of the urine in a water concentration and dilution test or in response to a test dose of anti-diuretic hormone.

Professor G. Brownlee. Dr. Prescott reminded us of the nephrotoxicity seen with bacitracin, and in particular of the excretion pattern of the cells showing a peak and then a falling off of the number of cells excreted. When Dr. Eileen Short and I described the nephrotoxicity of polymyxin B we were so impressed by the temporary nature of this acute effect in rats that we ventured to speak of a repair process. We found the effect could be prevented by the simultaneous administration of those amino-acids which donated methyl groups, like methionine and methylcystine.

Dr. L. F. Prescott. I cannot give Dr. Sørensen the true incidence of this condition in Aberdeen as I have not yet attempted to establish this. What I do know is that when I started to look for such patients I found them. The combination of peptic ulceration or gastrointestinal bleeding, refractory anaemia and "chronic pyelonephritis" seems virtually diagnostic—every patient that I have encountered so far with this triad has turned out to be a heavy consumer of analgesics.

Dr. Price Evans has raised the possibility that the four subjects responding to phenacetin with a great increase in renal tubular cell excretion in fact had latent pyelonephritis. While this cannot be entirely ruled out, an incidence of four out of 27 healthy adults would be unlikely, especially as two were males. They had no clinical history of renal disease and had normal urinary findings prior to the study. A study of the relatives both of these subjects and also of patients with analgesic nephritis would certainly be very valuable, and might provide evidence for a genetic mechanism.

DISCUSSION

It was incredibly difficult to find young healthy adults for this study who had not taken analgesics for six weeks previously. A person who has not taken analgesics for this period probably does not take analgesics very frequently, so in this respect the population was somewhat selected. I could find no difference in the control cell excretion or in the response to drugs between those subjects who rarely took analgesics and those who took them more frequently. As it happened, all the four subjects responding to phenacetin rarely took analgesics and there does not seem to be any way of predicting the response to phenacetin at present.

The weight of evidence is against methaemoglobin and sulphaemoglobin being the primary nephrotoxic agents. It is difficult to implicate tissue anoxia resulting from the formation of these pigments since patients with chronic anaemia do not have these renal lesions yet presumably also have a relative anoxia. Again, in congenital methaemoglobinaemia renal damage is not seen. Experimentally, methaemoglobin can produce acute tubular damage, but only in the presence of acidosis. Since acidosis can occur with salicylates and also in renal failure this mechanism could be responsible in theory, but would have to be a secondary effect. It could not apply, for instance to patients with normal or only moderately impaired renal function who were not taking salicylates.

As Dr. Davies points out, several workers have recently reported renal lesions in animals treated with phenacetin and A.P.C. mixtures. Nevertheless, it has taken a long time to do so, and there have been many more negative studies than positive. I think that the results of Fordham must be examined critically, because very large doses of phenacetin (up to 3,000 mg/kg/day) were required and the renal lesions were not comparable to those seen clinically.

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